Inspection générale
des affaires sociales
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Enquête sur le MEDIATOR®

RAPPORT DEFINITIF
TOME ANNEXES

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Liste des personnes auditionnées

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Dr Gérard Bapt, cardiologue, député de Haute-Garonne
Mme Catherine Hill, épidémiologiste, Institut Gustave Roussy, membre du conseil scientifique de l'Afssaps
Dr Bruno Toussaint, directeur de la rédaction de la revue Prescrire
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Christian Saout, président du Collectif interassociatif sur la santé

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Pr Bernard Bégaud, Professeur de pharmacologie à l'université de Bordeaux 2 et directeur de l'unité INSERM 657 « Pharmacoépidémiologie et évaluation de l'impact des produits de santé sur les populations».
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Pr Geneviève Derumeaux, présidente de la Société française de cardiologie
Pr Jean-Paul Giroud, Membre de l'Académie nationale de Médecine
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Pr Jacques Orgiazzi, professeur émerite
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Conseiller scientifique du directeur général, M. Eric Abadie
Adjoints au Directeur général : M. Philippe Lamoureux, Mmes Emmanuelle Wargon, Anne Burstin, Fabienne Bartoli
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Membres de la direction de l'évaluation du médicament :

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- chargées des affaires réglementaires : Mmes Arielle North, Françoise Mancel
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Secrétaire général : M. Michel Pot

Présidents de la Commission nationale de pharmacovigilance
Pr Jacques Caron, directeur du CRPV de Lille, CHU de Lille
Pr Merle,
Pr Christian Riché, directeur du CRPV de Brest, CHU de Brest

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Pr Charles Caulin
Pr Daniel Vittecoq

Commission de la transparence, Haute autorité de santé

Président du collège de la HAS : Pr Laurent Degos
Président de la Commission de la transparence : Pr Gilles Bouvenot
Secrétariat de la Commission : Mme Françoise Weber
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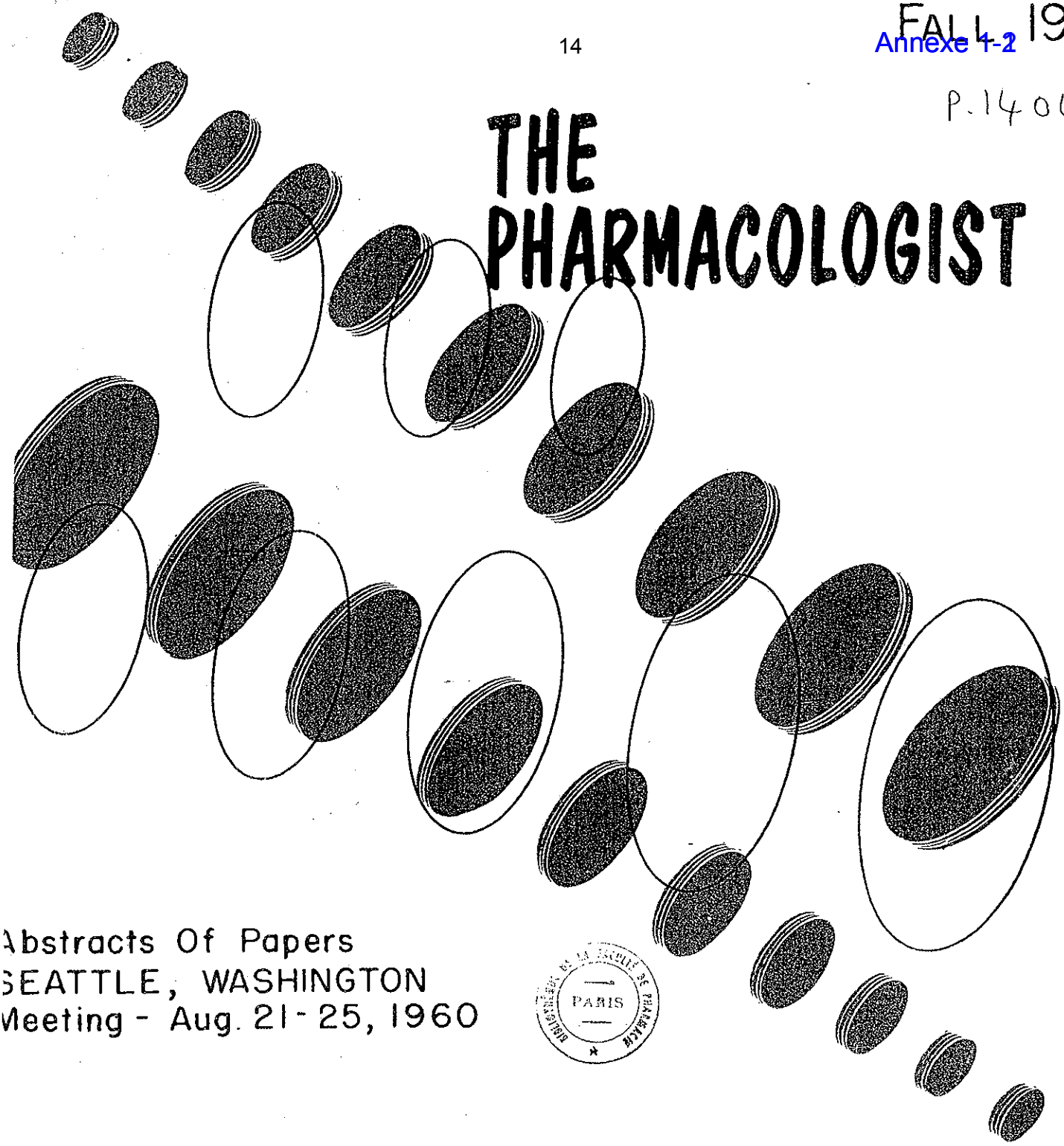
M. Christian Babusiaux, Président de l'institut des données de santé,
M. Richard Decottignies, Directeur de l'institut des données de santé

Personnes ayant représenté les laboratoires Servier
Pr Geneviève Derumeaux
Pr Bernard Iung

Nota : par exception certaines auditions ont été téléphoniques.

FALL 1960

THE PHARMACOLOGIST



Abstracts Of Papers
SEATTLE, WASHINGTON
Meeting - Aug. 21-25, 1960

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THE AMERICAN SOCIETY FOR PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS, INC.

Beaumont House Washington, D.C.

THE EFFECT OF METHAMINODIAZEPOXIDE (LIBRIUM) ON EXPERIMENTALLY INDUCED CONFLICT IN THE RAT. Irving Geller and Joseph Seifter. Wyeth Institute for Medical Research, Radnor, Pa.

Recently we reported an attenuation of experimentally induced conflict with meprobamate, urethanes, barbiturates and other C.N.S. depressants with anti-convulsant properties. Opposite effects upon conflict were obtained with phenothiazines. Here we report our findings with Librium, a compound of known clinical utility. Conflict was induced by simultaneously rewarding with food and punishing with shock all lever responses made in the presence of a tone stimulus. Between tone periods the rats worked only for food, permitting control observation for non-specific behavioral depression. Appropriate setting of the shock intensity resulted in a low but stable output of responses during the tone. Librium was administered in doses which ranged from 7.5 to 30 mg/kg. Most pronounced attenuation of the conflict occurred at the 15 mg/kg. dose. Lower doses generally were less effective and higher doses produced severe ataxia; the rats were unable to work in either the conflict trials or the control periods between tones. These findings are in accord with clinical studies which report some incidence of ataxia when Librium is administered at high therapeutic doses.

SOME FACTORS DETERMINING THE BEHAVIORAL EFFECTS OF CHLORPROMAZINE. W. H. Morse, Dept. of Pharmacology, Harvard Medical School, Boston, Massachusetts.

Experiments were conducted to determine the extent to which the behavioral effects of chlorpromazine are dependent upon the parameter values of some schedules of reinforcement. Food-deprived pigeons, previously trained to peck a key for food reinforcement, were studied under the following procedure: After a period of x seconds without a response, a white stimulus light appeared. Once every 3 minutes, on the average, a response in the presence of the white light was reinforced, otherwise a response simply terminated the stimulus. If no additional responses were made, the stimulus reappeared x seconds later, but each response prior to the appearance of the stimulus postponed its onset by x seconds. Other experiments were similar, except that the white light remained on all the time. Both of these procedures produced fairly steady control responding at rates which depended upon the value of x. At the parameter values studied, the average rate of responding was much higher when the white light was always present. For both procedures the tendency for chlorpromazine to decrease the output of behavior was greater when the animals were responding at higher rates. Increasing the value of x by 10-fold sometimes reversed the behavioral effect of a 10 mg dose from a decrease to an increase in the output of behavior. (Supported by U. S. P. H. S. Grant MY-2094.)

THE EFFECT OF HUMAN SERUM ON AVOIDANCE BEHAVIOR. Douglas Anger (intr. by P. H. Seay). Dept. of Pharmacology, The Upjohn Co., Kalamazoo, Mich.

With the classical avoidance procedure, appropriate doses of chlorpromazine eliminate the response of rats to the warning stimulus while leaving the response to electric shock. Intravenous injection of human serum into rats also produces this selective effect on the response to the warning stimulus, like chlorpromazine. A modification of the avoidance procedure is described that increases the sensitivity to serum. With the improved procedure there is a fairly consistent effect at 10 ml/kg of fresh serum, and a highly consistent effect at 20 ml/kg. The serum seldom kills the animal quickly until above 50 ml/kg, but at lower doses many animals die 2 - 6 days later. Human plasma has essentially the same effect. I.V. injections of rat and horse serum have only a slight effect at doses of 40 to 80 ml/kg. The activity is lost after standing 60 hours at room temperature, and declines by about one-half during 6 months at -30°C. The activity is centrifuged down at 105,000 xg, and does not dialyze, so apparently the active component is a large molecule. I.V. injections of trypsin do not show this effect except occasionally at or close to doses that kill immediately. However, crystalline egg albumin does show an effect rather similar to human serum.

INTERFERENCE BY NITROUS OXIDE WITH THE ABILITY OF MONKEYS TO DELAY A CHOOSING RESPONSE. Murray E. Jarvik. Dept. of Pharmacology, Albert Einstein Coll. of Med., New York City.

It has been demonstrated that administration of 80% nitrous oxide in oxygen could impair performance by monkeys in a 2 second delayed response test (Jarvik and Adler, The Pharmacologist, 1:51, 1959). In order to determine whether factors related to the delay are susceptible to the action of this gas or whether pre- and post-delay factors are entirely responsible for the effect monkeys were tested with two randomly presented delays. On a given day trials involving a one second delay were always interspersed among trials involving either a five or fifteen second delay. Five monkeys were employed in this task and tested with air, 20%, 50%, and 80% nitrous oxide in oxygen. The results with 20% were essentially the same as those obtained with air. With the higher concentrations of nitrous oxide there was a greater impairment of performance immediately following a long delay (five or fifteen seconds) than after a short delay (one second). It is concluded that mechanisms responsible for retention during the delay period are susceptible to the disrupting effect of nitrous oxide.

(Supported by PHS Grant M-1225 (C3).

SOME ANORECTIC AND BEHAVIORAL PROPERTIES OF P-1727, THE p-TRIFLUOROMETHYL ANALOGUE OF AMPHETAMINE. Albert Weissman* and Jurg A. Schneider. Dept. of Macrobiology, Chas. Pfizer & Co., Inc., Groton, Conn.

P-1727 (dl-β[-p-Trifluoromethylphenyl] Isopropylamine Hydrochloride) was examined in rats and dogs for anorectic potency. In rats it depressed food intake at 5-20 mg./kg. P.O., having about 1/2 the potency of d-amphetamine. In dogs its comparative potency was less than 1/12 that of d-amphetamine, activity beginning at about 3.5 mg./kg. P.O. When compared against phenmetrazine, however, P-1727 was significantly more potent in dogs and had a longer duration of activity. In both rats and dogs significant depression of food intake was not accompanied by observable CNS stimulation. When tested behaviorally in rats, oral doses of 8 mg./kg. of P-1727 on a simple CRF schedule, and 10 mg./kg. I.P. on a multiple schedule with a CRF component (Weissman: J. Exp. Anal. Behav. 2: 271, 1959.) were active in suppressing CRF responding. Behavioral changes suggesting stimulation (i.e. increased S$^{\Delta}$ rates and responses per reinforcement) were produced by d-amphetamine, but not by P-1727, on these schedules. Similarly, d-amphetamine, unlike P-1727, disrupted DRL performance by causing marked rate increases and much shorter interresponse times. It is concluded that P-1727 retains much of the anorectic potency of amphetamine in rats without concomitant behavioral stimulation, as measured by operant conditioning techniques.

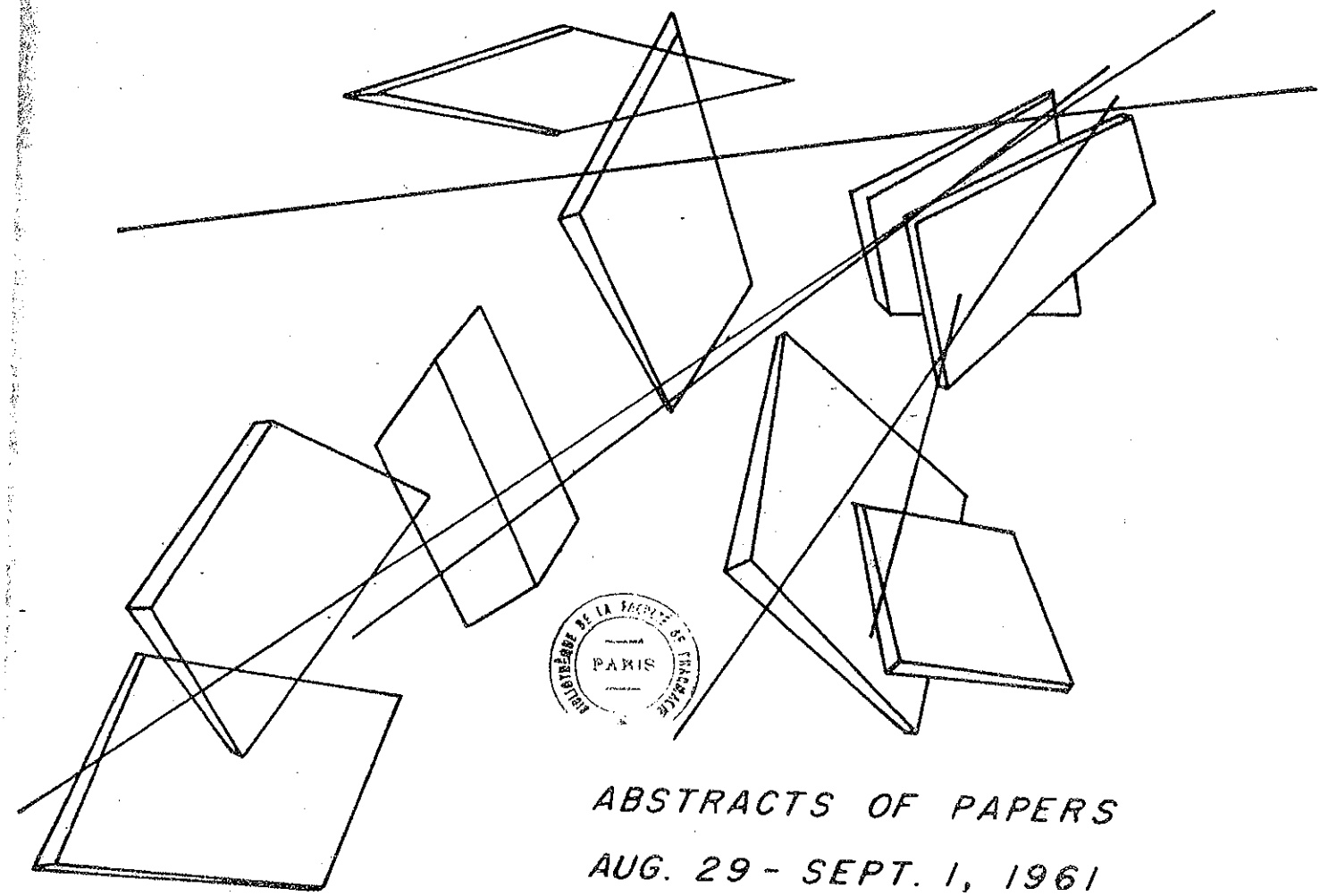
PROLONGATION OF ANOREXIA IN DOGS BY SUSTAINED-RELEASE D-AMPHETAMINE. H. Wendel, F. M. Sturtevant, and I. Shemano*. Pharmacology Section, Smith Kline & French Labs., Philadelphia

Offering 1/24th pound of food to starving dogs every 10 min. keeps the animals hungry for hours while still allowing frequently repeated food offerings to test for drug-induced anorexia. Refused offerings are removed from the cage and re-offered. Percent refusals of the total of 72-90 offerings per hour to 12-15 dogs were plotted against hours after drug administration. D-amphetamine was given in capsules in the first food offering. In doses with about the same peak effects sustained-release drug caused a 4-5 hours effect plateau and 50% or more refusals (= anorexia) per hour for 3-5 hours longer than ordinary drug. After equal weight doses 50% or more anorexia lasted about the same time with the 2 drug forms, but the peak effect of the ordinary drug was considerably higher. Besides demonstrating the utility of this test in determining time-action curves of sustained-release anorexigenic preparations the data show that the sustained-release d-amphetamine tested possesses the two desired advantages of such preparations over ordinary drug forms: prolonged effect and plateau effect without excessive peak action.

Annexe 1-3

FALL 1961

THE PHARMACOLOGIST



ABSTRACTS OF PAPERS

AUG. 29 - SEPT. 1, 1961

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THE AMERICAN SOCIETY FOR PHARMACOLOGY
and
EXPERIMENTAL THERAPEUTICS, INC.

Beaumont House Washington, D. C.

THURSDAY AFTERNOON

NEUROPHARMACOLOGY II

NEUROPHARMACOLOGY OF dl -α-METHYL-p-TRIFLUOROMETHYLPHENETHYLAMINE HYDROCHLORIDE (SK&F No. 7410-A). C.A.Leonard*, T. Fujita*, D.H.Tedeschi, and R.J.Fellows, Smith Kline and French laboratories, Philadelphia, Pennsylvania.

SK&F No. 7410-A was evaluated for anorexigenic activity and concomitant effects in rats, dogs and monkeys. In the anorexia tests 7410 was approximately 3/8 as potent as d-amphetamine in the rat and 1/7 as potent in the dog and monkey. Dogs and monkeys receiving 7410 did not show increased motor activity even at maximum tolerated dosages. In other tests 7410 was found to be approximately equal in potency to d-amphetamine in producing a blockade of the conditioned avoidance response in rats. Analgesia and in vivo inhibition of monoamine oxidase were not manifested in the rat. Anticonvulsant effects in the mouse maximal electroshock test were present but only in doses in the order of the LD_5. No antagonism to pentobarbital-induced depression in rats and dogs was observed with 7410. The oral LD50's compared with those of d-amphetamine showed that 7410 is only 1/3 as toxic in the rat and 1/6 in the mouse. In the unanesthetized dog only a slight hypotensive effect was noted and EKG effects were similar to those of d-amphetamine. Glucose tolerance studies in dogs showed no difference from d-amphetamine and controls.

DIFFERENTIAL EFFECTS OF DILANTIN ON VARIOUS COMPONENTS OF THE PYRAMIDAL RESPONSE. Baruch Blum*. Montreal Neurol. Inst., Montreal, Canada.

Motor cortex stimulation produces in the pyramidal tract an electrical response, composed of an initial "D wave", supposedly the direct response of the excited cells, and longer latency "I waves", thought to be synaptic, resulting from reexcitation of other Betz cells through collaterals of interneurones. Sensorimotor cortex or Thalamic VL stimulation produces "relayed" pyramidal responses. Different motor cortex cells appear to be involved in the elaboration of these responses. The anti-epileptic drug diphenylhydantoin (Dilantin) applied topically depressed all the above responses, but with regulation of dosage, it depressed first the D wave exerting later a stronger depression on the I waves, leaving almost unaffected the other responses. I.V. Dilantin 18 mg/kg markedly depressed the I wave with moderate effect on the D wave, whereas 24 mg/kg markedly depressed both. These dosages left unaffected the sensorimotor elicited response with small effect on the relayed thalamic-elicited ones. Larger doses (30 mg/kg), used in studies on after-discharges, depressed indiscriminantly all the above responses. It was concluded that the differential effect of the drug as shown here may be related to its specificity as a non-hypnotic, anti-epileptic drug.
Supported by The National Research Council of Canada.

AUTONOMIC AGENTS THAT CAUSE DEATH AFTER SUPRA-MAXIMAL ELECTROSHOCK IN MICE. C. D. Hendley, T. M. Mikiten*, and S. Irwin. Dept. of Neuropharmacology, Schering Corp., Bloomfield, N.J.

In some strains of mice there is a high mortality from respiratory depression shortly after the tonic extensor component (TE) of maximal electroshock seizures. This does not appear to occur in CF#1 male mice, 18-24 grams (40 ma., 0.2 sec., AC stimulus). The animals die under these conditions, however, if pretreated i.p. with dopamine (100 mg/kg) or iproniazid followed by dopamine (50 mg/kg). The same is observed after atropine or scopolamine alone (1 mg/kg), or other anticholinergics including scopolamine methylbromide, atropine methylnitrate, JB-329, or propantheline. Dibenzylene (2.5 mg/kg) reduces the mortality after dopamine; arecoline (10 mg/kg) or physostigmine (3 mg/kg), the mortality after atropine. Anticonvulsant drugs protect if they block the TE component of the seizures. Artificial respiration, until normal breathing returns, also prevents death. The data suggest that a mechanism involving catechol amines in the brain may delay recovery of the respiratory center after electroshock, and that a cholinergic mechanism may have the opposite effect. Thus, if the balance between these is upset, respiration may fail after TE. The extent to which peripheral or central mechanisms are involved is under investigation.

EFFECT OF ELECTRICAL STIMULATION ON THE NEURAL SYNTHESIS OF NORADRENALINE FROM L-TYROSINE-C^{14}. W.G. Clark, F.J. Kotichas*, H.F. Schott*, D.T. Masuoka*, and W. Drell*. VA Hosp., Sepulveda and Med. Ctr., U. Calif., Los Angeles.

Paired thoracic sympathetic chains of cats were extirpated under pentobarbital, placed in specially designed chambers at 37° and perfused with Krebs solution containing uniformly labelled L-tyrosine-C^{14}. One nerve was continually stimulated (0.5-0.8 volts, 30 C.P.S.) and the other used as an unstimulated control. After 2 to 3 hours the nerves were removed from the solution and the tissue extract and perfusion fluid separately analyzed by chromatography on alumina, and CG-50 resin. C^{14}-noradrenaline but no adrenaline and little or no dopamine appeared regularly in the tissue fraction. An as yet unidentified non-catechol amine appeared in the fluid fraction. The extract of the stimulated nerve regularly yielded 2 to 5 times as much labeled noradrenaline as that of the unstimulated nerve, and about twice as much total radioactivity. Similar results were obtained when the nerves were pretreated with C^{14}-tyrosine and then immersed in plain Krebs solution before commencing the stimulation. (Supported by N.I.H., Am. Heart Assoc. and Nat. Assoc. Mental Health).

SENSITIVITY OF THE NICTITATING MEMBRANE AFTER DENERVATION AND AFTER VARIOUS DRUGS. U. Trendelenburg and N. Weiner. Dept. of Pharmacology, Harvard Medical School, Boston, Massachusetts.

The sensitivity of nictitating membrane of spinal cats to norepinephrine (NE), tyramine (TYR) and acetylcholine (ACH) was studied after the following procedures: (a) chronic denervation, (b) chronic decentralization, (c) pretreatment with single, large dose of reserpine (3 mg/kg 24 hr prior to experiment), (d) 14 daily injections of 0.1 mg/kg reserpine, (e) 7 days of 10 mg/kg TM 10 per day, and (f) 7 days of ganglion blockade with chlorisondamine (2-5 mg/kg, twice daily). Supersensitivity to NE and ACH was observed in all groups of cats with the exception of (c); subsensitivity to TYR appeared in (a), (c) and (d), supersensitivity to TYR in (b), (e) and (f). Catecholamines in heart, aorta, iris, nictitating membrane and adrenal medulla were measured by fluorimetric method; they were normal in group (f), slightly reduced in (e) and severely reduced in (c) and (d). There is thus no relation between depletion of NE stores and supersensitivity to NE, which seems to be the result of interruption of tonic impulses for 7 days. Subsensitivity to TYR is related to depletion of NE stores. (Supported by USPHS grants B-1713 and B-2947 and US AF 41(657)-197.)

MODIFICATION OF AFFERENT INTERACTION PATTERNS BY CHLORPROMAZINE, MEPROBAMATE, MORPHINE AND PENTOBARBITAL. C.L. Mitchell*, S.D. Nelson* and K.F. Killam. Stanford Univ. School of Med., Palo Alto, Calif.

In cats surgically prepared under ether anesthesia and subsequently immobilized with gallamine triethiodide responses were evoked in mesoncephalic, thalamic, rhinencephalic and neocortical structures by pairing of photic and tooth pulp stimulation. Stimulus trains, programmed to be presented at random intervals of 50 to 95 seconds, consisted of 3 flashes of light 100 msec. apart followed in 350 msec. by a single stimulus to the tooth pulp (TPS). 25 control responses to the flash sequence alone followed by 100 or more responses to the flash plus TPS were elicited before drug administration. Evoked responses to TPS decreased with repetition. Chlorpromazine at 1, 2, and 5 mg/kg, pentobarbital at 5, 10 and 15 mg/kg, meprobamate at 10, 20 and 50 mg/kg and morphine sulfate at 0.5, 1, and 2 mg/kg were administered intravenously. In general, all drugs enhanced responses to photic stimulation in lateral geniculate and optic cortex. Responses to TPS were differentially affected by the various drugs in the specific and nonspecific systems. (Supported by NIH grants MY3241 and MY3374)

Annexe 1-4

INTERNATIONAL SYMPOSIUM ON AMPHETAMINES AND RELATED COMPOUNDS

Proceedings of the Mario Negri Institute for Pharmacological Research, Milan, Italy

Editors: E. Costa and S. Garattini

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..en Press, New York, © 1970.

STRUCTURE-ACTIVITY RELATIONSHIPS IN CF_3 SUBSTITUTED PHENETHYLAMINES

L. G. Beregi, P. Hugon, J. C. Le Douarec, M. Laubie and J. Duhault

Groupe de Recherches des Laboratoires Servier, Paris

More than a decade ago when our study started on this series of compounds, the problem of antiobesity drugs appeared to be rather simple. On the one hand, amphetamine was the choice drug in spite of its prominent side effects; on the other hand, very little was known on the mechanism of hunger inhibition by drugs. Since it is beyond the scope of this paper to relate the history of amphetamine-like substances, we shall limit ourselves to a few surveys which display an over-all picture of the state of knowledge in the late fifties.

The general subject of beta-phenethylamine derivatives has been brilliantly reviewed by W. H. Hartung (1945) and by K. H. Beyer (1945). The relationship between chemical structure and analgesic action was exhaustively surveyed by E. J. Fellows (1951) who concluded that in most of these derivatives, marked pain-threshold elevation was found near the toxic levels, accompanied always by central stimulation.

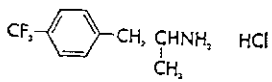
The clinical importance of amphetamine in the treatment of obesity was outlined by H. Gold (1945) who was the first to insist on its toxic reactions and the need for compounds with more selective actions.

Under these circumstances, a vast research effort was deployed in this field in our laboratory, without much hope of practical application. It was anticipated that a systematic study of fluorine and CF_3 substituted phenethylamines would reveal some relationship, thus giving us a better understanding of the problem. At the same time, we hypothesized that the CNS stimulant and anorexigenic activities of amphetamine were not necessarily linked in other structurally related compounds.

An early confirmation of the correctness of the above "working hy-

pothesis" came from Holm *et al.* (1960) who, while searching for a new anorexigenic agent, reported the low level of central stimulating effect of chlorophentermine (α,α-dimethyl-4-chlorophenethylamine).

While our work was in progress, Weisman (1960) and C. A. Leonard *et al.* (1961) disclosed independently of each other their results stating that the primary amine:



is anorexic and has little CNS stimulant effect.

At this time we were already convinced of the indisputable superiority of the secondary amines in this series. This option indeed proved to be rewarding and opened new vistas.

The unusual pharmacological properties and clinical usefulness of fenfluramine (1-(3-trifluoromethyl-phenyl)-2-ethylamino-propane) have stimulated further study of a large number of related compounds, and in this paper we propose to draw some generalizations from our work and also to illustrate some examples of structural specificities.

To the chemist working in medicinal chemistry, a pharmacologically active series whose similarities in basic structure are responsible for biological activity is an excellent tool for the development of a structure-activity rationale. But can we speak of structure-activity relationships in our case, when out of 280 new compounds, more than 50 of them presented almost equal anorexic effect without attaining the potency of amphetamine? Perhaps the title, *Choice of anorexic compounds considering their therapeutic indexes,* would more closely cover the scope of this study.

Before going into a detailed discussion of the structural modifications and their effect on anorexigenic activity, it is of interest to show the steps in the development of our work. These phases were the following:

1) separation of anorexigenic and CNS stimulant effects (successful at the very beginning);
2) diminution in acute toxicity, well demonstrated by the esterified hydroxyethyl compounds;
3) decrease in the hypertensive effect, beautifully shown in secondary amines;

4) possible development of analgesics;
5) comparison between trifluoromethylated phenylisopropylamine and phentermine derivatives.

COMPOUNDS TESTED FOR ANOREXIC ACTIVITY

The compounds covered in this paper can be divided broadly in primary, secondary and tertiary beta-phenylisopropylamines. A further division of the secondary amines into acylated, hydroxyalkyl and amino acid derivatives has been made.

Finally, a comparison between beta-phenylisopropylamine and phentermine derivatives was attempted.

CHEMISTRY

The synthesis of CF_3 substituted beta-phenylisopropylamine (Rocca, 1964) is outlined in Scheme 1.

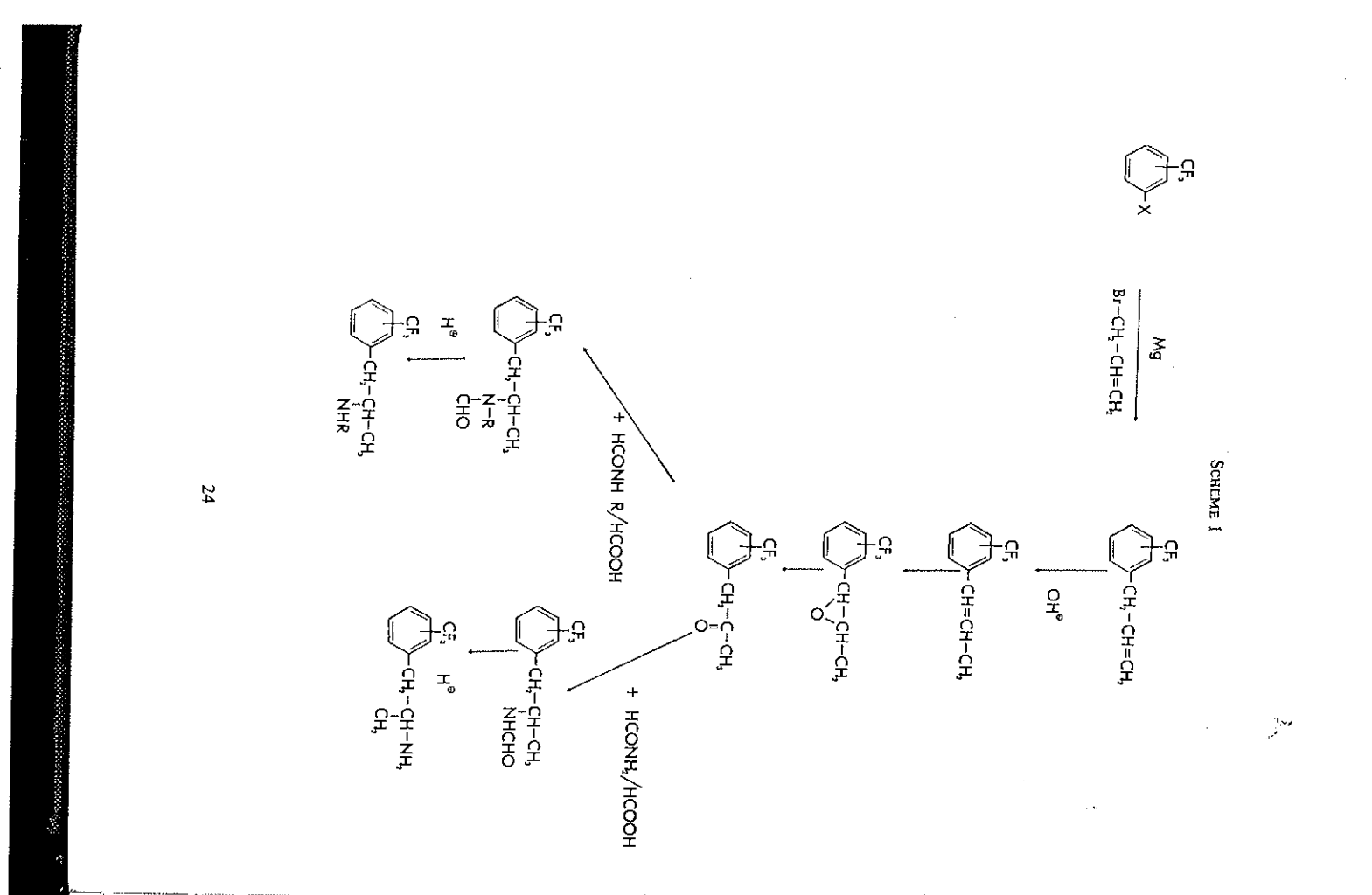
Typical methods used for the preparation of N-substituted derivatives are illustrated in Scheme 2.

FLUORO-AND TRIFLUOROMETHYL BETA-PHENYL ISOPROPYLAMINES

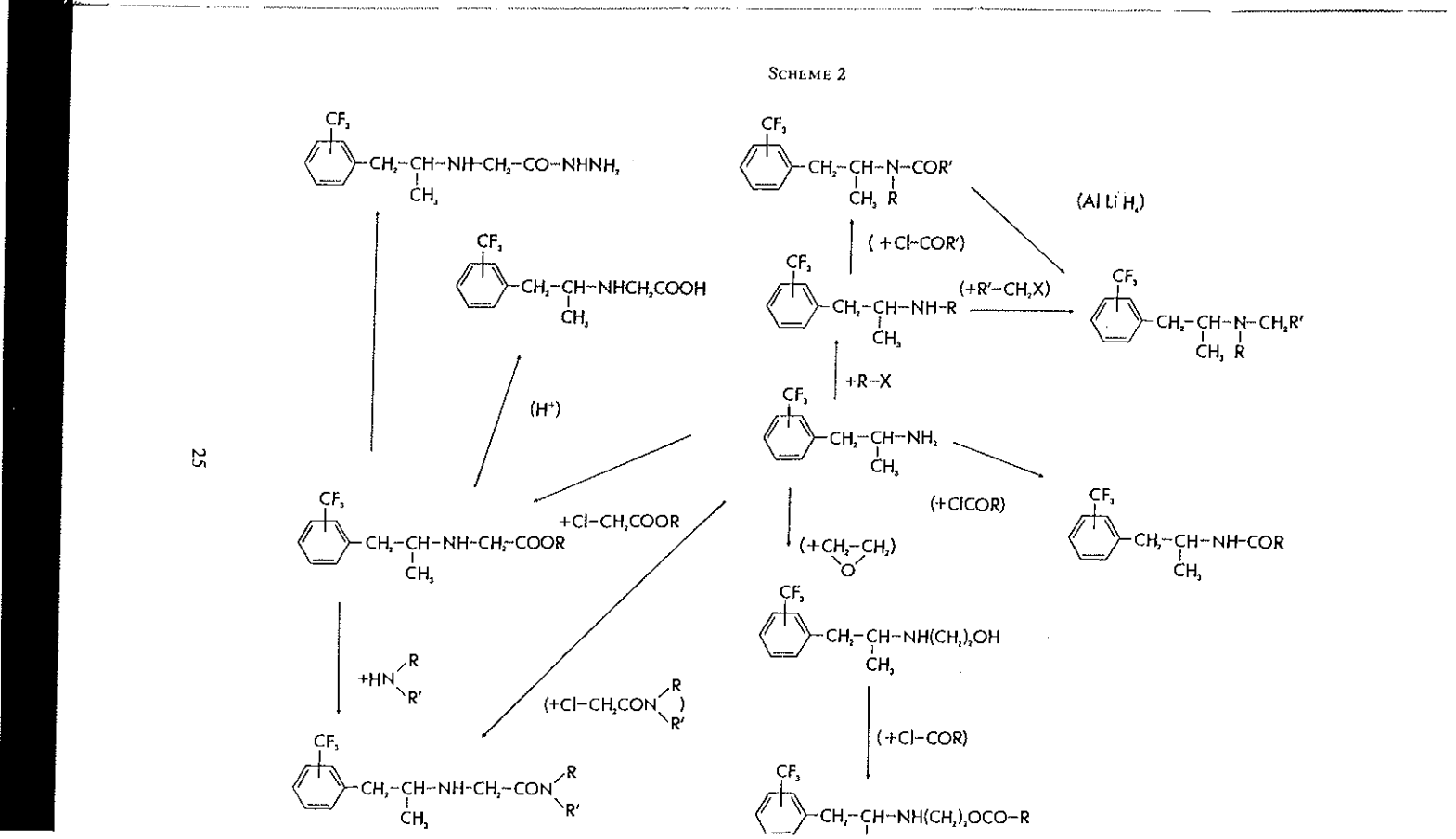
A systematic study of fluorinated and trifluoromethyl substituted beta-phenyl isopropylamines revealed to us that the whole spectrum of biological activity does not run parallel with amphetamine.

We have already shown (Le Douarec and Beregi, 1962), that the most striking finding was the reversal of the central stimulating action of amphetamine by means of CF_3 substitution, as judged by the index of locomotor activity and body temperature. It seemed clear, on the basis of these results, that the 3-CF_3 substitution was of particular interest. These findings were also substantiated by Holland *et al.* (1963).

A summary of other pharmacological activities is presented in Table I. It can be seen that compound 5 has a favorable vasopressive action in the dog, while in the rat there is no difference between amphetamine and this compound. The fluoro derivatives display a considerable amphetamine-like activity.



Scheme 1



Scheme 2

Explanation of Tables

Acute toxicity

Determined by intraperitoneal administration in mice, unless otherwise noted (NMRI strain, weight 20–22 g, in groups of 6). The experiments were carried out at a temperature of 21° ± 1° C.

Anorexia

Food intake in rats and dogs, as already published (Le Douarec, 1966). *Rat:* dose of the compound which inhibits food intake by 50% for 2 hours, when administered orally 1 hour previously. *Dog:* oral minimal dose delaying food ingestion for 2 hours.

Analgesia

Haffner's method in mice (in groups of 6): that dose which inhibits by 50% the reflex of biting the artery clip placed on the base of the mouse's tail. Intraperitoneal route of administration unless otherwise noted. We consider this test a tool for psychotropic activity, since many CNS active drugs inhibit the response, as recently showed by Weller (1968).

Anticonvulsant action

Experimental convulsions: electroshocks in mice (8 animals per dose). Bucco-occipital electrodes delivering electric shocks with the following characteristics: 7.5 to 30 volts lasting 1 second. Oral dose which protects by 50% against the tonic extension.

Vasopressive action

(a) *Blood pressure of the pithed rat.* The study of the intravenously administered derivative is based on the blood pressure of the rat prepared according to the procedure of Shipley and Tilden (1947). The results are expressed in terms of pressure variations in mm of mercury. At least 4 rats were used per dose studied.

(b) *Blood pressure in the anesthetized dog.* Dogs received chloralose anesthesia (120 mg/kg) intravenously. Blood pressure was recorded by mercury manometer at the femoral artery; we recorded the variations in pressure produced by intravenous injection of each of the compounds under study. The essential information concerning blood pressure has been recorded using the following symbols: (+) means an increase in mm Hg in the blood pressure; (−) means a decrease in mm Hg in the blood pressure.

Monoamine oxidase inhibition *in vitro*

This effect has been studied by Warburg's technique, using tyramine substrate. The incubation time was one hour, pH was 7.4, and temperature was 37° C. The percent inhibition is expressed as moles per liter concentration (M).

MODIFICATION OF THE SIDE CHAIN

In view of the promise shown by the CF_3 substitution in phenylisopropylamines, the optimum position (meta) constituted the basis for further investigations by alteration of the side chain.

Some of the compounds studied are listed in Table II. Noticeable decrease in activity was observed when the phenylisopropylamine structure was modified. The only allowable change was the methyl substitution of the beta carbon atom, as illustrated by the structure of compound 10.

N-MONOALKYLATED DERIVATIVES

Encouraged by these results, we undertook an extensive N-alkylation program in the beta-phenylisopropylamine series (Beregi *et al.*, 1960; 1964; 1965). A considerable number of pertinent analogs were prepared. Results with the more interesting of these derivatives are given in Table III.

N-Monoalkylation gives rise to high potency compounds. The major advantage which can be stressed is a dramatic decrease in the pressor effect, as compared with the primary amine. Moreover, some compounds, *e.g.*, 18 and 19, were almost completely devoid of pressor effect.

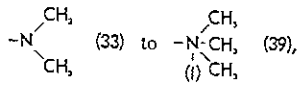
Considering both the toxicity and anorexic activity, the methyl (15), ethyl (16), chlorethyl (20), propenyl (22) and propargyl (26) derivatives were the most potent members. Generally, N-alkylation with larger groups resulted in considerable loss of activity.

From this table it is apparent that the most active anorexigenic substances also have significant analgesic potencies.

Compound 16, fenfluramine, stands out with a good balance between toxicity and other pharmacological properties, all of which have been studied rather extensively (Le Douarec, this volume).

N-DIALKYLATED DERIVATIVES

Data in Table IV show that disubstitution of the amine function results in decrease in anorexic and analgesic activities. There is a very marked increase in toxicity when going from



and a tenfold augmentation in pressor effect in the dog, while central actions are nearly abolished.

TABLE I

Fluoro and Trifluoromethyl beta-phenylisopropylamines

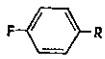
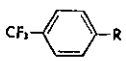
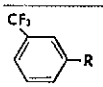
Compound R = CH_2—CH(—CH_3)—NH_2	Toxicity	Anorexia rat	Anorexia dog	Analgesia mouse	Anticonvul. action	Vasopressive action rat	Vasopressive action dog	MAO inhibition
 *d,l*-amphetamine	13	4.4	0.9	10	>20	1 mg/kg: 40 (+) 0.5 mg/kg: 32.5(+) 0.25 mg/kg: 10 (+)	0.1 mg/kg: 25(+) 0.3 mg/kg: 45(+)	10^{-3}M: 56% 2×10^{-4}M: 34%
 1.	46	3.5	2	10	>20	0.5 mg/kg: 37 (+) 0.25 mg/kg: 19 (+)		10^{-3}M: 40%
 2.	63	7.5	1.5	20	>20	0.25 mg/kg: 31 (+) 0.125 mg/kg: 21.5(+)		10^{-3}M: 27%
 3.	100	15	1	20	>20	1 mg/kg: 36 (+) 0.5 mg/kg: 29 (+)		10^{-3}M: 73%
 4.	153	3	8	20	⩾40	0.5 mg/kg: 21 (+) 0.25 mg/kg: 11 (+)	5 mg/kg: 50(+)	10^{-3}M: 57%
 5.	51	2	2	10	⩾10	5 mg/kg: 100 (+) 1 mg/kg: 41 (+) 0.25 mg/kg: 21 (+)	5 mg/kg: 80(+)	10^{-3}M: 33%
 6.	171	⩾40	>20	40	>40	3 mg/kg: 25 (+) 0.5 mg/kg: 9 (+)	5 mg/kg: 80(+)	10^{-3}M: 36%

TABLE II

Modification of the side chain

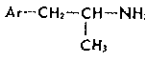
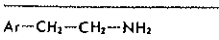
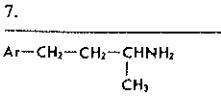
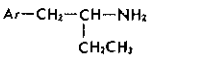
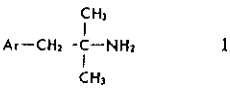
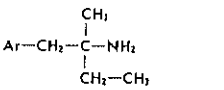
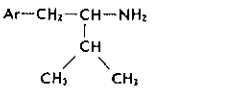
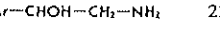
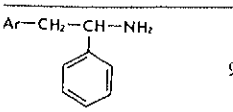
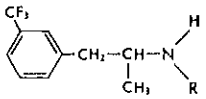
Compound	Tox.	Anorexia rat	Anorexia dog	Analg.	Anti-convul. action	Vasopressive Action rat	Vasopressive Action dog	MAO inhibition
5. 	51	2	2	10	⩾10	5 mg/kg: 100(+)	5 mg/kg: 80(+)	10^{-3}M: 33 %
7. 	131.5	>20		40	>20		5 mg/kg: 50(+)	10^{-3}M: 65 % 2×10^{-4}M: 21 %
8. 	152	>20		40	>20	0.25 mg/kg: 18(+)		10^{-3}M: 34 % 2×10^{-4}M: 10 %
9. 	130	⩾20		20	>20		5 mg/kg: 20(+)	10^{-3}M: 8.6%
10. 	127.5	10	10	5	>20	5 mg/kg: 20(+)		10^{-3}M: 25 %
11. 	83	>20		25	>10	5 mg/kg: 12(+)	5 mg/kg: 15(−)	10^{-3}M: 5.5%
12. 	84	⩾20		40	>10		5 mg/kg: 30(−)	10^{-3}M: 3 %
13. 	226	>20		>60	>20	1 mg/kg: 43(+)		10^{-3}M: 40 % 2×10^{-4}M: 25 %
14. 	90	>20		>40	>10		5 mg/kg: 70(−)	10^{-3}M: 0 %

TABLE III

N-Monoalkylated derivatives



R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog	MAO inhibition 10^{-3}M	MAO inhibition 2×10^{-4}M
$-CH_3$ 15.	130	6.8	2.5	15	>10	5 mg/kg: 24 (+)		53 %	14%
$-CH_2CH_3$ 16. fenfluramine	71	5.2	6.5	12.5	10	5 mg/kg: 26.9(+) 1 mg/kg: 8.6(+)	5 mg/kg: 56(+) 2 mg/kg: 25(+) 1 mg/kg: 6(+)	49 %	22%
$-CH_2CH_2CH_3$ 17.	87	10.4	7.5	35	⩾20	5 mg/kg: 21 (+)		58 %	14%
$-CH(CH_3)_2$ 18.	142	8.7	2.5	> 50	>20	5 mg/kg: 0 (+)	5 mg/kg: 30(—)	45 %	30%
$-CH_2CH_2CH_2CH_3$ 19.	94.6	10	2.5	15	20	5 mg/kg: 0 2 mg/kg: 10 (+)		77 %	25%
$-CH_2CH_2Cl$ 20.	123.4	10	2.5	30	>20	5 mg/kg: 15 (+)		41 %	10%
$-CH_2-C_6H_5$ 21.	144	10	5	> 40	>20	5 mg/kg: 20 (+)	5 mg/kg: 20(—)	18 %	
$-CH_2CH=CH_2$ 22.	109	8.4	2.5	40	⩾20	5 mg/kg: 17 (+)	5 mg/kg: 40(—) 70(+)	20 %	19%
$-CH_2-C(CH_3)=CH_2$ 23.	130	10	5	20	15		5 mg/kg: 60(—)	46.2%	
$-CH_2-CH=C(CH_3)_2$ 24.	79	>20		> 40	>10		5 mg/kg: 40(—)	66 %	
$-CH_2-CH=CHCH_3$ 25.	78	>20		> 40	20		5 mg/kg: 50(—)	36 %	27%
$-CH_2-C\equiv CH$ 26.	283	7.6	8	35	20	5 mg/kg: 11 (+)	5 mg/kg: 60(—)	100 %	62%
$-CH_2-CH_2-CH_2-C\equiv CH$ 27.	181.6	10	2.5	⩾ 40	10		5 mg/kg: 30(—) 20(+)	63 %	
$-CH_2-CH=CH-C_6H_5$ 28.	80	>15		> 40	>10		5 mg/kg: 50(—)	20 %	

TABLE III (*continued*)

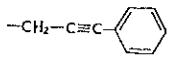
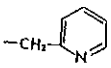
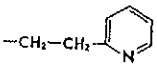
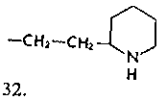
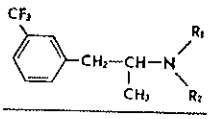
R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog	MAO inhibition 10^{-3}M	MAO inhibition 2×10^{-4}M
 29.	1600 p.o.	>20		>150 p.o.	>40			0%	
 30.	115	10	2.5	⩾ 60	>20	5 mg/kg: 25 (+)	5 mg/kg: 20(−) 10(+)		36%
 31.	76.5	15		⩾ 30	10	2 mg/kg: 15 (+)			14%
 32.	234	>20		> 60	>20	2 mg/kg: 30 (+)			47%

TABLE IV

N-Dialkylated derivatives



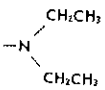
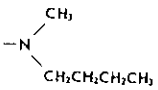
	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog	MAO inhibition 10^{-3}M	MAO inhibition 2×10^{-4}M
 33.	144	20	12	50	>20		5 mg/kg: 15(+)	43%	19%
 34.	132	20	2	30	30	5 mg/kg: 48(+)		52%	7%
 35.	149	⩾20		60	7.5	5 mg/kg: 15(+)		54%	

TABLE IV (*continued*)

	Toxicity	Anorexia		Anal-gesia	Anti-convul. action	Vasopressive action		MAO inhibition	
		rat	dog			rat	dog	10^{-3}M	2×10^{-4}M
36.	263	15	4	> 40	> 20				99%
37.	600	⩾ 20		150	> 20	5 mg/kg: 20(+)			2%
38.	940 p.o.	25		> 100 p.o.	> 40				
39.	35	> 20	> 10	> 10	> 10	5 mg/kg: 115(+)	5 mg/kg: 150(+)		33%
40.	72	⩾ 10	5	30	> 20	5 mg/kg: 2(+)			35%

N-AMIDES

The acylation of the amine group led, as expected, to compounds with substantially diminished toxicity (Beregi *et al.*, 1967). Surprisingly, with the exception of the propionyl derivative (52), these amides exhibited a very low order of activity (Table V).

TABLE V

N-amides[a]

	R	Toxicity p.o.	Anorexia rat	Anorexia dog	Analgesia p.o.	Anti-convul. action
41.		900	30	> 20	75	> 40
42.		> 2000	> 20		> 50	> 20
43.		2000	> 40		100	> 50
44.		433	> 20		⩾ 50	> 75
45.		> 2000	> 40		> 100	> 40
46.		⩾ 2000	> 20		> 100	50

[a] Not tested on blood pressure or MAO because of insolubility.

TABLE V (*continued*)

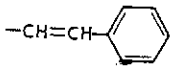
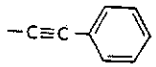
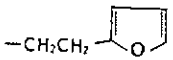
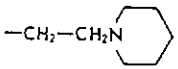
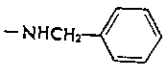
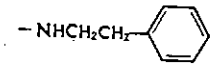
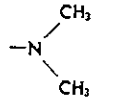
 47.	⩾2000	>20		>100	> 50
 48.	⩾2000	20		>100	> 50
 49.	⩾2000	20		> 50	> 50
 50.	300	>20		> 50	> 50
$-CH_3$ 51.	750	>20	>20	> 50	> 20
$-CH_2CH_3$ 52.	2000	4.3	⩾20	>100	> 50
 53.	>2000	>20		100	50
$-CH_2Cl$ 54.	⩾2000	⩾20		>100	> 50
$-CH_2CHOHCH_3$ 55.	712	>20		100	> 50
$-CH_2CH_2COOH$ 56.	⩾2000	>20		> 50	> 50
$-CH{=}CHCOOH$ 57.	⩾1000	>40		> 50	> 50
$-NH_2$ 58.	1500	>20		> 50	>120
 59.	>1000	>20		> 50	> 80

TABLE V (*continued*)

 60.	>1000	⩾20		> 50	> 80
 61.	1250	>20		> 50	100

On the basis of results shown in the preceding tables, the structure-activity relationships appeared to be rather straightforward, and at this very point we could well have stopped our investigations. In spite of these findings, further, unobvious structural modifications were attempted in two main directions: (a) amino alcohols, esters and ethers; and (b) amino acids and their derivatives.

HYDROXYALKYL DERIVATIVES : ESTERS

The esterification of the hydroxyalkyl beta-phenylisopropylamine was found to be beneficial in most cases, as shown in Table VI.

The most active anorexic among the carbinols (62) indicates that in this series of compounds optimum activity is associated with a two-carbon chain between the nitrogen atom and the hydroxyl group. This structural feature was conserved in the esterification study.

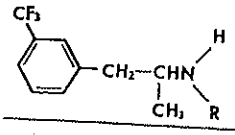
Various observations can be made regarding correlations between toxicity and anorexic activity. It should first be noted that the aliphatic esters (65 to 69) led to a slight decrease in activity and no significant changes in toxicity.

In the aryl and aralkyl series, many compounds exhibit very high anorexic activity accompanied by a significant diminution in toxicity. Substitution of the phenyl ring can result in retention or diminution in activity, depending upon the type and position of the substituent group.

We chose compound 70 (S 992), which appeared to be the most effective orally, both in rats and in dogs, in order to compare its intensity and duration of action with fenfluramine (16). Interestingly, this compound displayed an unusual discrepancy between the intraperitoneal and oral toxicities. This observation might well lead us to conclude rather hastily that the compound had a low rate of absorption. In fact, in recent work on buccal absorption

TABLE VI

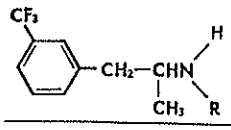
Hydroxyalkyl derivatives : esters



R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog
$-CH_2CH_2OH$ 62.	184 300 p.o.	5.2	4.6	25	>40	5 mg/kg: 10(—)	5 mg/kg: 20(—)
$-CH_2CH_2CH_2OH$ 63.	207	>20		> 60	>20	5 mg/kg: 10(+)	
$-CH_2CH_2OCOCH_3$ 64.	125	10	7.5	30	>20		5 mg/kg: 20(—)
$-CH_2CH_2OCOCH_2CH_3$ 65.	178	10	7.5	> 20	>20	5 mg/kg: 0	
$-CH_2CH_2OCO-$ 66.	150	⩾10		⩾ 20	>20	5 mg/kg: 0	
$-CH_2CH_2OCO-CH_2Cl$ 67.	213	7.5	3	⩾ 20	>40	5 mg/kg: 0	
$-CH_2CH_2OCOCH=C(CH_3)_2$ 68.	155	10	3	> 20	>50	5 mg/kg: 20(—)	
$-CH_2CH_2OCO-CH_2CH_2COOH$ 69.	192	10	5	> 20	>20		5 mg/kg: 5(—)
$-CH_2CH_2OCO-C_6H_5$ 70. S992	2300 p.o. 108 i.p.	5.4	7.5	32 p.o.	80	5 mg/kg: 5(—)	5 mg/kg: 50(—)
$-CH_2CH_2OCO-C_6H_4-CH_3$ 71.	1000 p.o.	10		⩾ 50 p.o.	>20		
$-CH_2CH_2OCO-C_6H_4-Cl$ 72.	1000 p.o.	15	7.5	⩾ 50 p.o.	>20		5 mg/kg: 20(—)
$-CH_2CH_2OCO-C_6H_4-NO_2$ 73.	1000 p.o.	20		50 p.o.	>40		
$-CH_2CH_2OCO-C_6H_4-NH_2$ 74.	400 p.o.	15	10	> 50 p.o.	>20		5 mg/kg: 10(—)
$-CH_2CH_2OCO-C_6H_4-NH_2$ 75.	1500 p.o.	30		> 50 p.o.	>40		
$-CH_2CH_2OCO-C_6H_4-F$ 6.	1000 p.o.	7.5		>50 p.o.	>20		

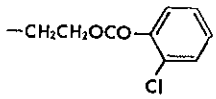
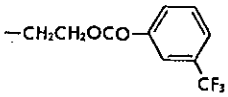
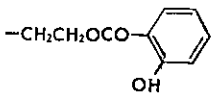
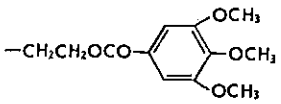
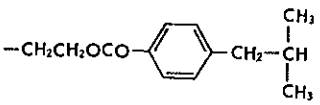
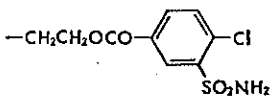
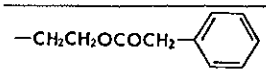
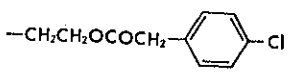
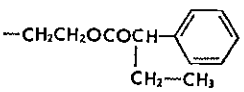
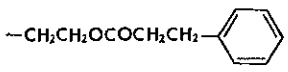
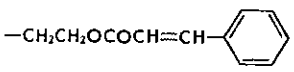
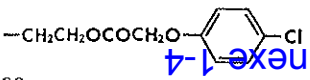
TABLE VI

Hydroxyalkyl derivatives : esters



R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog
$-CH_2CH_2OH$ 62.	184 300 p.o.	5.2	4.6	25	>40	5 mg/kg: 10(—)	5 mg/kg: 20(—)
$-CH_2CH_2CH_2OH$ 63.	207	>20		> 60	>20	5 mg/kg: 10(+)	
$-CH_2CH_2OCOCH_3$ 64.	125	10	7.5	30	>20		5 mg/kg: 20(—)
$-CH_2CH_2OCOCH_2CH_3$ 65.	178	10	7.5	> 20	>20	5 mg/kg: 0	
$-CH_2CH_2OCO-$ 66.	150	⩾10		⩾ 20	>20	5 mg/kg: 0	
$-CH_2CH_2OCO-CH_2Cl$ 67.	213	7.5	3	⩾ 20	>40	5 mg/kg: 0	
$-CH_2CH_2OCOCH=C(CH_3)_2$ 68.	155	10	3	> 20	>50	5 mg/kg: 20(—)	
$-CH_2CH_2OCO-CH_2CH_2COOH$ 69.	192	10	5	> 20	>20		5 mg/kg: 5(—)
$-CH_2CH_2OCO-C_6H_5$ 70. S992	2300 p.o. 108 i.p.	5.4	7.5	32 p.o.	80	5 mg/kg: 5(—)	5 mg/kg: 50(—)
$-CH_2CH_2OCO-C_6H_4-CH_3$ 71.	1000 p.o.	10		⩾ 50 p.o.	>20		
$-CH_2CH_2OCO-C_6H_4-Cl$ 72.	1000 p.o.	15	7.5	⩾ 50 p.o.	>20		5 mg/kg: 20(—)
$-CH_2CH_2OCO-C_6H_4-NO_2$ 73.	1000 p.o.	20		50 p.o.	>40		
$-CH_2CH_2OCO-C_6H_4-NH_2$ 74.	400 p.o.	15	10	> 50 p.o.	>20		5 mg/kg: 10(—)
$-CH_2CH_2OCO-C_6H_4-NH_2$ 75.	1500 p.o.	30		> 50 p.o.	>40		
$-CH_2CH_2OCO-C_6H_4-F$	1000 p.o.	7.5		> 50 p.o.	>20		

TABLE VI (*continued*)

R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog
 77.	750 p.o.	7.5		> 50 p.o.	>20		
 78.	750 p.o.	5	7.5	> 50 p.o.	>40		
 79.	750 p.o.	10	⩾20	⩾ 50 p.o.	⩾40		5 mg/kg: 60(+) then 80(—) 20(+)
 80.	2000 p.o.	15		> 50 p.o.	>40		
 81.	2000 p.o.	15		> 50	>40		
 82.	2000 p.o.	12.5	10	25	>80		5 mg/kg: 0
 83.	1000 p.o. 150 i.p.	10		20 i.p. 40 p.o.	>20		5 mg/kg: 0
 84.	450 p.o.	7.5	7.5	> 50 p.o.	>40		5 mg/kg: 0
 85.	2000 p.o.	20		⩾100 p.o.	>40		
 86.	850 p.o.	7.5	⩾20	100 p.o.	⩾50		
 87.	1750 p.o.	20		> 100 p.o.	⩾50		5 mg/kg: 30(—)
 88.	1250 p.o.	15	10	> 50 p.o.	>50		

studies (Brookes, 1968), only insignificant amounts of S 992 at all pH values could be recovered in spite of its low water solubility, thus evidencing a rapid absorption and a very important lipid solubility.

Whether S 992 is active *per se*, or its activity is a result of metabolic conversion by undergoing a rapid *in vivo* hydrolysis to liberate the parent hydroxyethyl compound, and whether the hypothesis of the re-arrangement of this drug could be accepted (Scheme 3), the active entity is clearly a potent anorexic.

SCHEME 3. *Possible re-arrangement of S 992 (Brookes, 1968).*

In any case, the particular interest of this drug lies in its extremely high therapeutic ratio and its lack of untoward effects (Beregi *et al.*, 1966).

Another substance (82) emerged from the study of these esters due to its anorexic and diuretic properties. In fact, this compound is a mild diuretic at a somewhat higher dosage than that needed for its anorexic effect.

HYDROXYALKYL DERIVATIVES : ETHERS

Table VII shows the effect of the introduction of the ether function. In comparison with the hydroxyethyl derivative (62), these compounds were more toxic and less active in rats.

AMINO ACID DERIVATIVES

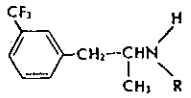
The comparative activity of selected compounds is summarized in Table VIII. Again, in this series, the requirement for high anorexic activity is fairly specific. The essential structural system consists of one carbon atom between the nitrogen atom and the carboxy group. On this basis, a great number of acid derivatives were prepared and pharmacologically tested. These data indicate that the nature of the substituent has practically no influence on the anorexic activity, and it may be summarily stated that these amino acid derivatives represent one of the most potent structural types of non-stimulating anorexigens (Beregi *et al.*, 1969).

TABLE VI (*continued*)

R	Anorexia: Toxicity rat	Anorexia: Toxicity dog	Analgesia	Anti-convul. action	Vasopressive action: rat	Vasopressive action: dog
89.	⩾2000 p.o.	10	> 100 p.o.	> 40	5 mg/kg: 0	
90.	1000 p.o.	> 20	> 50 p.o.	> 20	5 mg/kg: 50(−)	
91.	1500 p.o.	15	> 50 p.o.	> 40	5 mg/kg: 5(+)	
92.	2000 p.o.	10	⩾50 p.o.	> 40		

TABLE VII

Hydroxyalkyl derivatives: ethers

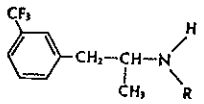


R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog
$-CH_2CH_2OCH_2CH_3$ 93.	118	10	5	20	>20		5 mg/kg: 45(—)
$-CH_2CH_2O-C_6H_5$ 94.	100	>20		>40	>20		5 mg/kg: 30(—)

46

TABLE VIII

Amino acid derivatives



R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog	MAO inhibition 10^{-3} M
$-CH_2COOH$ 95.	125 500 p.o.	4	10	⩾40	>40		5 mg/kg: 0	28.7%
$-CH_2COOCH_2CH_3$ 96.	200	5	10	40	>40		5 mg/kg: 30(—)	9.6%
$-CH_2CH_2COOH$ 97.	300	35	>20	>40	>40		5 mg/kg: 0	0
$-CH_2CH_2COOCH_3$ 98.	300	>40		>20	>40		5 mg/kg: 0	0
$-CH_2CONH_2$ 99.	350 p.o.	7.5	6	25 p.o.	>20			17 %
$-CH_2CONHCH_3$ 100.	250	3	7.5	20	>40	5 mg/kg: 28(+)		33.5%
$-CH_2CON(CH_3)_2$ 101.	150	7.5	7.5	>20	>20	5 mg/kg: 5(+)		32 %

47

TABLE VIII (*continued*)

R	Toxicity	Anorexia		Anal-gesia	Anti-convul. action	Vasopressive action		MAO inhibition 10⁻³M
		rat	dog			rat	dog	
—$CH_2CONHNH_2$ 102.	250	4	10	>20	>40	5 mg/kg: 0	2 mg/kg: 0	47.4%
—$CH_2CONHCONH_2$ 103.	750 p.o.	6	15	20 p.o.	>40			
—CH_2CONH—(CF₃) 104.	2000 p.o.	5	⩾20	⩾20 p.o.	>40			
—CH_2CO—(N) 105.	150	10	>10	>20	>20	5 mg/kg: 0		39 %
—CH_2CONH—(N) 106.	650 p.o.	7.5	10	20 p.o.	>40			

OPTICAL ISOMERS

The comparison of activity between the optical isomers and their racemic counterparts of the more interesting compounds is shown in Table IX. The general rule for the order of anorexic activity in the rat is: *dextro*-isomer > racemate > *levo*-isomer. However, a detailed analysis of results and a comparison of species turned up some anomalies. Thus, for the N-allyl compound (22), the order of anorexic activity in the dog is *dl* (22) > *d* (111) > *l* (112). The same is true in the case of the N-hydroxyethyl derivative (62) where *dl* (62) > *d* (113) > *l* (114).

If we consider now the isomers of S 992 we can see that the anomaly manifests itself in the rat (*dl* (70) > *d* (115) > *l* (116)), but not in the dog.

In the majority of cases, analgesic effectiveness is favorably influenced by resolution of isomers, the order of ranking by relative potency being: *dextro*-isomer > racemate > *levo*-isomer. Curiously enough, this rule does not seem to be followed by the two esters S 992 (70) and (82).

The vasopressive effect goes in accordance with the general order of activity for the N-ethyl compound (16), whereas all the other isomers studied are little active or inactive.

These discrepancies may be explained by differences in the rates of absorption and excretion, or by a preferential stereoselective elimination. The importance of species may be emphasized, and pharmacological interaction between isomers can also be an acceptable working hypothesis for further investigations in this field. However, if we consider an approximate therapeutic ratio, not computable here, it must be stressed that the enantiomers[1] have the best value.

POSITION ISOMERS

A. N-(2-benzoyloxyethyl)-beta-phenyl isopropylamine

Table X records the effect of different positions of the CF_3 group on the benzene nucleus in the very case of S 992 which appeared to have a high and sustained anorexic effect in animals. It seems apparent that a clear-cut relationship exists between anorexic activity and the position of substituents. As was evident with the CF_3 substituted beta-phenyl isopropylamines, and as is equally true in this series, high anorexic activity is always associated with the *meta*-position.

[1] Mirror image forms of the same compound.

TABLE IX

Optical isomers

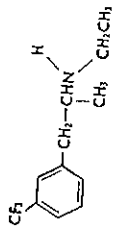
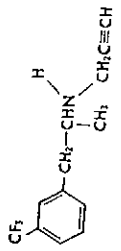
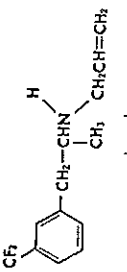
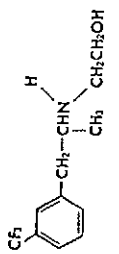
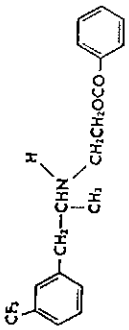
	No.	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anti-convul. action	Vasopressive action rat	Vasopressive action dog
	16.[a] *d,l*	71	5.2	6.5	12.5	32	5 mg/kg: 27 (+) 1 mg/kg: 8.6(+)	5 mg/kg: 56(+) 2 mg/kg: 25(+) 1 mg/kg: 6(+)
	107. *d*	60	2.8	4	12.5	33.5	5 mg/kg: 48.3(+) 1 mg/kg: 14.3(+)	5 mg/kg: 95(+) 2 mg/kg: 43(+)
	108. *l*	105.2	10	21.2	40	21	15 mg/kg: 11.6(−) 5 mg/kg: 13.2(+)	5 mg/kg: 8(−) 2 mg/kg: 0
	26. *d,l*	283	7.6	8	35	20	5 mg/kg: 11 (+)	5 mg/kg: 60(−)
	109. *d*	112	3.5	3.5	20		5 mg/kg: 15 (+)	
	110. *l*	250	7.5	10	48		5 mg/kg: 28 (+)	
	22. *d,l*	109	8.4	3.5	40	⩾20	5 mg/kg: 19 (+)	
	111. *d*	56	7.5	7.5	10	>10	5 mg/kg: 20 (+)	
	112. *l*	113	10	10	20	>20	5 mg/kg: 15 (+)	
	62. *d,l*	184	5.2	4.6	25	>20	5 mg/kg: 10 (+)	
	113. *d*	91	4	7.5	15	>20	5 mg/kg: 0	
	114. *l*	312	15	10	>40	>40	5 mg/kg: 0	5 mg/kg: 30(−)

TABLE IX (*continued*)



70.[b]	*d,l*	2300 p.o.	5.4	7.5	32 p.o.	80	5 mg/kg: 5 (—) 5 mg/kg: 50(—)
115.	*d*	300 p.o.	12.5	3	50 p.o.	>40	
116.	*l*	850 p.o.	⩾30	15	>50 p.o.	>40	

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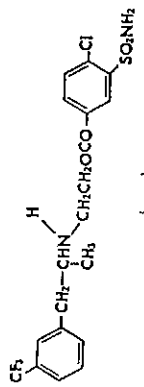
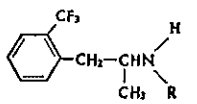
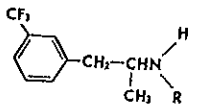
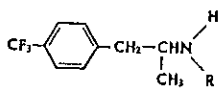


82.	*d,l*	2000 p.o.	12.5	10	25 p.o.	>80	5 mg/kg: 0
117.	*d*	500 p.o.	5	7.5	⩾50 p.o.	>40	
118.	*l*	1500 p.o.	⩾30	20	>50 p.o.	>40	

[a] Fenfluramine; [b] S 992

TABLE X

Position isomers

R=CH_2CH_2OCO–C$_6$H$_5$	Toxicity	Anorexia rat	Anorexia dog	Analgesia p.o.	Anti-convul. action	Vasopressive action rat	Vasopressive action dog
 119.	⩾1000 p.o. 300 i.p.	⩾20	>20	20	>40	5 mg/kg: 20(—) 14(+)	5 mg/kg: 40(—)
 70. S 992	2300 p.o. 108 i.p.	5.4	7.5	32	80	5 mg/kg: 5(—)	5 mg/kg: 50(—)
 120.	⩾1000 o.p.	20	10	>50	>40	5 mg/kg: 15(—)	

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B. Phentermines

Our structure-activity relationship survey would not be complete without a comparative pharmacological investigation of relationships between the phenylisopropylamine and the corresponding phentermine derivatives.

First of all, the effect of CF_3 substitution was investigated in the latter series as compared with chlorphentermine (Table XI).

The optimum position for the CF_3 group was here again the *meta* position on the benzene nucleus, as was shown by the low activity of the other isomers. These findings do not seem to be in agreement with the results of Lorenz (1969). The compound (10) appeared to equal, in the rat, the anorexic potency of chlorphentermine, taken here as a model substance. Here again, the dog seems to be less sensitive to the compounds of this very structure.

COMPARISON BETWEEN PHENYLISOPROPYLAMINES AND PHENTERMINES

The study of trifluoromethylated phentermine analogs was further extended to groups on the nitrogen which conferred the highest activity in the phenylisopropylamines (Table XII). Between the direct analogs in the two series, only the N-ethyl derivative showed somewhat equivalent potency in the phentermines. All other changes attempted led only to loss of activity.

DISCUSSION

From the foregoing data on the influence of structure upon pharmacological activity, some broad generalizations can be made concerning structural features that led to a high anorexigenic effect.

In view of the chemical resemblance between the amphetamines and their trifluoromethylated analogs, it would be interesting to examine their similarities and differences.

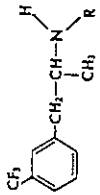
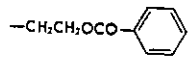
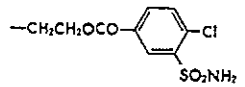
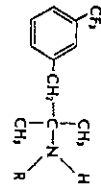
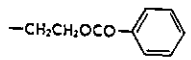
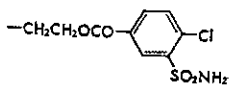
Let us first consider the similarities. The requirement to satisfy our criterion for high anorexic activity follows surprisingly well the rules established by Van der Schoot *et al.* (1962) in their study on the relationship between structure and locomotor activity in mice in phenylethylamine derivatives. Those rules are: (1) The chain between the amino group and the ring is restricted to two-carbon units. (2) The binding of the amino group to a secondary carbon atom seems to be required. (In fact, compounds without this branching are devoid of anorexic activity in our series.) (3) Substitution in

TABLE XI

Position isomers in phentermines

R= $CH_2-\underset{CH_3}{\overset{CH_3}{C}}-NH_2$	Toxicity	Anorexia		Anal-gesia	Anti-convul. action	Vasopressive action		MAO inhibition	
		rat	dog			rat	dog	$10^{-3}M$	$2 \times 10^{-4}M$
121. chlorphenterimine	110	12.5	11	10	> 80	1.5 mg/kg: 20.5(+)		15	5
122.	132	> 20	> 20	50	> 20	1 mg/kg: 0 5 mg/kg: 26 (+)		40	0
10.	127.5	10	10	5	> 20	5 mg/kg: 20 (+)		25	6.5
123.	201	20.7	> 20	30	30	5 mg/kg: 26 (+)			24

TABLE XII. *Comparison between phenylisopropylamines and phentermines*

	R	Toxicity	Anorexia rat	Anorexia dog	Analgesia	Anticonvul. action	Vasopressive action rat	Vasopressive action dog	MAO inhibition 10^{-3}M	MAO inhibition 2×10^{-4}M
	H	51	2	2	10	⩾10	5 mg/kg: 100 (+)	5 mg/kg: 80(+)	33%	
5.										
	$-CH_2CH_3$	71	5.2	6.5	12.5	10	5 mg/kg: 26.9(+) 1 mg/kg: 8.6(+)	5 mg/kg: 56(+) 2 mg/kg: 25(+) 1 mg/kg: 6(+)	49%	22%
16. fenfluramine										
	$-CH_2CH{=}CH_2$	109	8.4	2.5	40	⩾20	5 mg/kg: 17 (+)	5 mg/kg: 40(−) 70(+)	20%	19%
22.										
	$-CH_2C{\equiv}CH$	283	7.6	8	35	20	5 mg/kg: 11 (+)	5 mg/kg: 60(−)	100%	62%
26.										
	$-CH_2CH_2Cl$	123.4	10	2.5	30	>20	5 mg/kg: 15 (+)		41%	10%
20.										
	$-CH_2CH_2OH$	184	5.2	4.6	25	>40	5 mg/kg: 10 (−)	5 mg/kg: 20(−)	41%	19%
62.										
		2300 p.o.	5.4	7.5	32 p.o.	80	5 mg/kg: 5 (−)	5 mg/kg: 50(−)	15%	
70. S 992										
		>2000 p.o.	12.5	10	25 p.o.	80		5 mg/kg: 0		
82.										
	H	127.5	10	10	5	>20	5 mg/kg: 20 (+)			
10.										
	$-CH_2CH_3$	144	10	15	>30	>20			27%	11%
124.										
	$-CH_2CH{=}CH_2$	113	⩾20	15	⩾50	>20				
125.										
	$-CH_2C{\equiv}CH$	300	>20	>20	⩾60	>20				
126.										
	$-CH_2CH_2Cl$	150	⩾20	>20	⩾40	>20	5 mg/kg: 0	5 mg/kg: 40(−) 1 mg/kg: 10(−)		
127.										
	$-CH_2CH_2OH$	300	>20	⩾20	>60	>40		5 mg/kg: 25(+)		
128.										
		750 p.o.	⩾20	⩾20	>50 p.o.	>40		5 mg/kg: 15(−)		
129.										
		2000 p.o.	>20	⩾20	>50 p.o.					
130.										

the *ortho* position leads to a loss of activity. (As a general rule, in our series, *m*-CF_3 > *p*-CF_3 > *o*-CF_3.) (4) The introduction of substituents on the amino group is allowed. Large substituents result in a decrease or loss in activity.

The first and most striking difference is the absence of the stimulant effect regardless of the position of the CF_3 group on the ring. A further important consequence of the *meta*-CF_3 substitution in some secondary phenylisopropylamines is the reduction or even the suppression of the characteristic cardiovascular effects of amphetamine. Another essential feature of these compounds is a good balance between toxicity and anorexic activity, thus displaying significantly superior therapeutic indexes as compared to those of the amphetamine derivatives.

In fact, the various attempts made by several authors (Marsh *et al.*, 1950; Schmitt *et al.*, 1967; Beaton *et al.*, 1968; Owen, 1963) to alter the basic properties of amphetamine by the introduction of alkyl groups, chlorine or fluorine atoms on the phenyl ring resulted in the majority of cases only in the enhancement of toxicity with the appearance of hallucinogenic properties.

As we have shown in the course of this study by numerous examples of highly active anorexic substances, the *m*-trifluoromethylated phenylisopropylamine lends itself favorably to a mono-substitution on the amine group. In contrast, ring and N-substitution of the 1-phenyl-2-aminopropane lead only to a marked decrease in anorexic activity, as demonstrated in a fairly extensive study by R. Kopf *et al.* (1960).

A further difference can be observed by disubstitution on the amine group. While N-dialkyl, N-alkyl-alkylaryl, pyrrolidino and piperidino derivatives of CF_3 substituted phenylisopropylamine show only marginal activity, in the methamphetamine series the introduction of benzyl and furyl methyl groups bestows useful properties on these compounds by creating a balance between the CNS stimulant and anorexigenic activities (Veldkamp *et al.* 1964; Boissier *et al.*, 1966; 1967).

The hydroxyethyl substitution of the amine group seems to be beneficial. Some of its aryl and arylalkyl acid esters have outstanding pharmacological profiles. Maximal anorexigenic activity was obtained with a compound bearing a methylenecarboxy group on the nitrogen. Conversion of this amino acid into ester, amide, or hydrazide etc., increased the initial activity.

Finally, we established in the comparative study of some optical isomers with their racemates that there are no rules in these series to predict the higher activity.

A direct comparison between trifluoromethylated phentermine and beta-phenylisopropylamine derivatives demonstrated the higher level of activity of the latter.

It is clear from this survey that the introduction of a CF_3 group into the amphetaminic structure cannot be considered a simple, classical substitution, and it seems to us that the CF_3 substituted phenylisopropylamines can be

considered, without much exaggeration, as an independent class of compounds. This statement seems to be well supported by the results of comparative studies in different animal species with some of our more active compounds and their amphetaminic analogs. While trifluoromethylated derivatives have significant activities in mice, rats and dogs, it appears that their amphetaminic counterparts are species dependent. A similar discrepancy was pointed out by Boissier *et al.* (1966) in some benzylmethylamphetamine and furylmethylamphetamine derivatives.

We shall pass rapidly over the general inactivity of the compounds on monoamine oxidase *in vitro,* as well as the fact that we did not succeed in obtaining higher anti-convulsant activities than those seen in the few initial derivatives.

Finally, let us consider the intrinsic analgesic properties of these derivatives. There has been some question as to whether amphetamine is a true analgesic.

Evidence favoring this view was put forth by Goetz *et al.* (1944), Fellows and Ullyot (1951), Randall, Selitto and Valdes (1957), Moorman (1967) and Colville and Chaplin (1964), who insisted on the analgesic activity of sympathomimetic amines in laboratory animals. Cass *et al.* (1966) attribute the failure to find a clinically useful analgesic among the sympathomimetic amines to the difficulties in separating analgesic activity from CNS stimulatory and cardiovascular effects. The success in overcoming these sympathomimetic actions as well as the dramatic improvement of the narrow therapeutic ratio of the previously described amphetamine derivatives by the introduction of a CF_3 group on the phenyl ring cleared the way for a hopeful development of new analgesic compounds. Indeed, many members of the present series produced significant increases in pain threshold in the mouse, but generally analgesic and anorexigenic activities ran parallel.

One of the great difficulties encountered in the study of these analgesics remains in their clinical evaluation. Nevertheless, the analgesic activity found for several of these compounds in mice and rats has been substantiated in human beings.

Although our investigations in this field did not make a break-through, we have a deeper insight into the basic mechanism determining both analgesic and anorexigenic activities.

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Annexe 1-5

RÉPUBLIQUE FRANÇAISE

MINISTÈRE DE L'INDUSTRIE

SERVICE
de la PROPRIÉTÉ INDUSTRIELLE

BREVET D'INVENTION

P.V. n° 101.584 N° 1.517.587
Classification internationale : C 07 c

Nouveaux dérivés du phényl-amino propane et leur procédé de préparation.

(Inventionî: Laszlo BEREGI, Pierre HUGON et Jean-Claude LE DOUAREC.)

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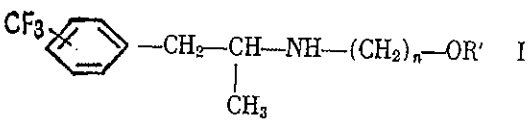
Demandé le 5 avril 1967, à 14h 56m, à Paris.

Délivré par arrêté du 5 février 1968.

(*Bulletin officiel de la Propriété industrielle*, n° 11 du 15 mars 1968.)

(*Demande de brevet déposée en Grande-Bretagne le 15 avril 1966, sous le n° 16.660/1966, au nom de la demanderesse.*)

La présente invention a pour objet les nouveaux dérivés trifluorométhylés du phényl-amino propane de formule générale I :



dans laquelle :

R représente un atome d'hydrogène ou un radical alcoyle inférieur jusqu'en 5 atomes de carbone;

n est un nombre entier égal à 2 ou 3; et

R' représente :

Un atome d'hydrogène; ou

Un groupe COR'' dans lequel R'' représente :

1° Un radical alcoyle inférieur renfermant de 1 à 6 atomes de carbone;

2° Un radical cycloalcoyle contenant de 3 à 7 atomes de carbone;

3° Un radical alcényle inférieur contenant de 2 à 6 atomes de carbone;

4° Un radical alcynyle inférieur contenant de 2 à 6 atomes de carbone; ou

5° Un radical aryle carbocyclique mono- ou bicyclique.

Le radical alcoyle inférieur 1° peut contenir un ou plusieurs substituants choisis parmi le groupe comprenant :

a. Des atomes d'halogène tels que, par exemple, chlore ou brome;

b. Des groupes oxygénés tels que, par exemple, les groupes hydroxyle, méthoxy, propyloxy ou carboxyle;

c. Des groupes aryles carbocycliques tels que, par exemple, phényle ou biphényle qui peuvent être substitués par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogène, de groupes hydroxyle, alcoxy inférieurs jusqu'en C_4, alcoyle inférieurs jusqu'en C_4, méthylène-dioxy, nitro, amino et trifluorométhyle;

d. Des groupes aryloxy-carbocycliques tels que, par exemple, phénoxy ou naphtoxy, qui peuvent être substitués par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogène, de groupes alcoxy inférieurs jusqu'en C_4 et de groupe nitro.

Comme radicaux cycloalcoyles 2 on peut citer, par exemple, les radicaux cyclopropyle, cyclopentyle ou cyclohexyle qui peuvent être eux-mêmes substitués par un ou plusieurs groupes aryle carbocycliques tels que, par exemple, le groupe phényle.

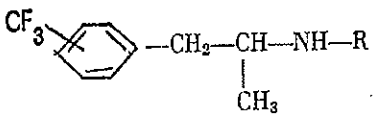
Parmi les radicaux alcényles inférieurs 3 on peut citer, par exemple, les radicaux éthényle, propényle-2, méthyle-2 propényle, butényle-2 et butényle-3. Ces radicaux alcényles inférieurs peuvent être substitués par un ou plusieurs groupes aryles carbocycliques tels que, par exemple, le groupement phényle qui peut être lui-même substitué par un ou plusieurs subsituants choisis parmi le groupe formé d'atomes d'halogènes, de radicaux hydroxyle, de groupes alcoxy inférieurs jusqu'en C_4, alcoyle inférieurs jusqu'en C_4 méthylène-dioxy, nitro, amino et trifluorométhyle.

Le radical alcynyle inférieur 4 peut être, par exemple, un radical propynyle ou méthyl propynyle et peut être lui-même substitué par un radical phényle.

Comme radicaux aryles carbocycliques 5 on peut citer, par exemple, les radicaux phényle,

naphtyle-1 et naphtyle-2. Ces radicaux peuvent être eux-mêmes substitués par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogène, et de radicaux hydroxyle, alcoxy inférieurs jusqu'en C_4, alcoyle inférieurs jusqu'en C_4, méthylène-dioxy, nitro, amino, trifluorométhyle et phényle.

Les composés de formule générale I sont nouveaux et peuvent être préparés en faisant réagir une phényl isopropylamine substituée de formule II :



II

dans laquelle R prend la signification définie ci-dessus, avec un composé hydroxy-halogéné contenant 2 ou 3 atomes de carbone tel que, par exemple, le bromo-éthanol, ou avec un oxyde d'alcoylène tel que, par exemple, l'oxyde d'éthylène ou l'oxyde de triméthylène, en vue d'obtenir les composés pour lesquels R′ = H.

Les alcools ainsi obtenus sont estérifiés avec un halogénure d'acyle, un anhydride ou un acide approprié en présence de dicyclohexylcarbodiimide, afin d'obtenir les dérivés pour lesquels R′ = COR″, R″ ayant les significations précédemment définies, et, pour obtenir les dérivés pour lesquels R″ est un groupe substitué par un radical amino, il convient, de plus, d'effectuer la réduction par l'hydrogène des dérivés nitrés correspondants.

L'estérification peut être réalisée sur les amino-alcools racémique, dextrogyre ou levogyre. Le dédoublement peut être conduit soit sur la phényl-isopropylamine substituée, afin d'utiliser les isomères optiques comme produits de départ, soit sur les composés hydroxy-alcoylés eux-mêmes.

La séparation des isomères optiques peut se faire en traitant les dérivés racémiques par l'acide *d* (—) dibenzoyl tartrique, pour obtenir les isomères lévogyres et ensuite par l'acide *d* camphorique pour obtenir les isomères dextrogyres. L'invention comprend également la séparation des isomères optiques.

Les nouveaux composés de formule générale I forment des sels d'addition avec les acides minéraux et organiques et font, à ce titre, partie de l'invention. Comme acides utilisés pour la formation de ces sels d'addition, on peut citer, dans la série minérale : les acides chlorhydriques, bromhydrique, méthane sulfonique, sulfurique, phosphorique, sulfamique, et dans la série organique : les acides acétique, propionique, maléique, fumarique, tartrique, citrique, oxalique benzoïque, anthranilique, etc.

Les dérivés du phényl-amino propane, objet de l'invention, et leurs sels d'addition sont des produits industriels nouveaux, utilisables comme produits de base dans l'industrie chimique et pharmaceutique. Il est bien entendu que le présent brevet ne concerne pas leur utilisation comme médicament.

Les exemples suivants, donnés à titre non limitatif, illustrent l'invention. Toutes les parties sont en poids, à moins qu'elles ne soient autrement précisées et les points de fusion sont déterminés par la méthode de Kofler.

Exemple 1. — (m - trifluorométhylphényl) - 1 [(β-hydroxy - éthyl) - amino] - 2 propane.

Dans un autoclave de 1 litre, on ajoute, en maintenant la température à —20 °C, 305 parties de (m - trifluorométhylphényl) - 1 amino - 2 propane à 53 parties d'oxyde d'éthylène et 37,5 parties d'eau. On laisse ensuite le mélange se réchauffer jusqu'à la température ambiante, on maintient l'agitation pendant une heure, à température ambiante, puis le mélange réactionnel est chauffé jusqu'à 100-110 °C et maintenu à cette température pendant quatre heures.

La distillation du produit brut donne 154 parties de (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane, $Eb/_{0,4\ mm}$ = 109-111 °C, dont le fumarate acide fond à 133 °C (isopropanol).

Exemple 2. — 1 (m - trifluorométhylphényl) - 1 [β-hydroxy - éthyl) - amino] - 2 propane.

On ajoute 75 parties de *dl* (*m* - trifluorométhylphényl) - 1 [(β-hydroxy - éthyl) - amino] - 2 propane à une solution de 147 parties d'acide *d* (—) dibenzoyl tartrique dans 1 800 parties d'acétate d'éthyle, maintenu à reflux, sous agitation. Après refroidissement à la température ambiante, le sel est filtré, lavé à l'acétate d'éthyle et séché. On obtient 95 parties de sel A qui, recristallisé deux fois dans l'éthanol, donne 65 parties de sel pur (P.F. 154 °C).

La libération de la base à partir de ce sel A et d'une solution aqueuse d'hydroxyde de sodium, suivie d'une extraction à l'éther et d'un séchage sur $Mg\ SO_4$ donne 23,5 parties de *l* - (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane, $Eb/_{0,7\ mm}$ = 109 °C, $[\alpha]_D^{22}$ = —13,7° (C. 16; éthanol) dont le fumarate acide fond à 135 °C (isopropanol).

Exemple 3. — d (m - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane.

Le filtrat restant après la séparation du sel A de l'exemple 2 est concentré sous vide et la base est libérée. On obtient 24 parties de base, $Eb/_{1,05\text{-}1,1\ mm}$ = 111-115 °C, $[\alpha]_D^{22,5}$ = + 6,5 °C (C. 16; éthanol). 25 parties de cette base sont traitées par 22 parties d'acide *d*-camphorique dans 80 parties d'acétate d'éthyle. Lorsque la cristallisation est complète, le sel B ainsi formé est filtré et séché. On

obtient 18 parties de *d*-camphorate acide, P.F. 126 °,C, qui recristallisées dans 56 parties d'acétate d'éthyle donnent 16 parties de sel B pur, P.F. 127 °C.

La libération de la base, à partir de ce sel B avec une solution aqueuse d'hydroxyde de sodium donne le *d* (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane, $Eb/_{0,05\ mm} = 111$-112 °C, $[\alpha]_D^{22,5} = +13,6°$ (C. 16; éthanol dont le fumarate acide fond à 135 °C (isopropanol).

Exemple 4. — (m - trifluorométhylphényl) - 1 [(γ - hydroxy - propyl) - amino] - 2 propane.

Dans un autoclave, on ajoute, en maintenant la température à — 10 °C, 100 parties de (*m* - trifluorométhylphényl) - 1 amino - 2 propane, 17 parties d'oxyde de triméthylène et 12 parties d'eau. On laisse ensuite le mélange se réchauffer jusqu'à la température ambiante, on maintient l'agitation pendant une heure, à température ambiante puis le mélange réactionnel est chauffé à 150 °C et maintenu à cette température pendant douze heures.

La distillation du produit brut donne 41 parties de (*m* - trifluorométhylphényl) - 1 [(γ - hydroxy - propyl) - amino] - 2 propane, $Eb/_{0,5\ mm} = 115$ °C, dont le chlorhydrate recristallisé dans l'acétate d'éthyle fond à 95-96 °C.

Exemple 5. — Chlorhydrate de (m-trifluorométhylphényl) - 1[(β - acétyloxy - éthyl) - amino]- 2 propane.

A une solution de 14,2 parties de chlorhydrate de (*m*-trifluorométhylphényl) - 1 [*β* - hydroxy - éthyl) - amino] - 2 propane dans 70 parties d'acétate d'éthyle, on ajoute 5,1 parties d'anhydride acétique. Après deux heures de reflux la solution est refroidie et le produit est essoré et recristallisé dans 70 parties d'acétate d'éthyle. On obtient 8,8 parties de chlorhydrate de (*m*-trifluorométhylphényl) - 1 [(*β* - acétyloxy - éthyl) - amino] - 2 propane, qui fond à 136 °C.

En opérant de façon identique on a préparé :

a. *Le chlorhydrate de (m - trifluorométhylphényl) - 1[(β - propionyloxy - éthyl) - amino] - 2 propane*, P.F. 135 °C (isopropanol), à partir du (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane et d'anhydride propionique;

b. *Le chlorhydrate de (m - trifluorométhylphényl) - 1 [(β - succinyloxy - éthyl) - amino] - 2 propane*, P.F. 113 °C (acétate d'éthyle) à partir de (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane et d'anhydride succinique.

Exemple 6. — Chlorhydrate de (m - trifluorométhylphényl) - 1 [(β - salicyloyloxy - éthyl) - amino] - 2 propane.

A une solution de 24,7 parties de (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane dans 140 parties de benzène anhydre on ajoute, successivement, 15 parties d'éther chlorhydrique 4,7 N et une solution de 15,6 parties de chlorure de salicyloyle dans 24 parties de benzène anhydre. L'addition dure dix minutes, et le mélange réactionnel est ensuite chauffé à reflux pendant trois heures.

Le produit solide est filtré et recristallisé dans 180 parties d'acétate d'éthyle. On obtient 30,5 parties de chlorhydrate de (*m* - trifluorométhylphényl) - 1 [(*β* - salicyloyloxy - éthyl) - amino] - 2 propane qui fond à 144 °C.

Exemple 7. — (m - trifluorométhylphényl) - 1 [(β - benzoyloxy - éthyl) - amino] - 2 propane.

A une solution de 24,7 parties de (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane dans 140 parties de benzène anhydre on ajoute, successivement 15 parties d'éther chlorhydrique 4,7 N et une solution de 14 parties de chlorure de benzoyle dans 24 parties de benzène anhydre. L'addition dure dix minutes, et le mélange réactionnel est ensuite chauffé à reflux pendant huit heures.

Le produit solide est filtré et recristallisé dans 230 parties d'acétate d'éthyle. On obtient 15 parties de chlorhydrate de (*m* - trifluorométhylphényl) - 1 [(*β* - benzoyloxy - éthyl) - amino] - 2 propane, qui fond à 161 °C.

10 parties de ce chlorhydrate sont mises en suspension dans 100 parties d'eau. On ajoute 80 parties d'éther puis 10 parties d'une solution concentrée d'hydroxyde d'ammonium. Après quelques instants d'agitation durant lesquels le sel disparaît, la solution éthérée est décantée et séchée.

Après élimination de l'éther sous vide, on obtient 9 parties de (*m* - trifluorométhylphényl) - 1 [(*β* - benzoyloxy - éthyl) - amino] - 2 propane, à l'état de base, sous forme d'une huile incolore.

5,5 parties de cette base sont dissoutes dans 38 parties d'éthanol absolu et la solution ainsi obtenue est ajoutée à 2,2 parties d'acide fumarique dans 90 parties d'éthanol absolu. Le précipité formé est redissous à chaud. Après refroidissement, essorage et séchage, on obtient 5 parties de fumarate acide de (*m* - trifluorométhylphényl) - 1 [(*β* - benzoyloxy - éthyl) - amino] - 2 propane, qui fond à 161-162 °C.

En opérant de la même façon, on a préparé :

a. *Le chlorhydrate du d (m - trifluorométhylphényl) - 1 [(β - benzoloxy - éthyl) - amino] - 2 propane*, P.F. 156 °C (isopropanol), à partir du *d* (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane et du chlorure de benzoyle;

b. *Le chlorhydrate du l (m - trifluorométhylphényl) - 1 [(β - benzoyloxy - éthyl) - amino] - 2 propane*, P.F. 156-157 °C (isopropanol), à partir du *l* (*m* - trifluorométhylphényl) - 1 [(*β* - hydroxy - éthyl) - amino] - 2 propane et du chlorure de

benzoyle.

Exemples 8 à 34. — Par un procédé identique à celui décrit dans l'exemple 7, les dérivés suivants ont été préparés :

8. Le chlorhydrate du (*p* - trifluorométhylphényl) - [β - benzoyloxy - éthyl) - amino] - 2 propane, P.F. : 170-171 °C (acétate d'éthyle), à partir du (*p* - trifluorométhylphényl) - [β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de benzoyle.

9. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - chloroacétyloxy - éthyl) - amino] - 2 propane, P.F. : 128-130 °C (isopropanol/éther de pétrole), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide chloroacétique.

10. Le chlorhydrate du trans (*m* - trifluorométhylphényl - 1 [(β - cinnamoyloxy - éthyl) - amino) - 2 propane, P.F. : 159-160 °C (acétate d'éthyle), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du trans chlorure de cinnamoyle.

11. Le chlorhydrate du (*m* - trifluorométhylphényl - 1 [(β - *p* - chlorophénoxyacétyloxy - éthyl) - amino] - 2 propane, P.F. : 124-125 °C (xylène), à partir du (*m* - trifluorométhyl - phényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide *p* - chlorophénoxyacétique.

12. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - phénylpropionyloxy - éthyl) - amino] - 2 propane, P.F. : 93-94 °C (benzène/cyclohexane), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide phénylpropionique.

13. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - β' - β' - diméthylacryloyloxy-éthyl) - amino] - 2 propane, P.F. 153-154 °C (isopropanol), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl - amino] - 2 propane et du chlorure de l'acide β, β diméthylacrylique.

14. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - cyclopropylcarboxyloxy - éthyl) - amino] - 2 propane, P.F. : 136 °C (isopropanol), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide cyclopropylcarboxylique.

15. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [N - (β - salicyloyloxy - éthyl) N - éthyl amino] - 2 propane, P.F. : 136-138 °C (acétone/éther de pétrole), à partir du (*m* - trifluorométhylphényl) - 1 [N - (β - hydroxy - éthyl) N - éthyl - amino] - 2 propane et du chlorure de salicyloyle.

16. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *m* - trifluorométhyl α - méthyl cinnamoyloxy - éthyl) - amino] - 2 propane, P.F. : 105-108 °C (xylène/cyclohexane), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide *m* - trifluorométhyl α - méthyl cinnamique.

17. Le chlorhydrate du (*m* - trifluorométhylphényl - 1 [(β - phénylcyclopentane carboxyloxy - éthyl) - amino] - 2 propane, P.F. : 142 °C (acétate d'éthyle), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide phénylcyclopentane carboxylique.

18. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *o* - chlorobenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 147 °C (acétate d'éthyle), à partir du (*m* - trifluorométhyl - phényl) - 1 [(β - hydroxy - éthyl - amino] - 2 propane et du chlorure d'*o* - chlorobenzoyle.

19. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *m* - trifluorométhylbenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 137 °C (acétate d'éthyle, à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de *m* - trifluorométhylbenzoyle.

20. Le chlorhydrate du (*m* - trifluorométhylphényl - 1[(β - phénylacétyloxy - éthyl) - amino] - 2 propane, P.F. : 102-104 °C (xylène), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide phénylacétique.

21. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *p* - chlorobenzoyloxy - éthyl) - amino]-2 propane, P. F. : 169 °C (acétone), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de *p* - chlorobenzoyle.

22. Le chlorhydrate du (*m* - trifluorométhylphényl - 1 [(β - *p* - fluorobenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 160-162 °C (xylène), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de *p* - fluorobenzoyle.

23. Le chlorhydrate du (*m* - trifluorométhylphényl - 1 [(β - *p* - phénylbenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 180 °C (éthanol/acétone), à partir du (*m* - trifluorométhylphényl - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de *p* - phénylbenzoyle.

24. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *p* - méthylbenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 186-187 °C (éthanol), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de *p* - méthylbenzoyle.

25. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - α' - phénylbutyryloxy - éthyl) - amino] - 2 propane, P.F. : 109-110 °C (acétate d'éthyl), à partir du (*m*-trifluorure méthylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2

propane et du chlorure de l'acide α - phénylbutyrique.

26. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - méthylène dioxy - 3',4' benzoyloxy - éthyl) - amino] - 2 propane, P.F. : 150-151 °C (acétate d'éthyle), à partir du (*m* - trifluorométhylphényl - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de méthylène dioxy - 3,4 benzoyle.

27. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - diméthyl - 3',4' benzoyloxy - éthyl) - amino] - 2 propane, P.F. : 172 °C (éthanol), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de diméthyl - 3,4 benzoyle.

28. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *p* - isobutyl phényl acétyloxy - éthyl) - amino] - 2 propane, P.F. : 123 °C (acétate d'éthyle), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide *p* - isobutyl phényl acétique.

29. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *p* - chlorophénylacétyloxy - éthyl) - amino] - 2 propane, P.F. : 115 °C (acétate d'éthyle), à partir du (*m* - trifluorométhylphényl - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de l'acide *p* - chlorophénylacétique.

30. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - α' - naphtoyloxy - éthyl) - amino] - 2 propane, P.F. : 171 °C (isopropanol), à partir du (*m* - trifluorométhylphényl - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure d'α - naphtoyle.

31. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - β' - naphtoyloxy - éthyl) - amino] - 2 propane, P.F. : 205-206 °C (éthanol), à partir du (*m* - trifluorométhylphényl - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de β - naphtoyle.

32. Le chlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *p* - nitrobenzoyloxy - éthyl) - amino] -2 propane, F.F. : 180-182 °C (éthanol), à partir du (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane et du chlorure de *p* - nitrobenzoyle.

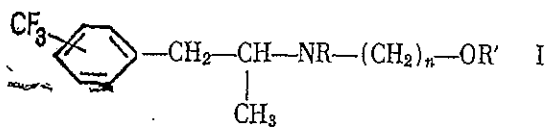
33. Le chlorhydrate du (*m* - trifluorométhylphényl - 1 [(β - *p* - aminobenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 166-168 °C (isopropanol), par hydrogénation, sous une pression de 6 kg/cm², en présence de platine comme catalyseur, du chlorhydrate de (*m* - trifluorométhylphényl) - 1 [(β - *p* - nitrobenzoyloxy - éthyl) - amino] - 2 propane mis en suspension dans l'éthanol absolu.

34. Le dichlorhydrate du (*m* - trifluorométhylphényl) - 1 [(β - *o* - aminobenzoyloxy - éthyl) - amino] - 2 propane, P.F. : 160-165 °C (éthanol/isopropanol), par hydrogénation du chlorhydrate de (*m* - trifluorométhylphényl) - 1 [(β - *o* - nitrobenzoyloxy - éthyl - amino] - 2 propane.

RÉSUMÉ

La présente invention concerne :

1° A titre de produits industriels nouveaux, les dérivés trifluorométhylés du phényl - amino propane de formule générale I :



dans laquelle :

R représente un atome d'hydrogène ou un radical alcoyle inférieur jusqu'à 5 atomes de carbone;

n est un nombre entier égal à 2 ou 3; et

R' représente :

Un atome d'hydrogène; ou

Un groupe COR'' dans lequel R'' représente :

a. Un radical alcoyle inférieur jusqu'à 6 atomes de carbone qui peut être substitué par un ou plusieurs substituants choisis parmi le groupe formé :

D'atomes d'halogène;

De radiacux oxygénés, tels que, par exemple, hydroxyle, méthoxy, propyloxy, carboxyle;

De groupes aryles carbocycliques, tels que, par exemple, phényle ou biphényle qui peuvent être substitués par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogène, de groupes hydroxyle, alcoxy inférieur jusqu'en C_4, alcoyle inférieur jusqu'en C_4, méthylène-dioxy, nitro, amino et trifluorométhyle;

De groupes aryloxy carbocycliques tels que, par exemple, les groupes phénoxy ou naphtoxy, qui peuvent être substitués par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogène, de groupe alcoxy inférieurs jusqu'en C_4 et de groupe nitro;

b. Un radical cycloalcoyle contenant de 3 à 7 atomes de carbone, tel que, par exemple, les radicaux cyclopropyle, cyclopentyle, cyclohexyle qui peuvent être substitués par un ou plusieurs groupes aryles carbocycliques tels que, par exemple, le radical phényle;

c. Un radical alcényle inférieur contenant de 2 à 6 atomes de carbone tels que, par exemple, les radicaux éthényle, propényle-2, méthyl-2 propényle, buténule-2, buténule-3, qui peuvent être substitués par un ou plusieurs groupes aryles carbocycliques tels que, par exemple, le groupement phényle qui peut être substitué par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogène, de radicaux hydroxyle, alcoxy inférieur jusqu'en C_4, alcoyle inférieur jusqu'en C_4, méthylène-dioxy, nitro, amino et trifluorométhyle;

d. Un radical alcynyle inférieur contenant de 2

à 6 atomes de carbone tel que, par exemple, les radicaux propynyle ou méthyl-propynyle qui peuvent être substitués par un radical phényle;

e. Un radical aryle carbocyclique, mono ou bicyclique tel que, par exemple, les radicaux phényle, naphtyle-1 et naphtyle-2 qui peuvent être substitués par un ou plusieurs substituants choisis parmi le groupe formé d'atomes d'halogènes, de radicaux hydroxyle, alcoxy inférieur jusqu'en C_4, alcoyle inférieur jusqu'en C_4, méthylène-dioxy, nitro, amino, trifluorométhyle et phényle, sous forme de racémiques et d'isomères optiques.

2° Le (*m* - trifluorométhylphényl) - 1 [(β - hydroxy - éthyl) - amino] - 2 propane, ainsi que ses isomères dextrogyre et lévogyre.

3° Le (*m* - trifluorométhylphényl) - 1 [(β - benzoyloxy - éthyl) - amino] - 2 propane, ainsi que ses isomères dextrogyre et lévogyre.

4° Le (*m* - trifluorométhylphényl) - 1 [(β - chloracétyloxy - éthyl) - amino] - 2 propane.

5° Le (*m* - trifluorométhylphényl) - 1 [(β - phénylpropionyloxy - éthyl) - amino] - 2 propane.

6° Le (*m* - trifluorométhylphényl) - 1 [(β - cyclopropylcarboxyloxy - éthyl) - amino] - 2 propane.

7° Le (*m* - trifluorométhylphényl) - 1 [(β - *m* - trifluorométhyl α - méthyl cinnamoyloxy - éthyl) - amino] - 2 propane.

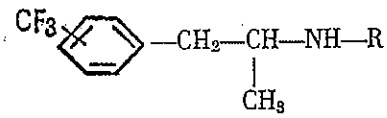
8° Le (*m* - trifluorométhylphényl) - 1 [(β - *o* - chlorobenzoyloxy - éthyl) - amino] - 2 propane.

9° Le (*m* - trifluorométhylphényl) - 1 [(β - *m* - trifluorométhylbenzoyloxy - éthyl) - amino] - 2 propane.

10° Le (*m* - trifluorométhylphényl) - 1 [(β - *p* - fluorobenzoyloxy - éthyl) - amino] - 2 propane.

11° Les sels d'addition physiologiquement tolérables des dérivés selon 1° à 10° avec les acides minéraux ou organiques.

12° Le procédé de préparation des dérivés selon 1° à 11°, caractérisé en ce que l'on fait réagir un trifluorométhylphényl isopropylamine de formule générale II :



II

dans laquelle R a les significations définies dans la revendication 1°.

Avec un composé hydroxy-halogéné contenant 2 ou 3 atomes de carbone, ou avec un oxyde d'alcoylène, l'on estérifie les composés ainsi obtenus avec un halogénure d'acyle, un anhydride ou un acide appropriés, et, l'on réduit, le cas échéant, par l'hydrogène sous pression et en présence d'un catalyseur, les dérivés nitrés en vue d'obtenir les dérivés aminés correspondants.

13° Le procédé de préparation des isomères optiques des dérivés selon la revendication 1°, caractérisé en ce que l'on dédouble les dérivés racémiques de formule générale I par l'acide *d* (—) dibenzoyl tartrique pour obtenir les isomères lévogyres, et par l'acide *d* camphorique, pour obtenir les dérivés dextrogyres.

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Annexe 1-6

UNIVERSITÉ DE PARIS

FACULTÉ DE PHARMACIE

ANNÉE 1962-1963 SÉRIE U N° 382

La prise de nourriture. Etude physiologique, action pharmacologique des médicaments

THESE

présentée à la Faculté de Pharmacie de l'Université de Paris pour l'obtention du titre de Docteur en Pharmacie (Diplôme d'Université)

présentée et soutenue le 1er Juillet 1963

par

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Pharmacien

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Y. RAOUL Professeur

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8, Faubourg Poissonnière
PARIS

A Monsieur Henri Schmitt, Maître de Conférences Agrégé, que nous remercions profondément des encouragements qu'il nous a prodigués et de l'attention qu'il a bien voulu accorder à notre travail.

En hommage reconnaissant.

A Monsieur le Docteur Jacques Servier,

A Madame le Docteur Jeanine Servier,

qui ont compris l'importance de la recherche pharmacologique et n'ont pas hésité à nous donner tous les moyens nécessaires à l'aboutissement de ce travail.

En hommage de notre reconnaissance et de notre respectueux dévouement.

A mes parents,

A ma femme,

A toute ma famille

En témoignage de ma profonde affection

A mes amis,

A mes collaborateurs,

JE DEDIE CE TRAVAIL.

INTRODUCTION

La découverte de l'action inhibitrice de l'amphétamine sur l'appétit a amené les thérapeutes à utiliser abondamment cette propriété particulière. Le traitement de base de l'obésité est la diminution de l'apport calorique au moyen de la restriction alimentaire. Aussi il est nécessaire d'aider le malade à supporter ce régime restrictif en lui administrant des drogues susceptibles de lui couper l'appétit.

Les mécanismes physiologiques de la faim et de l'appétit ont donné lieu à un grand nombre de travaux physiologiques, surtout depuis la dernière guerre mondiale. Ont été acquises ainsi des connaissances fondamentales sur la régulation psycho-physiologique de la faim.

Parallèlement le développement de nouveaux médicaments dits anorexigènes amena des tentatives pour élucider le mode d'action de ces corps sur la prise de nourriture chez l'homme et chez l'animal.

On ne trouve cependant pas un grand nombre d'études pharmacodynamiques de ces médicaments; il en va de même pour les méthodes d'étude qui n'ont guère été codifiées jusqu'à présent.

Il nous a semblé intéressant de tenter d'apporter une contribution à l'étude des substances agissant sur la faim et l'appétit.

Nous avons d'abord effectué l'étude critique des méthodes expérimentales, puis nous avons démontré la réalité de l'action pharmacodynamique de l'amphétamine et de 6 de ses dérivés chez l'animal. Nous avons ensuite envisagé les répercussions de l'anorexie médicamenteuse sur l'équilibre corporel. Finalement, nous avons étudié certains aspects du mode d'action de ces médicaments.

Chapitre III

RESULTATS

§ I - LES PROPRIÉTÉS ANOREXIGÈNES DES MÉDICAMENTS

Le premier objectif que nous avons poursuivi est la mesure chez trois espèces animales des variations de la prise de nourriture sous l'influence de médicaments utilisés en thérapeutique comme adjuvants du traitement de l'obésité. Les médicaments anorexigènes que nous avons étudiés sont d'introduction plus ou moins récente en France et nous avons limité notre choix aux plus importants.

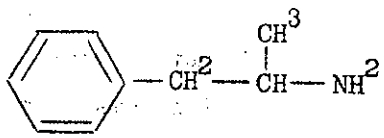
1) Structure chimique des sept médicaments anorexigènes étudiés.

Ces produits sont chimiquement apparentés aux groupes des phenyl-ethyl amines.

Amphétamines

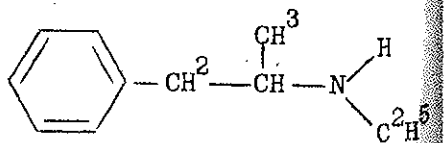
forme d l Benzédrine

forme d Dexedrine



N-ethyl amphétamine

Adiparthrol



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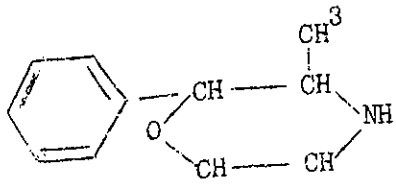
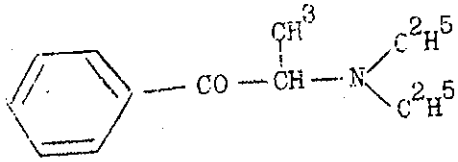
Phenmetrazine d l

Preludine.



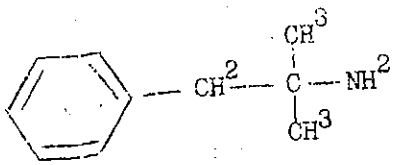
Diethylpropion

Regenon. Derfon.



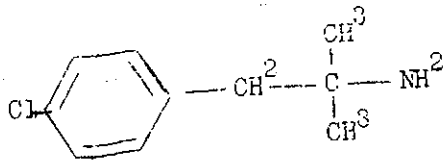
Phentermine

Wilpo. Ionamin.



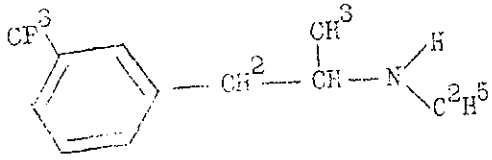
Chlorphentermine

Lucofène. Avicol.



Phenfluoramine d l

Ponderal.



Chapitre IV

CONCLUSIONS GENERALES

Un état de faim, mesuré par la quantité de régime consommé, peut être créé chez la Souris, le Rat et le Chien par des jeûnes réguliers ou intermittents. Cette faim est susceptible d'être inhibée par des médicaments anorexigènes proportionnellement à la dose administrée.

Des comparaisons quantitatives entre différents corps peuvent être établies dans des conditions définies de stabilité du comportement alimentaire. Une bonne corrélation existe entre ces résultats expérimentaux et ceux obtenus chez l'Homme.

La possibilité d'étudier l'anorexie médicamenteuse comme toute autre propriété pharmacodynamique, existe donc et l'étude comparative de séries de corps peut être envisagée.

La restriction alimentaire est la cause principale de l'amaigrissement chez le Rat, néanmoins il semble qu'une action propre sur les réserves lipidiques soit exercée par ces médicaments.

Dans l'étude du mode d'action de l'amphétamine et de ses dérivés sur la prise de nourriture chez le Rat, nous avons tenté d'intégrer certains faits expérimentaux aux grandes théories de la faim, de Mayer, de Brobeck et de Kennedy.

Les variations de la température rectale ne sont pas parallèles à celles du pouvoir anorexigène et, en fonction des produits administrés, se manifestent en sens opposé. Il est ainsi difficile chez le Rat de lier l'une à l'autre ces deux propriétés.

De nos résultats, il ressort que la différence de glycémie artério-veineuse (Δ glucose) varie dans le sens attendu, d'après la théorie de Mayer. L'amphétamine est en effet capable d'augmenter le Δ glucose dans ces conditions.

L'inhibition du transit gastro-intestinal a lieu à dose anorexigène. La présence plus longue des aliments dans le tractus gastro-intestinal

et l'inhibition déjà prouvée des contractions de l'estomac dues à la faim peuvent être des déterminants de l'action anorexigène de l'amphétamine et de ses dérivés.

L'exaltation de la secrétion gastrique entraînée par l'amphétamine cadre avec les travaux d'Ivy, Lin et Langberg (54). Ces auteurs ont montré que les relations entre la quantité de nourriture ingérée et la réponse secrétoire gastrique est représentée par une courbe sigmoïde. Dans la dernière portion de la courbe, il apparaît que la capacité de secrétion maxima est atteinte ou presque, c'est à ce moment que l'animal s'arrête de manger et que l'homme ressent la satiété. Si l'amphétamine est capable d'accélérer le taux de la secrétion gastrique en présence ou en l'absence d'aliments, elle peut troubler le déroulement normal de la digestion et le jeu des réflexes subséquents.

En somme, l'amphétamine et ses dérivés sont susceptibles de provoquer un ensemble de réactions concomitantes :

l'inhibition de la faim
l'augmentation du Δ glucose
le ralentissement du transit gastro-intestinal
la stimulation de la secrétion gastrique.

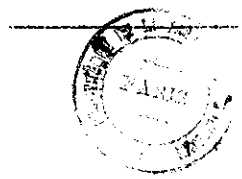
Dans nos expériences il est impossible de savoir si le déclenchement de ces effets est d'origine centrale ou périphérique.

Il est maintenant communément admis que l'anorexie amphétaminique est d'origine centrale, en fonction des actions de ce corps sur le système nerveux central. Nous pensons que les actions périphériques de l'amphétamine ne doivent pas être exclues de son mécanisme d'action sur la faim, certaines autres s'exerçant en l'absence de tout système nerveux central comme l'inhibition de la fibre lisse et l'hypertension.

Au cours de cette étude, nous avons montré que l'anorexie n'était pas le corollaire de la stimulation centrale et que différents états du système nerveux central pouvaient entraîner une anorexie avec ou sans modification visible du comportement de l'animal.

L'inhibition et même l'inversion de l'effet anorexigène de l'amphétamine par les sympathicolytiques et sa potentialisation par les inhibiteurs de la monoamine oxydase ont été démontrées chez le Rat. Quelle que soit l'origine de l'anorexie amphétaminique, centrale, périphérique ou mixte, il est probable qu'un mécanisme adrénergique y participe.

Nous admettrons pour conclure que l'anorexie amphétaminique peut être considérée comme une propriété sympathicomimétique, au même titre que celles déjà connues.



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Comparaison pharmacologique de sept médicaments anorexigènes (*)

Par J.-C. LE DOUAREC (**) et H. SCHMITT (***)

La thérapeutique de l'obésité utilise un certain nombre de substances destinées à limiter les apports caloriques en freinant l'appétit. On les a nommées anorexiantes ou anorexigènes. Dès 1937, les propriétés anorexiantes de l'amphétamine ont été découvertes chez l'homme [7, 17, 26] : elles furent étudiées ensuite chez l'animal par TAINTER [25]. L'emploi des dérivés de l'amphétamine comme adjuvants du traitement de l'obésité est une prescription aujourd'hui classique [8, 18, 19].

Toutefois, les effets secondaires des médicaments utilisés jusqu'à présent en limitent l'emploi. L'action excitante centrale et les actions hypertensives sont des propriétés indésirables de ces produits.

L'appétit et la faim sont des phénomènes subjectifs qui se prêtent mal à une analyse physiologique précise. Les connaissances sur ce sujet se sont accrues cette dernière décade, mais il ne nous appartient pas de les exposer ici ; citons seulement les importantes revues de MINER [16], de MAYER [15], de SOULAIRAC [22], de ANAND [1], de ANDERSSON et LARSSON [2].

On peut mesurer avec précision la prise de nourriture chez l'animal et étudier les facteurs qui conditionnent le comportement alimentaire de celui-ci. Nous avons étudié les propriétés anorexigènes

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de sept médicaments (*figure 1*) chimiquement proches, mais se différenciant par leur action secondaire sur le système nerveux central et la pression artérielle.

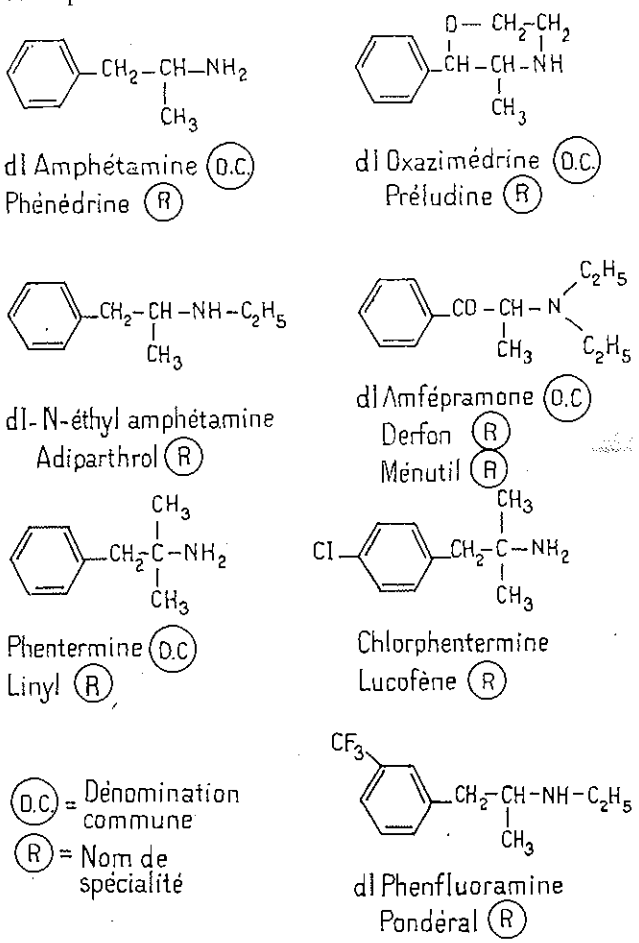

FIG. 1. — Formules chimiques des produits étudiés.

MÉTHODES

1) Toxicité aiguë.

La toxicité aiguë des corps étudiés a été déterminée par voie intrapéritonéale chez des souris blanches mâles de race Swiss, pesant de 18 à 22 g. Les expériences ont été effectuées à température constante (24° ± 1) dans des cages transparentes de 17 × 12 × 12 cm ; les animaux étaient isolés ou groupés par 10. Le nombre de morts

TABLEAU VI

Amphétamine	100
Oxazimédrine	12
N-éthylamphétamine	3,8
Amfépramone	0,8
Phentermine	14,1
Chlorphentermine	5
Phenfluoramine	3,5

Les chiffres du tableau VI montrent que les corps étudiés sont bien moins actifs que l'amphétamine sur la pression artérielle du Rat.

DISCUSSION

Les résultats obtenus dans cette étude permettent donc de chiffrer chez une même espèce animale le pouvoir anorexiant, l'action excitante centrale et l'activité tensionnelle de sept anorexiants utilisés en thérapeutique humaine.

Le chien semble l'animal le plus sensible aux effets anorexigènes de l'amphétamine et autant qu'on puisse en juger par les posologies utilisées il semble que chez l'homme les activités relatives des différents médicaments soient du même ordre.

Nos résultats obtenus avec l'amphétamine, l'oxazimédrine et l'amfépramone sont en bon accord avec ceux de SPENGLER et WASER [23]. De même, CAHEN [5] a obtenu des chiffres voisins des nôtres pour l'amphétamine et l'amfépramone. En ce qui concerne la phentermine et la chlorphentermine, nous confirmons les travaux respectivement de BECKER [4] et de HOLM [12].

Il nous paraît par ailleurs intéressant de comparer l'activité anorexiante aux autres effets.

L'action excitante centrale est encore très appréciable dans les dérivés tels que l'oxazimédrine, la N-éthylamphétamine, l'amfépramone et la phentermine. Par contre, elles est nulle pour la chlorphentermine et la phenfluoramine même à des doses bien supérieures aux doses anorexigènes.

Les activités tensionnelles des différents dérivés étudiés sont encore appréciables pour l'oxazimédrine, la phentermine et même la chlorphentermine. Elles sont, par contre, faibles pour l'amfépramone et la phenfluoramine.

Les recherches expérimentales effectuées ces dernières années sur les médicaments anorexigènes ont engendré des corps possédant un meilleur index thérapeutique que l'amphétamine puisque l'activité anorexigène est presque entièrement conservée alors que les propriétés secondaires sont considérablement diminuées.

A partir des chiffres obtenus au cours de cette étude nous avons établi la figure 2 où la partie supérieure représente l'effet principal

(anorexie) chiffré 100 pour l'amphétamine et la partie inférieure les effets secondaires chiffrés 100 chacun. Il apparaît clairement que des corps comme la chlorphentermine et la phenfluoramine possèdent chez le rat une balance plus favorable entre leur action principale et leurs actions secondaires.

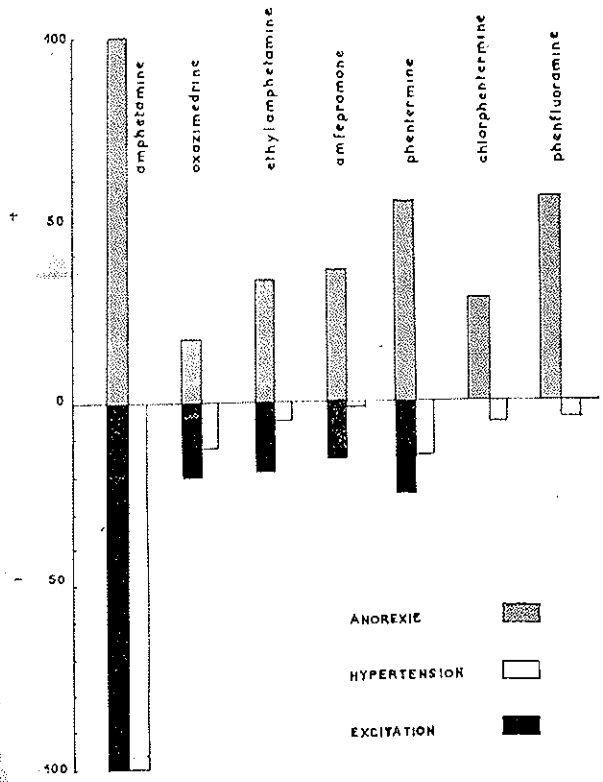

FIG. 2. — Comparaison des différents anorexiants.
En ordonnées : activité en p. 100 par rapport à l'amphétamine ; en haut (+) : effet anorexigène ; en bas (—) : activité excitante centrale et hypertensive.

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RÉSUMÉ

Les activités anorexiantes, centrales et tensionnelles de six dérivés de l'amphétamine ont été étudiées (amphétamine, oxazimédrine, N-éthylamphétamine, amfépramone, phentermine, chlorphentermine et phenfluoramine).

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The Effects of Chronic Fenfluramine Administration on Behaviour and Body Weight

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Abstract. Two experiments were conducted on the effects of chronic administration of fenfluramine on behaviour and body weight in rats. In Experiment One the effects of 28 day chronic administration were studied. A dose related rapid weight loss was observed in treated subjects, with development of tolerance to the effects of the drug on body weight after 14 days administration. Observations of behaviour were made on days 1, 14 and 28 of chronic administration according to a "time sampling" procedure of behavioural categorisation. The incidence of some behavioural patterns varied significantly between observation days, although observations of control subjects were never significantly different. By the 28th day of administration tolerance to the behavioural effects of the drug had developed, no dose/response effects being noted in contrast to the results for prior observation days.

In Experiment Two confirmation of the development of behavioural tolerance was obtained. Abnormal, "stereotyped" behaviour induced by a very high dose of fenfluramine showed a much lower incidence in subjects that hadr eceived fenfluramine for 30 days than in saline controls. Attention is drawn to the difficulties inherent in describing psychotropic agents as either sedatives or stimulants. It is suggested that although fenfluramine is generally considered to be a sedative, stimulant effects may be observed after chronic administration of anorexic doses. Similarities between the effects of high doses of fenfluramine and amphetamine are described.

Key words: Fenfluramine — Anorexia — Activity Analysis — C.N.S. Stimulation — Stereotyped Behaviour.

Fenfluramine has often been described as an anorexic amphetamine derivative which lacks the stimulant and addictive properties of other phenylethylamines (Boissier *et al.*, 1965; Duhault, 1972; Elliot, 1970; Fink *et al.*, 1971; Hill and Turner, 1967; Sedgwick, 1972). However, a number of reports of human overdosage have demonstrated a marked stimulant effect (Campbell and Moore, 1969; Fleischer and Campbell, 1969; Gold *et al.*, 1969) and similarities to amphetamine psychosis (Brandon, 1969; Riley *et al.*, 1969). Similar observations have been made in animal studies (Yelnosky and Lawlor, 1970; Southgate *et al.*, 1971; Kun-

dig, 1971). At anorexic doses fenfluramine has been reported to act as a stimulant under certain conditions [Everitt and Hacket, 1972; Le Douarec *et al.*, 1966; Offermeir and Potgeiter, 1972; Ziance (personal communication)]. Lewis *et al.* (1971) and Johnson *et al.* (1971) have shown that administration of fenfluramine, to humans and cats respectively, causes suppression of paradoxical sleep time similar to that observed with *d*-amphetamine, with rebound phenomena on withdrawal, and bruxism (in humans) similar to that observed in amphetamine addicts (Ashcroft *et al.*, 1965).

All these reports indicate that the description of fenfluramine as a non-addictive sedative anorexiant may be an oversimplification of its pharmacological properties. It is true that a number of authors have reported reduction in spontaneous motor activity following acute fenfluramine administration (Le Douarec *et al.*, 1966; Ziance *et al.*, 1967; 1972) and a similar reduction in exploration (Boissier *et al.*, 1965; Valzelli, 1971). Inhibition of aggression in isolation reared mice has also been reported (Weischer and Opitz, 1972) as has protection from ECS (Ziance *et al.*, 1967). Clearly, in many "classical" psychopharmacological screening tests fenfluramine acts in a manner that is generally considered to reflect sedative properties.

A number of authors, however, have stressed that psychotropic drugs generally have multiple effects and that the terms "stimulant" and "sedative" are confusing unless the exact behavioural or neurophysiological effects observed are specified (Weiss and Laties, 1964; Dews, 1958; Schiørring, 1971). The use of the terms sedative and stimulant as mutually exclusive descriptive labels is to a large extent due to the fact that screening for C.N.S. active compounds frequently involves apparati such as photobeam cages, ultrasonic motion detectors and stabilimeters; all of which provide a gross measure of "general activity". The usefulness of such measures is questionable. For example, fenfluramine has been shown to reduce (Ziance *et al.*, 1972), to have no effect on (Van Rossum and Simmons, 1969; Offermeir and Potgeiter, 1972) and to increase (Le Douarec *et al.*, 1966; Everitt and Hacket, 1972) spontaneous motor activity as measured by such methods. Draper (1963) noted that such measures are "apparatus bound" and susceptible to large numbers of variables. As an alternative to these contradictory purely quantitative measures Bindra and Spinner (1958) proposed the use of a "time sampling" method of behavioural categorisation, using well defined, mutually exclusive, behavioural categories arranged in a hierarchy. This technique allows both quantitative and qualitative measurement of activity.

Taylor *et al.* (1971) used this technique, with categories modified after Winocour *et al.* (1969), to study the effects of acute fenfluramine on be-

haviour. Experiment one replicates this study and extends the analysis to 28 days chronic administration. Observations of possibile "stimulant" effects of fenfluramine, and definite behavioural and anorexic tolerance are reported. Tolerance to the behavioural effects of the drug was confirmed in Experiment Two, the results of which justify the proposal made above that "time sampling" activity analysis is superior to gross measures of activity, since significant differences in behavioural patterns, observed in tolerant and nontolerant subjects after injection of a very high dose of fenfluramine, were not reflected in simultaneous measurements of activity with an ultrasonic motion detector.

Experiment One

Method

Subjects were 24 male hooded rats, weighing between 200 and 250 g on arrival. They were randomly assigned to groups of threes, one group being placed in each of eight cages. From each cage one subject received saline control injections, whilst the other two subjects received 3 and 9 mg per kg of fenfluramine respectively. Subjects in any one cage were randomly assigned to dose conditions; they were injected daily, subcutaneously, with the relevant solution at a volume equivalent to 2 ml per kg of body weight. Drug solutions were made up in saline. On arrival, subjects were adapted to a 23 h deprivation schedule for three weeks, and were maintained on this schedule throughout the study. Saline injections were administered to all subjects for four days prior to drug administration in order to habituate them to the injection procedure; they were weighed and injected daily when $22^1/_2$ h food deprived, and fed half an hour after injection.

Behavioural Observations. These were made on days 1, 14 and 28 of the chronic study. On observation days subjects from each cage were injected in random order at five minute intervals, then placed in individual holding cages for half an hour prior to observation. Immediately after observation subjects were fed for one hour then returned to their home cages. Subjects were observed when 23 h food deprived, observations being made in a large plastic lined box with a perspex lid and with dimensions of 90 cm × 45 cm × 50 cm. The box was uniformly illuminated and placed in a soundproof room.

The following mutually exclusive behavioural categories were used, arranged in the hierarchical order as shown:

Rearing: Front limbs off floor with hind limbs extended
Walking: Movements involving all four limbs
Sniffing: Head movements with rear limbs immobile, twitching of vibrissae
Grooming: Scratching, biting or licking of coat
Immobile: Freezing, total inactivity
Miscellaneous: Eating faeces and other infrequent behaviours

This hierarchy follows that of Winocour *et al.* (1969), the justification for its use being that sniffing is frequently observed in conjunction with rearing or walking. A behavioural pattern may be categorised as rearing or walking even though the subject may be sniffing simultaneously. For each subject observations were made every $2^1/_2$ sec, for a total of 100 observations per subject. The experiment was run in a

double blind manner, observations always being made by the same individual who was well practised prior to day 1. Pilot studies indicated a high degree of concordance between observers. Statistical analysis was by the Mann Whitney *U* Test (one tailed) in all cases.

Results

(a) Weight Changes

Fig. 1 shows the cumulative sum of the daily differences between the mean body weights of the two treated groups and the mean body weight of the saline controls. Fluctuations in the baseline control body weights are small; however, the effects of such fluctuations are eliminated by presenting the data in the form shown, providing a reliable index of drug effects. There is a clear dose related initial rapid weight loss in treated subjects, followed by a consistent reduction in rate of weight loss, tolerance to the effects of the drug on body weight being apparent around day 14, for those subjects which received 9 mg per kg and around day 5 for those subjects which received 3 mg per kg. Once subjects had become tolerant to the drug effect they did not regain weight, indicating a permanent effect of fenfluramine.

(b) Behavioural Observations

Comparisons between controls observed on days 1, 14 and 28 were not significant for any behavioural category, so that repeated exposure to the chamber for the observation period of just over 4 min had no effects on behaviour on the spaced observation days. It is consequently possible to make comparisons between observations on different days for treated

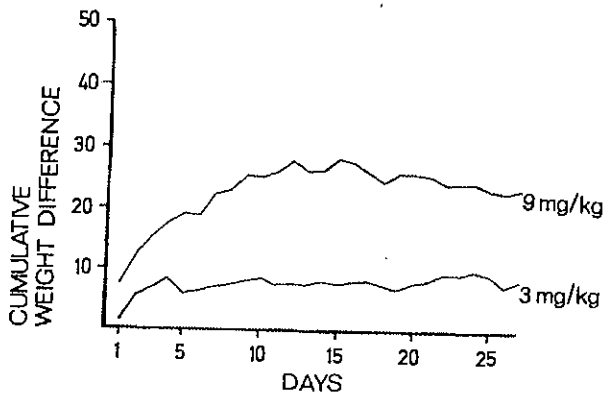

Fig. 1. Cumulative sum of the daily differences (gms) between mean weights of subjects receiving 3 and 9 mg per kgm of Fenfluramine, and saline controls

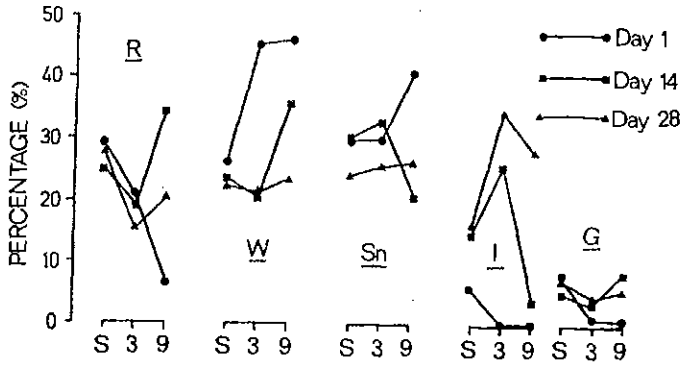

Fig. 2. Mean percentage incidence of Rearing (*R*), Walking (*W*), Sniffing (*Sn*), Grooming (*G*) and Immobility (*I*), after the 1st, 14th and 28th daily dose of Saline (*S*), 3 mg per kg (*3*) and 9 mg per kg (*9*) Fenfluramine

Table 1. Statistical comparisons between acute subjects (Observations on Day One) Mann Whitney *U* Test. NS = not significant

Behavioural category	Controls compared with subjects dosed with 3 mg per kg	Controls compared with subjects dosed with 9 mg per kg	Subjects dosed with 3 mg per kg compared with subjects dosed with 9 mg per kg
Rearing	$p < 0.05$	$p < 0.001$	$p < 0.005$
Walking	$p < 0.001$	$p < 0.005$	NS
Sniffing	NS	$p < 0.05$	$p < 0.005$
Grooming	$p < 0.05$	$p < 0.05$	NS
Immobile	NS	$p < 0.05$	NS

subjects. Fig. 2 shows the mean incidence of each behavioural category, for each of the three groups of subjects on the three observation days. Miscellaneous behaviour is omitted because very few instances of this category were recorded.

(i) *Acute Administration.* Table 1 shows the comparisons between control subjects and treated subjects, and the comparisons between the two dosed groups for each behavioural category. Acute administration leads to a dose related reduction in the incidence of rearing, a significant increase in walking, a significant increase in sniffing which is dose related and significant decreases in grooming and immobility. Acute fenfluramine administration has a profound effect on the "spectrum" of behaviour recorded.

Table 2. Statistical comparisons between subjects receiving 9 mg per gm Fenfluramine on Days 1 and 14. (Control comparisons are not significant)

Behavioural category	Coparisons between subjects dosed with 9 mg per kg on Days 1 and 14
Rearing	$p < 0.001$
Walking	$p < 0.05$
Sniffing	$p < 0.005$
Grooming	$p < 0.01$
Immobile	$p < 0.01$

(ii) *Chronic 14 Day Administration.* No *significant* effects were noted on any categories of behaviour when comparisons were made between 14 day treated subjects and controls except for a significant increase (at the $p < 0.05$ level) in the incidence of walking for the subjects receiving the high dose of drug. However, many of the effects approach significance and the patterns of results is very different to that observed following acute administration. For example, some of the drug effects after 14 days administration are in the opposite direction to that observed after acute administration (rearing and sniffing categories). Whilst comparisons with controls are not significant for all categories except walking, there are significant differences ($p < 0.05$ level) between subjects dosed with 3 and 9 mg per kg for rearing (significant increase at high dose), walking (increase), sniffing (decrease) and grooming (increase). The dose/response effect is in the opposite direction to that recorded for acute administration for the rearing and sniffing categories.

Comparisons between subjects receiving 9 mg per kg of fenfluramine on days 1 and 14 indicate a significant difference on all categories as shown in Table 2.

(iii) *Chronic 28 Day Administration.* No significant differences were noted between treated and control subjects for any behavioural category, nor were there any differences between subjects receiving 3 and 9 mg per kg of fenfluramine, in contrast to the dose/response effects reported for some categories on both days 1 and 14.

Discussion

(a) Weight Changes

The effect of fenfluramine on body weight with the development of "anorexic tolerance" is similar to that reported by many other authors. The development of anorexic tolerance would *not* appear to be related to that of behavioural tolerance, since subjects had ceased to lose weight by day 14 when the drug still had pronounced effects on behaviour. It is not

clear whether the permanent effect on body weight is due to the anorexic effects of fenfluramine or to its metabolic ("glycolyptic") effects (Butterfield *et al.*, 1971; Turtle *et al.*, 1971).

Similar results were obtained in a comparable study with Norfenfluramine (Taylor *et al.*, unpublished), the effects of Norfenfluramine being more pronounced at equal doses in accord with the suggestion of some authors that Norfenfluramine may be involved in the actions of fenfluramine (Campbell, 1971).

(b) Behavioural Observations

The acute data replicate those of Taylor *et al.* (1971), and differ significantly from observations made on day 14 in two ways. Firstly, the dose/response effect is in the opposite direction for the rearing and sniffing categories, and secondly, cross day comparisons indicate significant differences (at very high levels) for treated subjects but not for controls on *all* categories. Behavioural tolerance has developed by day 28 as shown by the absence of any dose/response effect on any category in contrast to the results from days 1 and 14. A very similar pattern of results was observed in a comparable study with Norfenfluramine (Taylor *et al.*, unpublished).

Due to the exhaustive nature of the behavioural categorisation system used in this study, the frequencies of the various categories are not independently variable. A drug induced change in the incidence of any one category will, by definition, be reflected in opposite changes in the incidence of one or more other categories. The effects of psychotropic agents can be considered as changing the "spectrum" of activities. However, it is clear that fenfluramine has pronounced effects on those categories at the head of the hierarchy (*i.e.* rearing and walking). The drug induces a significant increase in the incidence of rearing on day 14 even though it causes a reduction on acute administration, and it also increases the incidence of walking following both acute and chronic administration. These effects of fenfluramine on "active" exploratory behaviour may reflect genuine "stimulant" effects of the drug. Everitt and Hacket (1972) have shown that motor activity in a confined space which allows only rearing behaviour to occur is stimulated by acute administration of fenfluramine, an effect similar to that observed with *d*-amphetamine. This result may also reflect a stimulant effect of fenfluramine on active exploratory behaviour. The effects on sniffing behaviour may be secondary to those on categories higher in the hierarchy since, as noted by Winocour *et al.* (1969) sniffing is often observed concurrently with rearing and walking. The stimulation of sniffing observed after acute administration would not seem to be related to amphetamine induced "stereo-

typed" sniffing as described by Quinton and Halliwell (1963), Randup and Munkvad (1967) and Schiørring (1971) because in Experiment Two (described below) a very high dose of fenfluramine induced almost continuous vigorous sniffing, which differed in kind to that observed following acute and chronic administration of the lower doses.

A number of authors have suggested that rearing behaviour may provide an index of general "C.N.S. excitability" (Lat, 1963: Garg, 1969). However, Holland and Gupta (1967) have proposed that the incidence of rearing is related to two orthogonal factorial dimensions of "Activity" and of "Emotionality"; they have also shown that while amphetamine increases rearing frequency so does the depressant Sodium Amytal, the latter effect being attributed to an action on emotionality. Drugs may act on separate factorial dimensions to induce the same behavioural effect. Consequently the stimulation of rearing after 14 days chronic administration of fenfluramine reported in this study can not definitely be attributed to an effect on "C.N.S. excitability", nor can the results of Everitt and Hackett (1972), especially since fenfluramine *has* been reported to be an effective anxiolytic in clinical studies (Gaind, 1972), although this result is not unquestioned (Raich *et al.*, 1966).

The complexity of the interpretation of the results of fenfluramine on behaviour clearly illustrate the difficulties inherent in describing a psychotropic agent as either a stimulant or a sedative. Many previous studies of the effects of the drug on activity appear to have led to spuriously simplistic conclusions. However, the effects of fenfluramine on rearing and walking suggest that the drug may have stimulating properties, especially after chronic administration. In the light of these results it is probably necessary to draw a distinction between acute and chronic effects of fenfluramine, similar to that reported by Lewis *et al.* (1971) from sleep studies, and Costa *et al.* (1971) from studies of effects of fenfluramine on monoamine stores of rat tissues.

Experiment Two

Introduction

Yelnosky and Lawlor (1970) have shown that injection of 50 mg per kg of fenfluramine in rats induces stereotyped behaviour which is similar but not identical to that observed with high doses of amphetamine (Randrup and Munkvad, 1969). Southgate *et al.* (1971) showed that 5 or 32 mg per kg fenfluramine given in conjunction with a Monoamine Oxidase Inhibitor results in similar stereotyped behaviours in mice. The typical behavioural patterns reported by these authors included: excessive head movements, sniffing, backward locomotion and a very low incidence of normal behaviour such as those recorded in Experiment One.

As a result of the observation that behavioural tolerance to fenfluramine had developed by day 28 of chronic administration, it was hypothesised that tolerant subjects (*i.e.* those that had received fenfluramine for 28 days) would show a much lower incidence of stereotyped behaviours, and a higher incidence of normal behaviours than the saline treated subjects.

Method

Two groups of subjects were used from Experiment One; those which had received saline and 9 mg per kg of fenfluramine. There were eight subjects per group and they were maintained on the same schedule of injection and feeding times as in Experiment One. Chronic drug administration was continued for a total of 30 days, behavioural observations being made on day 31, after all subjects had received injections of 50 mg per kg of fenfluramine.

Behavioural Categorisation. As a result of the reports of steteotyped behaviours considered above and from the authors' own pilot studies, the following behavioural categories were introduced in addition to those already defined in Experiment One:

Backward locomotion: a behavioural pattern never observed in control subjects.
Head movements: characterised by being aimless and repeated
Circling: characterised by the back legs being dragged around the front legs as pivots

Subjects were observed for a 15 min period, 20 min after drug injection in a wooden box of dimensions 35 cm × 30 cm × 25 cm, with a perspex lid to which was attached an ultrasonic motion detector system. In contrast to the sampling procedure used in Experiment One categories were recorded only when a change of behavioural pattern occurred or when one pattern was prolonged for a period of greater than ten seconds (this was usually only true of the immobility category). The number of observations made per subject varies so that the data are presented in the form of the percentages of the total number of observations made per subject for each category. The subjects were run in a double blind manner, but the differences between the two groups of subjects was obvious to the observer.

Results

Fig. 3 presents the mean incidence of the various categories in the two groups. All the "normal" behavioural categories were observed at a higher level of incidence in the tolerant than in the non-tolerant subjects, the converse being true of the "stereotyped" categories. Table 3 shows the significant levels of the differences between the two groups (Mann Whitney *U* Test).

All subjects showed continuous vigorous sniffing of a type never observed in Experiment One; because of this the incidence of sniffing was ignored as it was not possible to quantitate it. No significant differences were observed between the two groups of subjects when activity was assessed by the ultrasonic motion recorder, although the form of activity was clearly different in the two groups.

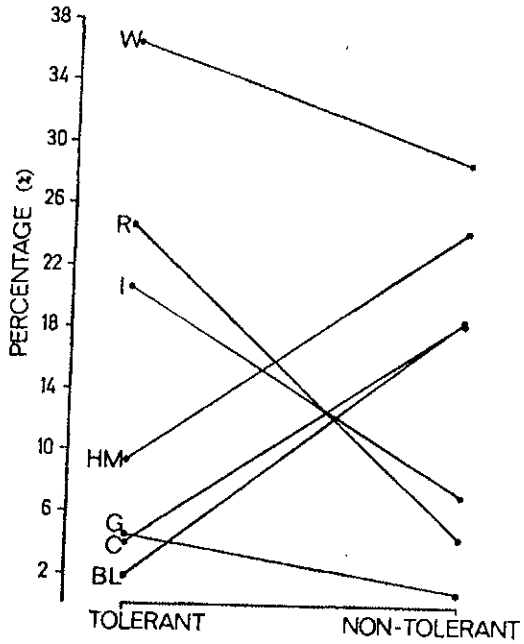

Fig. 3. The mean percentage incidence of behaviours after a 50 mg per kg dose of Fenfluramine to tolerant (30 days 9 mg per kg Fenfluramine) and nontolerant (30 days saline) groups. Walking (*W*), Rearing (*R*), Immobile (*I*), Head Movements (*HM*), Grooming (*G*), Circling (*C*) and Backward Locomotion (*BL*)

Table 3. Statistical comparisons between tolerant and nontolerant subjects in experiment two. (NS = not significant)

Behavioural category	Comparisons between tolerant and nontolerant subjects
Rearing	$p < 0.001$
Walking	NS
Grooming	$p < 0.05$
Immobile	$p < 0.001$
Head movements	$p < 0.001$
Circling	$p < 0.001$
Backward locomotion	$p < 0.001$

Discussion

The results confirm the development of behavioural tolerance after 30 days chronic administration of 9 mg per kg fenfluramine, in accord with those from Experiment One. Although tolerance to the behavioural

effects of fenfluramine had been convincingly demonstrated, informal observations of the treated subjects for a week after cessation of drug administration failed to indicate the presence of any withdrawal symptoms.

Randrup and Munkvad (1969) have shown that amphetamine induced stereotypy is due to stimulation of dopamine receptors in the corpus striatum, the characteristic pattern of stereotopy observed in rats involving vigorous sniffing, biting, gnawing and, occasionally, backward locomotion. The stereotopy observed after high doses of fenfluramine in rats appears similar in some ways to that induced by amphetamine, although there are differences between the two syndromes. Southgate *et al.* (1971) have shown that fenfluramine induced stereotopy in mice is at least partially due to direct activation of 5 HT receptors, fenfluramine in contrast to amphetamine being known to affect cerebral 5 HT metabolism (Costa *et al.*, 1971; Duhault and Verdavainne, 1967), so that the modes of action of fenfluramine and amphetamine in inducing stereotyped behaviour may differ in that the effects of fenfluramine may be mediated, at least partially, by 5 HT receptors. However, Costa *et al.* (1971) have shown that high doses of fenfluramine affect cerebral catecholamine metabolism in a manner similar to that observed with amphetamine. It is consequently possible that the induction of stereotyped behaviours by fenfluramine involves catecholamine receptors as well as 5 HT receptors and that the similarities between the behavioural syndromes of stereotopy may be paralleled by similarities in neurochemical modes of action. It is not clear however, to what extent such effects are related to behavioral effects observed with anorexic doses; they can hardly be termed "stimulatory effects" and may differ in kind from effects with therapeutic doses.

Taken together the possible stimulatory effects observed after 14 days chronic administration of fenfluramine in Experiment One and the similarities observed in the stereotopy syndromes reported in Experiment Two, suggest that the behavioural effects of fenfluramine and amphetamine may not be as different as have been suggested in the past.

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Annexe 1-8

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Time Sampling of Rat Exploratory Behaviour: A Reliable Screening Test for the C.N.S. Effects of Anorexic Agents

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Abstract. A series of eight experiments were conducted on the acute effects of a number of anorexic agents on rat exploratory behaviour, as assessed by a "time sampling" procedure of behavioural categorisation. Compounds studied were of three types. Firstly, some well known anoroxiants (Amphetamine, Diethylpropion, Fenfluramine); secondly, a series of fenfluramine derivatives (Norfenfluramine, SE 780, SE 1513 and SKF 1-39728); and thirdly, an indole derivative (U 22-394A). All the compounds except the latter are based upon a phenylethylamine configuration. The results indicate that amphetamine and diethylpropion are stimulants whilst fenfluramine is a sedative, in accord with the clinical reports of the effects of acute administration of these compounds. All the other phenylethylamines and U 22-394A were found to be sedatives. The technique of activity analysis described here is a useful screening test for psychotropic agents which affect C.N.S. excitability in humans, which is probably superior to other measures of activity in its predictive value. However, it is noted that the effects of acute administration do not always provide a reliable index of chronic effects. The compounds SE 780 and SKF 1-39728 would seem to merit further study. It is suggested that all the fenfluramine derivatives, except SKF 1-39728, have a similar mode of anorexic action to U 22-394A.

Key words: Anorexiants — Activity Analysis — Time Sampling — Screening Tests — Phenylethylamines — Serotonin.

Introduction

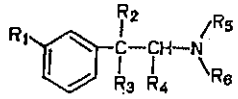
A very large number of anorexic agents such as phenmetrazine, phentermine, diethylpropion and all the amphetamines are derived from a phenylethylamine base and all have pronounced C.N.S. stimulant properties (Martindale, 1972). Fenfluramine is generally considered to be a sedative phenylethylamine; however, there are reports of stimulant effects in animals under some conditions (Everitt and Hacket, 1972; Le Douarec *et al.*, 1966; Taylor *et al.*, 1973; Kundig, 1971), and in humans at high doses (Campbell and Moore, 1969; Fleischer and Campbell, 1969; Gold *et al.*, 1969; Riley *et al.*, 1969; Brandon, 1969; Belvedere *et al.*, 1972). Furthermore, withdrawal mood depression has been reported after fenfluramine administration (Oswald *et al.*, 1971; Harding, T., 1971; Harding, T., 1972; Steel and Briggs, 1972). It is clear that even fenfluramine, which is

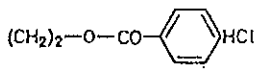
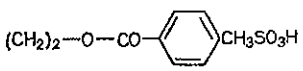
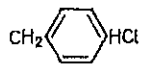
generally considered to be the anorexiant of choice, has adverse side effects.

The present paper reports on the effects of a series of anorexic agents on activity after acute administration; the technique used being a "time sampling" procedure of behavioural categorisation of rat exploratory behaviour. This screening test provides a reliable indication of the probable effects of psychotropic agents on the C.N.S. in humans; such effects being a very important aspect of the therapeutic validity of anorexiants.

Some of the compounds studied were well known and some were relatively unknown, their structures being as shown below:

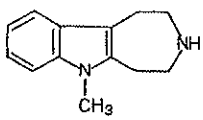
a) Phenylethylamines



Drug	R_1	R_2	R_3	R_4	R_5	R_6
Amphetamine (+)	H	H	H	CH_3	H	$H \cdot SO_4$
Diethylpropion	H	O		CH_3	C_2H_5	$C_2H_5 \cdot HCl$
Fenfluramine	CF_3	H	H	CH_3	C_2H_5	$H \cdot HCl$
Norfenflur-amine	CF_3	H	H	CH_3	H	$H \cdot HCl$
SE 780[1]	CF_3	H	H	CH_3	H	
SE 1513	CF_3	H	H	CH_3	H	
SKF 1-39728	CF_3	H	CH_3O	H	H	

[1] This compound has also been referred to as "S 992".

b) U 22-394A



Methods

Methods were made as similar as possible throughout the series of eight experiments in order to facilitate inter-drug comparisons. However, procedural differences between experiments became necessary when it was found that some compounds were not active when injected S.C. but *were* active by the I.P. route

(SE 1513 and SE 780). In addition the injection vehicle had to be varied between experiments. The table below summarises the details of each experiment.

	Drug	Dose (mg per kg)	Injection route	Vehicle
Group one	*d*-Amphetamine	0.5, 1.0	S.C.	Saline
	Diethylpropion	2, 8	I.P.	Saline
	Fenfluramine	3, 9	S.C.	Saline
Group two	Norfenfluramine	3, 9	I.P.	Saline
	SE 1513	3, 9	I.P.	Sterile water
	SE 780	3, 9	I.P.	Tween 80 and sterile water
	SKF 1-39728	3, 9	I.P.	Saline
Group three	U 22-394A	0.5, 1.0	S.C.	Saline

The doses used were such that they were active anorexically; the effective doses for the novel compounds being determined by pilot studies in this laboratory. No attempt was made to administer equipotent doses of the compounds for two reasons. Firstly, because of the need to introduce procedural differences between experiments, as described above; and secondly, because any attempt to use equipotent doses is to some extent arbitrary, since a large number of variables (diets, times etc.) affect the measurement of the ED_{50} of any particular compound. Measurements of the ED_{50} of any drug are critically dependant upon procedures used, so that cross drug comparisons are only possible with identical procedures. The use of different procedures may well lead to different rankings of anorexic potency of a series of drugs. Weischer and Opitz (1972) attempted to administer equipotent doses of a range of anorexic agents by injecting a fixed percentage of the LD_{50}s. However, this procedure also fails to ensure that equipotent *anorexic* doses are administered since the therapeutic margins of the various compounds may vary considerably between drugs. For example, in this study that of SE 780 is approximately equal to seven times that of fenfluramine when determined acutely (unpublished Internal Report of Servier Laboratories).

Subjects were divided into eight experimental groups of male albino rats weighing between 200 and 300 g. In each experiment there were 24 subjects, eight per dose group and eight controls. Separate control groups were used in each experiment because it has been shown that exploratory behaviour is greatly influenced by handling habituation (Thompson and Lippman, 1972); and it was thought possible that control baselines might differ between experiments because of the influence of this variable, which is difficult to control for adequately when dealing with large numbers of subjects. Subjects were housed in threes and randomly allocated to dose conditions, being fed and watered ad lib prior to injection. Drugs were administered, in a volume equivalent to 2 ml per kg of body weight, 30 min prior to observation in a uniformly illuminated open field of dimensions $90 \times 45 \times 50$ cm. Activity was measured by a time sampling procedure of behavioural categorisation, with categories arranged hierarchically in the order, Rearing, Walking, Sniffing, Grooming, Immobile. Subjects were always observed blind by the same well trained observer, observations being made every $2^1/_2$ sec, 100 per subject. Further details of the procedure used and the rationale behind it, are described in Taylor *et al.* (1971); and in Taylor *et al.* (1973).

Results

A. Group One. Well Known Anorexiants: (Amphetamine, Diethylpropion and Fenfluramine). The behavioural effects of these compounds are shown in Table 1. Amphetamine induced a significant increase in the incidences of the active exploratory behaviours rearing and walking, with reductions in all other categories; some of the effects being dose related. No evidence of stereotyped behaviour was noted at the doses used. Diethylpropion induced a significant increase in the incidence of walking, which was dose related. Fenfluramine, in contrast to amphetamine reduces the incidence of rearing, also in a dose related manner. The significant increase in the incidence of sniffing observed with the high dose is considered to be an effect secondary to that on rearing (as described by Taylor *et al.*, 1973). It is not suggested that fenfluramine induces stereotyped sniffing at the dose used.

Discussion

A number of authors suggested that the incidence of rearing in a novel environment provides a reliable index of "C.N.S. Excitability" (Garg, M., 1969; Lat, J., 1963; Holland and Gupta, 1967), and it has been shown to be reduced by anxiolytics such as chlorodiazepoxide (Hughes, 1972; Iwahara and Sakama, 1972), and neuroleptics such as haloperidol and chlorpromazine (Janssen *et al.*, 1960; Brimblecombe, 1963). However, it is acknowledged that there are paradoxical effects of drugs on open field exploration; for example Bainbridge (1970) reported that low doses of amphetamine reduce ambulation. whilst Christmas and Maxwell (1970) reported that many benzodiazepines increase ambulation in a novel environment. These results may be interpreted in terms of the report of Holland and Gupta (1967) that exploration measures are influenced by two orthogonally related factorial dimensions, those of general activity and emotionality. The effect of a sedative or stimulant drug is dependant upon the state of the animal at the time of administration; for example, Christmas and Maxwell (1970) reported that benzodiazepines do *not* influence exploration when subjects are habituated to the open field. Paradoxical results can be obtained by drugs acting on *either* factorial dimension, the effect of any particular drug being dependant upon (i) the dose of drug administered, and (ii) the state of the subject at the time of administration. One way of minimising the complexity of interpretation of results of open field exploration is by using a range of doses of the drugs to be tested. Given the doses and "time sampling" technique of behaviour used in this study, *no* paradoxical effects were observed; this is

Table 1. Significance levels of comparisons between the three experimental groups (Mann-Witney U test). ↑ Indicates significant increase; ↓ a significant decrease. N.S. = Not significant

	Amphetamine			Fenfluramine			Diethylpropion		
	Controls vs 0.5 mg/kg	Controls vs 1 mg/kg	0.5 mg/kg vs 1 mg/kg	Controls vs 3 mg/kg	Controls vs 9 mg/kg	3 mg/kg vs 9 mg/kg	Controls vs 2 mg/kg	Controls vs 8 mg/kg	2 mg/kg vs 8 mg/kg
Rearing	N.S.	P 0.041 ↑	N.S.	P 0.05 ↓	P 0.005 ↓	P 0.004 ↓	N.S.	N.S.	N.S.
Walking	N.S.	P 0.001 ↑	P 0.001 ↑	N.S.	N.S.	N.S.	N.S.	P 0.05 ↑	P 0.05 ↑
Sniffing	N.S.	P 0.001 ↓	P 0.001 ↓	N.S.	P 0.015 ↑	N.S.	N.S.	N.S.	N.S.
Grooming	N.S.	P 0.01 ↓	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Immobile	N.S.	P 0.005 ↓	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

probably because two doses of each drug were used, both of which were comparatively high.

The increases in the incidences of rearing and walking observed after amphetamine injection reflect the well known stimulant properties of the drug. Diethylpropion would also seem to possess stimulant properties, in accord with the results of Offermeir and Potgeiter (1972). The effects of fenfluramine suggest that it has sedative properties after acute administration, as was reported with food deprived subjects by Taylor *et al.* (1971), and Taylor *et al.* (1973).

The results obtained from these well known compounds provide a baseline against which to assess the effects of less well known compounds, and provide striking parallels with reports of their effects in humans. Amphetamine is universally acknowledged to be a potent central stimulant in humans, and to be a potential drug of abuse; as is diethylpropion (Clein and Bernady, 1969), whilst fenfluramine has often been claimed to be a sedative in humans (Elliot, 1970; Gaind, 1972). It is consequently suggested that the technique of activity analysis described here provides a very useful screening test for C.N.S. active compounds, the results of which give a reliable indication of the probable effects of such compounds in humans. Comparisons between the acute and chronic effects of fenfluramine in humans and rats provide further evidence of the predictive validity of this technique. Chronic administration of fenfluramine to rats may result in stimulant effects, in contrast to the sedative effects observed following acute administration (Taylor *et al.*, 1973). These results closely parallel those of Oswald *et al.* (1971) and Steel and Briggs (1972) in humans. These authors described stimulant properties of fenfluramine and mood depression following withdrawal after chronic administration, in contrast to the sedative properties noted after acute administration.

The technique used here is considered to be superior to those involving gross measures of activity such as are obtained with running wheels, stabilimeters, photocell cages and ultrasonic motion recorders, since such measures have been shown to be susceptible to a large number of variables (Draper, 1963), to provide activity measures which are not related to drug induced behavioural changes (Krsiak *et al.*, 1970) and which are correlated at a very low level (Gross, 1968; Tapp *et al.*, 1968). Furthermore, for any one drug the results obtained with this method of activity analysis show a high degree of concordance between different observers after a suitable training period.

B. Group Two. Fenfluramine Derivatives: (Norfenfluramine, SE 1513, SE 780, SKF 1-39728. The behavioural effects of these compounds are shown in Table 2. All possess sedative properties after acute administration; however the data does not allow ranking of the four compounds

Table 2. Significance levels of comparisons between the three experimental groups (Mann-Witney U test). ↑ Indicates significant increase; ↓ a significant decrease. N.S. = Not significant

	Norfenfluramine			SE 1513		
	Controls vs 3 mg/kg	Controls vs 9 mg/kg	3 mg/kg vs 9 mg/kg	Controls vs 3 mg/kg	Controls vs 9 mg/kg	3 mg/kg vs 9 mg/kg
Rearing	*P* 0.001 ↓	*P* 0.001 ↓	N.S.	*P* 0.001 ↓	*P* 0.001 ↓	N.S.
Walking	*P* 0.032 ↓	*P* 0.032 ↓	N.S.	N.S.	*P* 0.025 ↓	N.S.
Sniffing	*P* 0.001 ↑	*P* 0.001 ↑	N.S.	*P* 0.001 ↑	*P* 0.001 ↑	N.S.
Grooming	*P* 0.001 ↓	*P* 0.001 ↓	N.S.	*P* 0.01 ↓	N.S.	N.S.
Immobile	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

	SE 780			SKF 1-39728		
	Controls vs 3 mg/kg	Controls vs 9 mg/kg	3 mg/kg vs 9 mg/kg	Controls vs 3 mg/kg	Controls vs 9 mg/kg	3 mg/kg vs 9 mg/kg
Rearing	N.S.	*P* 0.002 ↓	N.S.	N.S.	*P* 0.02 ↓	N.S.
Walking	N.S.	*P* 0.027 ↓	N.S.	N.S.	*P* 0.05 ↓	N.S.
Sniffing	N.S.	*P* 0.002 ↑	*P* 0.009 ↑	N.S.	N.S.	N.S.
Grooming	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Immobile	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

along a scale of sedative potency because of the procedural differences between experiments described above and the use of doses which are not equipotent anorexically.

Discussion

The sedative properties of these compounds are similar to those of their parent compound, fenfluramine, at least after acute administration. The presence of the m-trifluromethyl group on the benzene rings seems to confer sedative properties on the phenylethylamine series. A similar effect of direct halogenation of the benzene ring confering sedative properties on phenylethylamines has been suggested by Tang and Kirch (1971) and Weischer and Opitz (1972). The highly potent

Table 3. Significance levels of comparisons between the three experimental groups (Mann-Witney U test). ↑ Indicates significant increase; ↓ a significant decrease. N.S. = Not significant

	U 22-394A		
	Controls vs 0.5 mg/kg	Controls vs 1.0 mg/kg	0.5 mg/kg vs 1.0 mg/kg
Rearing	N.S.	P 0.001 ↓	P 0.005 ↓
Walking	N.S.	P 0.01 ↓	P 0.05 ↓
Sniffing	P 0.019 ↑	P 0.014 ↑	N.S.
Grooming	N.S.	N.S.	N.S.
Immobile	P 0.027 ↓	N.S.	P 0.003 ↑

sedative effects observed with norfenfluramine are in accord with suggestions that this compound may be an active metabolite involved in fenfluramine's actions (Le Douarec, 1971). At 9 mg per kg I.P. there was some evidence of stereotyped behaviour (Backward locomotion, Head movements and Circling) similar to that observed with high doses of fenfluramine (Taylor *et al.*, 1973; Yelnosky and Lawlor, 1970). SE 1513 and SE 780 were only active when injected I.P. and not when injected S.C. and it is suggested that they may be highly lipid soluble, in agreement with the findings of Galton and Wilson (1971). Chronic administration of SE 780 does not appear to result in the stimulant effects noted after chronic fenfluramine administration; the drug also seems to be active anorexically over longer periods of time than amphetamine and fenfluramine (Taylor and Goudie, 1973). Since it is active in humans (Pawan *et al.*, 1971) it would seem to merit further study. Groppetti *et al.* (1972) have reported that SKF 1-39728 reduces confinement motor activity in rats at anorexic doses, confirming the sedative properties of this compound, which also merits further investigation in chronic studies.

C. Group Three. The Indole Derivative: (U22-394A). The behavioural effects of this compound are shown in Table 3. The drug appeared to be a potent sedative which facilitated handling of the subjects. At the highest doses used abnormal head twitchings were noted in seven out of eight subjects, an effect absent in controls. Some indications of stereotyped behaviour similar to that observed after fenfluramine and norfenfluramine injections were also present.

Discussion

Acutely administered U 22-394A has been reported to have a slight sedative effect at high doses in monkeys, when activity is assessed by an ultrasonic motion recorder (Tang and Kirch, 1971). The

results reported here suggest that it is a potent sedative, although clinical trials of the compound as a potential neuroleptic in schizophrenics have failed to illustrate any therapeutic effects (Gallant *et al.*, 1971). The head twitching noted is similar to that reported by Tang *et al.* (1968) in mice. Such behaviour is thought to be due to stimulation of 5HT receptors since it is blocked by methysergide (Corne *et al.*, 1963, 1967). It is consequently likely that U 22-394A acts directly on 5HT receptors, an effect which is not surprising in that the drug is a tryptamine derivative (Hester *et al.*, 1968).

Southgate *et al.* (1971) have shown that fenfluramine induced stereotypy in mice is at least partially due to activation of serotonin receptors. The stereotypy syndrome reported here after injection of U 22-294A is similar to that reported after fenfluramine injection; this would seem to provide further evidence that U 22-394A acts on 5HT receptors. Since serotonin is known to be involved in the control of rat eating behaviour (Soulairac, 1969) and since there is some evidence that fenfluramine anorexia is mediated by 5HT receptors (Jespersen and Scheel-Kruger, 1970; Funderbunk *et al.*, 1971; Blundell *et al.*, 1973) it is possible that U 22-394A's *anorexic* mode of action also involves such receptors and is similar to that of fenfluramine, and maybe that of its derivatives SE 780 and SE 1513. In contrast, Gropetti *et al.* (1972) have reported that the anorexic action of SKF 1-39728 is dissociated from any actions on monoaminergic neurones so that this compound may differ qualitatively from the other anorexiants studied here.

Acknowledgements. The work reported here was supported by a research grant from Servier Laboratories Ltd., England, who also supplied the amphetamine, fenfluramine, norfenfluramine, SE 1513 and SE 780 used in this study. We are indebted to the Upjohn Company Ltd. for supplies of U-22-394A, and to Smith Kline and French Ltd. for supplies of SKF 1-39728.

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Note Added in Proof. Chronic study of SKF 1-34728 A over 35 days indicates that although it is a potent anorexicant at doses of 3 and 9 mg per kg (I.P.), it also possesses marked aggression inducing properties.

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After fenfluramine therapy 3 obese patients lost weight and showed increased peripheral glucose uptake. Peripheral oxygen consumption was also increased. In acute studies where fenfluramine was perfused intra-arterially into one arm, it appeared to have a direct effect in increasing glucose uptake.

SUMMARY

(1) Studies of metabolism in the human forearm (mainly muscle) tissues *in vivo* have shown that during an oral glucose tolerance test glucose uptake is high in lean nondiabetic and low in obese and diabetic subjects. There is, in fact, a close inverse correlation between skin fold thickness and glucose uptake. Exercise increases glucose uptake, as does weight reduction by diet in obese subjects.

(2) Small doses of fenfluramine (0.4 μg/min) infused intra-arterially into one arm increase the glucose uptake and blood flow, above that in the control arm.

(3) Following 2 weeks of fenfluramine therapy, 3 obese subjects lost weight and showed an increased glucose uptake and oxygen utilization in peripheral tissues.

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EFFECT OF A FENFLURAMINE DERIVATIVE (S 992) ON LIPID AND SUGAR METABOLISM

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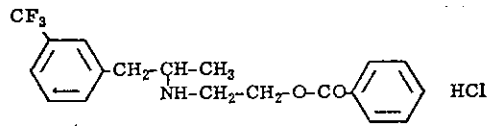
The availability of fenfluramine has made it possible to show that an anorexic activity (Le Douarec, Schmitt, and Laubie, 1966; Opitz, Kemper, and Loeser, 1965) may be obtained without the central stimulation exerted by amphetamine (Le Douarec, 1963). Fenfluramine retains the metabolic effects of amphetamine, such as the adipokinetic activity (Duhault and Boulanger, 1966; Herold, Kemper, and Opitz, 1965; Pawan, 1969), and in addition it increases the tolerance to carbohydrates (Butterfield and Whichelow, 1968). Continuing the screening of fenfluramine congeners (Beregi, Hugon, Le Douarec, Laubie, and Duhault, 1969), we have recently been interested in a derivative, namely (*meta*-trifluoromethyl-phenyl)-1-[β-(benzyloxy)ethyl] amino-2-propane (see formula), referred to here as S 992, which shows properties similar to those of fenfluramine, but 10 times less toxic. This study summarizes some findings concerning the effect of S 992 on lipid and carbohydrate metabolism.



Structure of S 992

METHODS

Male Sprague-Dawley (Charles River) rats averaging 200-250g were treated with single or repeated doses of S 992. In the acute experiments food was removed at 9 A.M. and the drug was given orally 1 hour later.

In the chronic study the administration of S 992 was given daily (suspended in tragacanth gum) at 4:30 P.M. The animals were sacrificed 16 hours after the last treatment. The schedule of treatment was kept constant because of the known daily rhythms in lipid metabolism (Muncker, 1959). Blood glucose was measured according to Hoffman (1937) with a Technicon autoanalyzer, plasma free fatty acids (FFA) according to Dole (1956), plasma glycerol according to Garland and Randle (1962), and plasma phospholipids according to Wachter and Zelger (1965). Liver glycogen was measured according to Weber, Kleine, and Wachter (1965). The gas chromatographic analysis of FFA was performed with a Perkin-Elmer instrument after esterification of FFA with methanol and H_2SO_4 in sealed vials at 90°C for 15 hours. The separation was carried out on a 2 m column filled with 5% DEGS on Aeropack under nitrogen and by using a flame ionization detector.

RESULTS

The *acute oral administration* of S 992 induced in fed rats an increase in plasma FFA which is proportional to the dose. Figure 1 shows the percent increase in FFA when animals were sacrificed one hour after the administration of S 992 or *dl*-amphetamine. A 50% increase was obtained with 3.4 mg/kg of amphetamine or 18 mg/kg of S 992. The increase in plasma FFA was accompanied by an increase in plasma glycerol and a marked decrease in

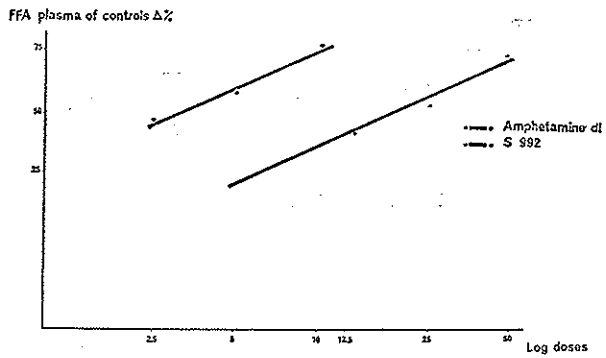


FIG. 1

plasma triglycerides (Table I). This metabolic effect did not occur if rats were fasted for 18 hours, even when the dose of S 992 was raised to 100 mg/kg orally.

TABLE I

Treatment (mg/kg, oral)	Plasma glycerol μEq/l ± S.E.	Δ percent	Plasma triglycerides g/l ± S.E.	Δ percent
controls (5)	133.7 ± 10.8			
S 992, 12.5 (5)	153.2 ± 8.7	14.6		
controls (5)			0.78 ± 0.16	
S 992, 25 (5)			0.36 ± 0.04	51**
controls (10)	175 ± 16.3		1.29 ± 0.09	
S 992, 50 (10)	238 ± 15.2	36*	0.39 ± 0.14	69.7**
controls (5)	133.7 ± 10.8			
amphetamine, 5 (5)	178.2 ± 16.2	33**		

Rats were killed 3 hr after treatment. The number of animals used is in brackets.
* $p \leqslant 0.01$
** $p \leqslant 0.001$

The analysis of specific FFA did not reveal major changes under the influence of S 992 with the exception of a 30% decrease in linoleic acid. As far as carbohydrate metabolism is concerned, S 992 is similar to fenfluramine in increasing the levels of liver glycogen and blood glucose of rats submitted to a severe food restriction. Amphetamine was without effect on blood glucose, and it decreased the liver glycogen in similar experimental conditions (Table II). In other experiments, the administration of S 992 (2.5 mg/kg orally or 5 mg/kg i.v.) to dogs did not influence the tolerance curve after a glucose load.

The chronic administration of S 992 reduced food intake in normal rats for about 7 days. After that period the values tended to return to control values (Fig. 2). When the treatment was prolonged up to 20 days there was a decrease in body weight more pronounced in the animals treated with S 992 than in the rats kept under conditions of pair feeding (Fig. 3). Since the animals received the same amount of food, it is evident that the decrease in body weight induced by S 992 could not be due solely to its anorexic effect. The weight of the epididymal fat pads was also decreased in the group treated with S 992 with respect to the pair-fed animals. It is interesting to note that

TABLE II

Effect of S 992, fenfluramine and amphetamine in single dose on blood glucose and liver glycogen level in the rat

Treatment (mg/kg, oral)	Food consumption g/24 hr	Liver glycogen content mg/g ± S.E. wet tissue	Blood glucose mg/100 ml ± S.E.
controls (18)	24	39.3 ± 2.7	78 ± 1.4
pair-feeding (17)	4	3.08 ± 1.13	48 ± 1.6
S 992, 50 (19)	4	*11.6 ± 1.79	*74 ± 4.7
fenfluramine, 30 (6)	4	**11.25 ± 2.57	*74 ± 2.8
dl-amphetamine, 10 (12)	4	***0.69 ± 0.23	53 ± 1.4

Number of animals appears in brackets. * $p < 0.001$ ** $p < 0.01$ *** $p < 0.10$

the blood glucose or plasma FFA levels (measured after 20 days of treatment) were not different in the two experimental groups. However, significant changes were observed in the composition of FFA in plasma, white (epididymal) and brown (interscapular) adipose tissues. The changes, not reported here in detail, include for the S 992 an increase in C15 fatty acids (from 22 to 75%), C18:2 (from 15 to 63%), C18:3 (from 15 to 66%), and a decrease in C16:1 (from 14 to 40%) with respect to the pair fed group.

When S 992 was given to rats fed a high lipid diet the anorexic effect was not evident, but after 20 days of treatment there was a significant reduction

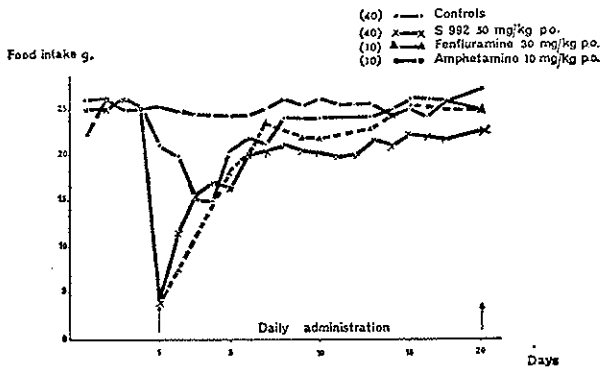


FIG. 2

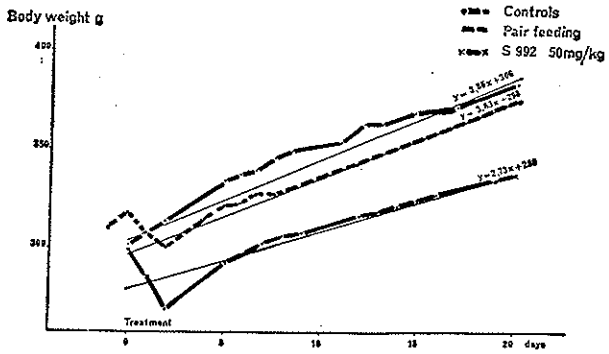


FIG. 3

in the epididymal adipose tissue without any change in body weight (Table III). The FFA of white and brown adipose tissues but not of plasma, as well as liver triglycerides, were reduced by S 992. Plasma glycerol and phospholipids, blood glucose, and liver glycogen were not affected (Table III). In this experimental condition the qualitative and quantitative composition of FFA in plasma and white and brown adipose tissue was not altered by S 992.

DISCUSSION AND CONCLUSIONS

We have established that in fed rats *dl*-amphetamine and S 992 produce an increase in the levels of plasma FFA and glycerol. These results are interpreted as evidence of an adipokinetic action taking place in the adipose tissue. The mechanism of this action is not elucidated, although it may be ascribed to a sympathomimetic effect. This increase in plasma FFA, which is proportional to the dose of S 992, is not accompanied by hyperglycemia or by a change in the glucose tolerance test. The effect of S 992 on plasma FFA was not evident during chronic treatment with S 992 when rats were submitted to a normal or a high lipid diet. The changes in the composition of FFA in plasma or adipose tissue were not related to the absolute level of FFA. In fact, after an acute treatment there was a decrease in linoleic acid, while after repeated administration of S 992 the pattern of FFA was changed, there being an increase in the unsaturated FFA. However, if the diet was rich in lipids, S 992 was unable to affect the composition of FFA. It is interesting to recall that previous unpublished data from this laboratory showed that

amphetamine was without effect in similar experimental conditions. Another metabolic difference between amphetamine and S 992 is represented by the capacity of the latter to increase blood glucose and liver glycogen in rats submitted to severe food restriction. This difference may not necessarily be related only to an intrinsic difference in activity between amphetamine and S 992, because some metabolic changes may be explained on the basis of the excitation and increased locomotor activity induced by amphetamine in contrast to the mild sedative action of S 992. The compound under study differs from amphetamine and even from fenfluramine because it does not increase water consumption during subacute treatment (Holm, Huus, Hopf, Nielsen, and Peterson, 1960; Shapiro and Freedman, 1957; Tormey and Lasagna, 1960). In this respect S 992 may serve as a useful tool to dissect and understand the multiple effects exerted by amphetamine. For instance, the effect of S 992 in decreasing body weight with respect to pair fed animals cannot be interpreted, as in the case of amphetamine, in relation to an increase in energy requirement because of the increased locomotor activity. It is suggested that S 992 may decrease body weight by changing the metabolic pattern, particularly with respect to lipids and carbohydrates. The available data do not permit us, however, to work out a precise hypothesis.

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TABLE III

Chronic administration of S 992 (20 days) to rats fed a high lipid diet

High lipid diet	Epididymal fat pads (g)	Plasma FFA (μEq/l)	Plasma glycerol (mg/100 ml)	Plasma phospho-lipids (g/l)	White adipose tissue FFA (μEq/g)	Brown adipose tissue FFA (μEq/g)	Blood glucose (mg/ 100 ml)	Liver glycogen (mg/g)	Liver triglycerides (mg/g)
controls (20)	3.03 ± 0.19	370 ± 49	2.15 ± 0.08	2.25 ± 0.13	3.37 ± 0.38	4.49 ± 0.94	70 ± 2	46.2 ± 4.5	29.8 ± 5.3
S 992, 50 mg/kg (20)	2.42 ± 0.09	400 ± 44	2.17 ± 0.15	2.60 ± 0.16	2.47 ± 0.25	3.21 ± 0.51	71 ± 2	44.1 ± 4.3	22.4 ± 4.9
Δ percent	↓20	—	—	—	↓27	↓28	—		↓29
P	$p = 0.01$	NS		NS	$p = 0.05$	NS		NS	$p = 0.10$

Number of animals appears in brackets.

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ADIPOKINETIC ACTION OF AMPHETAMINE—A STUDY IN THE BEAGLE DOG

Klaus Opitz

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Six years ago we published our observation that chlorphentermine-treated rats lost more weight than untreated control animals under equal nutritional conditions, that this weight loss was due to a depletion of fat stores, and that amphetamine, phentermine, and chlorphentermine cause an increase in plasma free fatty acid (FFA) concentration. We were not able to demonstrate a direct lipolytic action of amphetamines *in vitro* (Opitz and Loeser, 1963). Other authors confirmed that the administration of amphetamines is followed by an increase in circulating FFA in rat (Bizzi, Garattini and Veneroni, 1965; Fassina, 1964, 1966; Khan, Forney and Hughes, 1964), dog (Zsoter, Tom, Kraml and Dvornik, 1966), and man (Balasse and Thys, 1964; Pinter and Pattee, 1968). It is true that the concentration of FFA in blood plasma results from various factors, and increased plasma FFA concentrations do not necessarily indicate fat mobilization.

However, Pinter and Pattee (1968), with their kinetic studies in human volunteers, have recently produced strong evidence that amphetamine leads to an augmentation of the plasma FFA pool by increasing the rate of production of FFA, *i.e.*, by fat mobilization.

Several investigators studied the influence of amphetamine on isolated adipose tissue but they all found that amphetamines, unlike the catecholamines, are devoid of direct lipolytic activity (Fassina, 1966; Finger, Page and Feller, 1966; Finger and Feller, 1966; Mühlbachová, Wenke, Schusterová, Krčiková and Elisová, 1964). There is only one exception: Cucurachi, Strata, Zuliani, Castello and Cucurachi (1965) reported increased fatty acid release from fat pads incubated with amphetamine, but we were not able to reproduce their results.

Summing up, there is no doubt that amphetamines stimulate fat mobilization by some indirect mechanism, but this mechanism is not well understood. Do the amphetamines act by liberating norepinephrine from the

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MEDIATOR

N° du principe actif S. 992

N° expérimental du produit terminé 780 SE

NOTE DU FABRICANT

Annexe 1-12

Supplement to S.A. Medical Journal, 19 June 1971

SEMINAR ON FENFLURAMINE

AND

OBESITY

Nassau, Bahamas

22 - 26 February 1971

Supplement to the South African Medical Journal

Bylaag tot die Suid-Afrikaanse Mediese Tydskrif

Annexe 1-12

Supplement to S.A. Medical Journal, 19 June 1971

Seminar on Fenfluramine

and

Obesity

Seminar sponsored by Servier Laboratories (UK)

Supplement to S.A. Medical Journal, 19 June 1971

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Annexe 1-12

Byvoegsel tot die S.-A. Mediese Tydskrif, 19 Junie 1971

PROGRAMME

Monday 22 February

OPENING

MONSIEUR A. BOIS AND MR N. SANTER

SESSION I, PART 1

CHAIRMAN: PROFESSOR S. GARATTINI, MILAN

THE METABOLISM OF FENFLURAMINE IN MAN

Professor A. H. Beckett, London
The metabolism and distribution of fenfluramine and N-(2-benzoyloxyethyl)-norfenfluramine (J.P. 992) in man.

Mr D. B. Campbell, London
Absorption, distribution and metabolism of fenfluramine.

CENTRAL EFFECTS OF FENFLURAMINE IN MAN AND ANIMALS

Mr H. Kündig, Johannesburg
Studies in primates on the manifestations and treatment of fenfluramine intoxication.

Professor C. W. M. Wilson, Dublin
Effect of fenfluramine on alcohol consumption.

Professor Dr K. Opitz, Munster
Effect of p-chlorphenylalanine and fenfluramine on alcohol and saccharin consumption in rats.

Professor B. K. Anand, New Delhi
Effects of fenfluramine on the activity of feeding and satiety centres of hypothalamus.

Dr J. E. Blundell, Leeds
Hypothalamic model for investigating the central site of action of anorexic agents.

Dr P. Turner, London
Further studies on the human pharmacology of fenfluramine.

SESSION I, PART 2

CHAIRMAN: PROFESSOR C. W. M. WILSON, DUBLIN

COMPARISON OF SOME ANTI-OBESITY TREATMENTS IN ANIMALS

Professor S. Garattini, Milan
Pharmacological and metabolic studies on fenfluramine.

Professor J. Offermeier, Potchefstroom, South Africa
On the possible mechanisms of central stimulant actions of some phenylethylamine derivatives.

Dr G. L. S. Pawan, London
Comparative study of the effects of fenfluramine, S992, diethylpropion and phenformin on food intakes, body composition, blood lipids and oxygen uptake in mice.

COMPARISON OF SOME ANTI-OBESITY TREATMENTS IN MAN

Dr A. A. H. Lawson, Dunfermline and
Dr P. Roscoe, Edinburgh
Fenfluramine and metformin in the treatment of obesity.

Dr C. Wakes-Miller, Bedfordshire
Fifty patients treated with fenfluramine by a family doctor compared with fifty clients attending a 'beauty farm'.

Dr Hans ørskov, Dr Klaus Johansen and
Dr Johan Iversen, Aarhus
Effects of fenfluramine and other amphetamine derivatives on blood glucose, serum insulin, growth hormone and urinary insulin excretion.

Tuesday 23 February

SESSION II, PART 1

CHAIRMAN: DR P. TURNER, LONDON

SOME PERIPHERAL EFFECTS OF FENFLURAMINE IN ANIMALS

Dr Johan Iversen, Dr Hans ørskov and
Dr Klaus Johansen, Aarhus
Studies of the effect of fenfluramine on the secretion of immunoreactive insulin and glucagon from the isolated perfused canine pancreas.

Professor R. E. Moore, Dublin
The effect of fenfluramine on heat production in rats.

Professor N. Sapeika, Cape Town
The action of fenfluramine in reducing obesity: the inhibitory effect on certain enzymes.

Dr G. M. Kneebone, Adelaide
The non-anorectic aspects of fenfluramine hydrochloride at an experimental level.

SOME PERIPHERAL EFFECTS OF FENFLURAMINE IN MAN

Dr D. J. Galton, London
Effects of drugs on lipogenesis from glucose and palmitate in human adipose tissue.

Professor W. J. H. Butterfield and
Miss M. Whichelow, London
Peripheral metabolism in obesity: the effects of weight reduction by diet and fenfluramine.

Dr J. R. Turtle and
Dr J. A. Burgess, Sydney
The metabolic effects of fenfluramine:
1. Forearm perfusion and intravenous infusion in normal subjects.
2. Therapeutic value as a hypoglycaemic agent in diabetes mellitus.

Dr G. L. S. Pawan, London
Metabolic effects of S992 in man.

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SESSION II, PART 2

CHAIRMAN: PROFESSOR J. YUDKIN, LONDON

PERIPHERAL EFFECTS OF FENFLURAMINE IN THE CLINICAL SITUATION

Professor J. A. Strong, Edinburgh
Glucose tolerance and the metabolic response to exercise in obese patients treated with fenfluramine.

Dr V. K. Summers, Liverpool
Metabolic studies of fenfluramine with particular reference to fat-mobilizing substances.

Mr B. P. Bliss, London
The effect of fenfluramine on glucose tolerance, and lipid and lipoprotein levels in patients with peripheral arterial disease.

Dr P. H. W. Rayner, Birmingham
Fenfluramine in childhood obesity: clinical experience and effects of fenfluramine and weight loss on blood glucose, plasma insulin and plasma growth hormone response to oral glucose load.

Professor W. P. U. Jackson, Cape Town
Fenfluramine trials in a diabetes clinic.

Dr J. R. W. Dykes, Leeds
Effect of a low-calorie diet alone and with fenfluramine on the glucose tolerance and insulin secretion of maturity-onset diabetics and overweight non-diabetics.

Dr A. N. Chremos, Richmond, Va., USA
Body weight and blood lipid levels in obese subjects treated with fenfluramine.

Thursday 25 February

SESSION III, PART 1

CHAIRMAN: PROFESSOR J. A. STRONG, EDINBURGH

THE QUESTION OF DEPENDENCE

Dr H. S. Jones, Western Australia
Fenfluramine used as a substitute for methyl amphetamines and dexamphetamine in the treatment of dependence on these drugs.

Dr K. G. Götestam and
Professor L.-M. Gunne, Uppsala
Clinical evaluation of central stimulant effects of fenfluramine and AN. 448.

Dr S. A. Lewis, and Dr I. Oswald, Edinburgh
Fenfluramine: cerebral effects and dependence in chronic use.

SPECIAL PAPERS

Dr J. F. Munro, Edinburgh
Therapeutic starvation in obesity.

Dr J. W. Evans, Andover
Double-blind trial of fenfluramine as an aid to stop smoking.

Dr P. Ghalioungui, Kuwait
The respiratory quotient of patients on fenfluramine.

Dr C. M. Lewis, Cape Town
The acute effects of fenfluramine on coronary haemodynamics and myocardial energy metabolism in man.

SESSION III, PART 2

CHAIRMAN: PROFESSOR N. SAPEIKA, CAPE TOWN

WIDER APPLICATION IN CLINICAL MEDICINE

Dr R. Gaind, London
Psychological aspects in the aetiology and treatment of obesity.

Dr B. D. Hughes, Ashton-under-Lyne
Report on the use of Ponderax in mentally disturbed patients.

Dr F. J. Prime, London
An assessment of the value of anti-obesity treatment in a chest clinic.

Dr D. N. Golding, Harlow
Report on Ponderax trial to see if loss of weight relieves pain in arthritic weight-bearing joints.

Dr J. M. Court, London
A double-blind controlled trial of fenfluramine in children with obesity associated with reduced muscle activity.

Dr J. Lorber, Sheffield
The treatment of severe childhood obesity with fenfluramine: a controlled therapeutic trial.

Dr G. M. Kneebone, Adelaide
The non-anorectic effects of fenfluramine hydrochloride at a clinical level.

Friday 26 February

SESSION IV, PART 1

CHAIRMAN: PROFESSOR W. J. H. BUTTERFIELD, LONDON

WIDER APPLICATION IN CLINICAL MEDICINE

Dr J. V. G. Durnin and
Dr J. Womersley, Glasgow
The measurement of obesity and some comments on its treatment by fenfluramine with special reference to changes in metabolic rate and body composition.

Dr J. Runcie, Glasgow
A controlled trial of fenfluramine in obese patients following therapeutic starvation.

Dr F. J. Prime, London
Effects of fenfluramine on steroid induced obesity.

Dr J. P. Sedgwick, High Wycombe
A treatment for 'refractory obesity' in general practice.

Dr B. C. Sproule, Australia
Treatment of the grossly obese with a high dosage of fenfluramine.

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Professor F. O. Simpson, Dunedin
Use of fenfluramine in obese patients on antihypertensive therapy.

Professor J. Yudkin, and
Dr D. S. Miller, London
Dietary induced obesity and its treatment with fenfluramine and analogues.

SESSION IV, PART 2

CHAIRMAN: PROFESSOR A. H. BECKETT, LONDON

OPEN FORUM TO SUMMARIZE FINDINGS OF THE SEMINAR AND DISCUSS FUTURE RESEARCH

Dr J. V. G. A. Durnin, Glasgow
Definition of overweight and obesity.

Mr D. B. Campbell, Middlesex, Harrow
Signs and symptoms of fenfluramine overdosage and its treatment; the question of drug interaction.

Dr G. L. S. Pawan, London
The actions of fenfluramine on carbohydrate and lipid utilization—possible role of the drug in the treatment of diabetes.

Professor L.-M. Gunne and Dr A. Svanborg, Uppsala
Drug abuse: the problem of testing and control.

Dr J. C. Le Douarec, Neuilly-sur-Seine, France
The role of norfenfluramine in fenfluramine activity.

Professor B. K. Anand, New Delhi and
Dr J. E. Blundell, Leeds
An integrated theory involving the hypothalamus to explain the pharmacological effects of fenfluramine activity.

Professor S. Garattini, Milan
Absorption, distribution and metabolism of fenfluramine: species distribution.

Dr P. Turner, London
Intra- and inter-subject variations—the need for rationalization in experimental procedures.

Professor C. W. M. Wilson, Dublin
The relationship between *in vitro* and *in vivo* studies.

this institute. Three main points will be discussed as a continuation of studies already published:

1. Fenfluramine was measured by gas chromatographic procedure in the brain of normal and obese mice. The levels obtained are in agreement with the finding that fenfluramine exerts a more marked anorexic activity in obese than in normal mice. A metabolic interaction between amphetamine and fenfluramine was established and this may explain some pharmacological interactions observed between these two compounds.

2. Amphetamine and fenfluramine have been compared for their effect on the adrenergic system. Studies *in vitro* and *in vivo* have been carried out by stimulating chemically or electrically the sympathetic activity. The results are consistent with the hypothesis that the main difference between these two compounds is mostly quantitative, fenfluramine being much less stimulant than amphetamine.

Another aspect of the interaction of these drugs with the adrenergic system is their effect on the accumulation of homovanillic acid (HVA) in the striatum. While a resistance to the increase of HVA can be easily demonstated for amphetamine, it was not apparent for fenfluramine.

3. Amphetamine and fenfluramine show peculiar effects on lipid metabolism. They increase plasma glycerol and free fatty acids *in vivo* without showing a clear lipolytic effect on the adipose tissue. The two drugs decrease plasma and heart triglycerides without affecting liver triglycerides. The effect may be related to a decreased absorption of triglycerides present in the food because of the inhibition exerted by these drugs on gastric and intestinal motility.

DISCUSSION

Professor Offermeier: You were suggesting the possibilities of different side-effects of amphetamine and fenfluramine. Isn't it possible that the tolerance you get with amphetamine is the result of an enzyme-induction type of metabolism? It isn't necessarily a different type of action.
Garattini: Yes, we have the answer to that. We have measured the effect of amphetamine on the brain on two occasions and there was no difference in the brain function due to amphetamine. Furthermore, we tried to block the metabolism by using SKN-525 and even in a resistant animal—even by doubling the concentration of brain amphetamine—there was no effect.
Professor Moore: Three things, please. What was the environmental temperature of your tests? Room temperature?
Garattini: It was at room temperature. If you lower room temperature so that you don't get increase of body temperature from amphetamine, you still have the effect of the other tests.
Professor Moore: Did you do plasma glycerol levels in any of these?
Garattini: Yes.
Professor Moore: Does it match molecule to molecule?
Garattini: No, I would say that perhaps glycerol level is a little bit lower.
Dr Anderson: How chronic were your experiments?
Garattini: Eight days.
Dr Anderson: Do you know what happens after that?
Garattini: No, not yet. Because all of our experiments are not complete. Our experiments have been done only on rats and mice, in whom a long period of time is about 3 hours. We couldn't show any stimulation of lipolysis.
Dr Turtle: Have you incubated them for more than 90 minutes?
Garattini: Well, no. We have incubated them for 60 minutes.

Dr Svanborg: You have said that there may be a decrease in intestinal absorption of triglyceride. My question is: Do you think that this observation has some connection with the complication of diarrhoea and maybe the absorption of either compounds in the food?
Garattini: Well, I think your question is very interesting, because fenfluramine as well as amphetamine may react in different ways in the intestinal tract by decreasing the absorption of triglycerides, but one also has to consider, particularly with amphetamine, that there is an effect on the motility and an assimilatory effect. Furthermore, for fenfluramine there may be the complication of the release of serotonin which is very important in the intestines. The picture is quite complicated, and brings in several factors at the same time. I do not know which one is the most important.

ON THE POSSIBLE MECHANISMS OF CENTRAL STIMULANT ACTIONS OF SOME PHENYLETHYLAMINE DERIVATIVES

PROFESSOR J. OFFERMEIER AND B. POTGIETER, *Potchefstroom, South Africa*

The probable mechanisms involved in the central stimulant action (as measured by an increase in locomotor activity in mice and rats) were investigated for a number of phenylethylamine derivatives. Amphetamine, methylamphetamine, propylhexedrine, phentermine, mephentermine and p-choramphetamine probably produce their stimulant action by a release of catecholamines from neuronal extragranular pools since these compounds are inactive when the extragranular pools have been depleted by pre-treatment of the animals with a-methyl-p-tyrosine. The action of these compounds in pre-treated animals can be restored by treating the animals with the catecholamine precursor L-dopa 30 minutes before the experiment. The activity of the compounds mentioned is not decreased by pretreatment with reserpine, which is known to deplete the intraneuronal granular storage sites of catecholamines.

Chlorphentermine and diethylpropion are inactive after pretreatment with reserpine, but their activity is not affected by pretreatment with a-methyl-p-tyrosine. This indicates that chlorphentermine and diethylpropion probably produce an increase in locomotor activity by a release of catecholamines from neuronal granular pools.

Norfenfluramine, methylnorfenfluramine, fenfluramine, S992 and S1204 do not produce an increase in locomotor activity when given alone, but do increase locomotor activity in mice after pretreatment with an inhibitor of MAO. The increase in locomotor activity produced by S992 and S1204 only starts about 4 hours after administration, suggesting that neither S992 and S1204 is active as such, but that they are probably metabolized to active metabolites.

Norfenfluramine, methylnorfenfluramine and fenfluramine react the same way to a-methyl-p-tyrosine and reserpine pretreatment as amphetamine, suggesting that these fenfluramine derivatives produce an increase in locomotor activity (after inhibition of MAO) by liberating catecholamines from neuronal extragranular pools and not from neuronal granular pools.

Some evidence that some compounds presumably acting by releasing catecholamines from extragranular pools, may also release catecholamines from granular pools *in high doses*, was also presented.

A COMPARATIVE STUDY OF EFFECTS OF FENFLURAMINE, S992, DIETHYLPROPION AND PHENFORMIN ON FOOD INTAKE, BODY COMPOSITION, BLOOD LIPIDS AND OXYGEN UPTAKE IN MICE

DR. GASTON L. S. PAWAN, *London*

Several anorexigenic agents are known to produce weight loss in man and laboratory animals. This had been attributed to the reduction in food intake caused by these substances.

...ntly, it has been shown that amphetamine and some ... derivatives appear to have fat-mobilizing actions in ... conditions in addition to effects on food intake (Duhault ... Boulanger, 1966; Fassina, 1964; Santi and Fassina, 1964; ... and Pattee, 1968; Pawan, 1969). Moreover, it has been ...onstrated that fenfluramine-treated animals lose more ...weight and body fat than control animals on an identical ...e intake (Pawan, 1970).

...his paper reports some experiments on the effects of some ...ntly used 'anti-obesity' agents on food intake, blood ... oxygen consumption and body composition of mice. The ... used were fenfluramine, (S992) N-(2-benzoyloxyethyl)-...fluramine, diethylpropion and phenformin, administered ...intraperitoneal injection on alternative days, over a 42-day ..., to groups of adult male albino mice. The animals ...ved a normti well-balanced diet and water *ad libitum*. ...types of experiments were performed.

...*libitum* Feeding

...roups of mice (ten animals/group) were used. Each animal ...injected every other day with the following:
...trol group: 0·5 ml 0·9% aqueous sodium chloride
...fluramine group: 10 mg/kg.
... group: 40 mg/kg.
...ethylpropion group: 10 mg/kg.
...enformin group: 10 mg/kg.
...food consumption and body weight of each group of ...were measured daily. At the end of each week, each ...of animals was studied in the metabolic chamber ...Kekwick and Pawan, 1963) for 24-hour measure-...of oxygen uptake and respiratory quotient. At the end ...six-week period, the animals were killed by decapitation ...carcass composition and blood lipids analysed (Pawan, ...).

...*d Restriction*

...his experiment, the effects of intraperitoneal injection of ...ame doses of the drugs was studied in the same way, ...ept that the animals were given a restricted diet of well-...ed composition (60% of the normal daily food intake ...r group of 10 mice). Water was allowed *ad libitum*.

...ults

...*libitum* feeding, fenfluramine, S992, and diethylpro-...all produced a significant loss in body weight and a ...in food intake of the animals. Fenfluramine and ...ropion were the more effective. The rate of weight ...was lower during the first 3 weeks in the fenfluramine ...than in the diethylpropion group, but in the last 21 days ...was rapid in the former. The weight reducing effect of ...ropion tended to be absent in the last 3 weeks on the ...

...ramine, S992 and diethylpropion, all produced an ...in oxygen uptake and a fall in the RQ, which was ...nounced with fenfluramine. The effects of phenformin ...uptake were not significant.

...ty acids, free glycerol, and 'ketones' in the plasma ...ased by fenfluramine, S992, and by diethylpropion. ...formin effect on these parameters was very slight.

...analyses showed a significant reduction in body fat ...the animals which had received fenfluramine, S992 ...ylpropion.

...diet restricted to 60% of the normal daily intake of ...which all groups of mice readily consumed), the drugs ...greater losses in body weight than that of the control ...the same calorie intake. Fenfluramine was the most ...this respect, followed by diethylpropion. S992 ...more effective than phenformin.

...uptake of the control mice showed a typical and ...rgen response to the calorie restriction. The oxygen ...the fenfluramine and the diethylpropion groups ..., which in the case of the fenfluramine group ...throughout the 42 days, but in the diethylpropion ...to control values by the 28th day on the drug.

...alysis at the end of the experiment showed a ...body fat in the diethylpropion and fenfluramine ...the control group.

Conclusions

It would appear that the 'anti-obesity' agents used in the present experiments, exert effects on the metabolism of mice compatible with a fat-mobilizing and fat-catabolic action. These effects are not completely explained by a reduction in food intake of the animals.

DISCUSSION

Professor Garattini: Was food given throughout the day, or was it given only at a given period, and at which time was the drug given?

Pawan: The food was given daily at the same time, which was about 10.00 a.m., and the drug was injected in the afternoon, every other day.

Mr Miller: I understand Dr Pawan to say that in the first experiment at any rate, there was a change in food intake but an increase in oxygen consumption, which is very remarkable. Did you try and balance the calories?

Professor Moore: Can you tell us what was the temperature at which you measured the oxygen consumption, and did you measure them in groups of 10 altogether?

Pawan: 22°C.

Dr Svanborg: Do you think the figures could be explained only by a change in the food intake and maybe, as we heard earlier, triglyceride reabsorption? Do you really think that your figures indicate a direct catabolic effect, I mean, a direct effect on the lipolysis?

Pawan: Well, here we have a situation where the animals did consume all the diet. It was 60% of what they have normally, and we superimposed on this experimental set-up the various drugs, and we found these differences, so it implies that the drugs were producing something over and above the effects of calorie reduction.

Chairman: We have had three papers this afternoon dealing specifically with metabolism, and the effects of the drugs in the brain, and the interrelationships of the drugs. We could have a general question session on the effect of fenfluramine and other drugs on lipid and glucose metabolism. Professor Garattini, I am very interested in the effects of fenfluramine on triglyceride absorption.

Professor Butterfield: Is there any clinical evidence of an increased absorption of fats after fenfluramine?

Chairman: Following the first session, I think we all realized that a very great deal that has been done on the animals has considerable application to carbohydrate-fat metabolism, and the activity of the drug in human beings.

FENFLURAMINE AND METFORMIN IN THE TREATMENT OF OBESITY

DR A. A. H. LAWSON, *Dunfermline* AND DR P. ROSCOE, *Edinburgh*

A double-blind trial was conducted to compare the efficacy of fenfluramine (1-3-trifluoromethyl 2-ethyl aminopropane) and metformin (methylbiguanide HCl) at 2 dose levels in promoting weight reduction in a group of 34 women with simple polyphagic obesity. The effect of fenfluramine in a total daily dose of 80 mg was still evident even after 32 weeks on a reducing regimen and was free of important side-effects. Metformin in the dosage used was less effective and a total daily dose of 3·0 g produced unacceptable side-effects.

A further double-blind trial was conducted on 18 of these obese women after they had been on continuous dietary treatment for 48 weeks, to study the effect and suitability for long-term maintenance treatment of fenfluramine in a total daily

sulphonylurea alone, or a combination including biguanides in certain circumstances. The addition of a biguanide may achieve normoglycaemia in some patients who are inadequately controlled on diet and a sulphonylurea alone. Although they are frequently useful and satisfactory, the biguanides may cause nausea, anorexia and may contribute to the occasional appearance of lactic acidosis.

The present study has been undertaken to evaluate the effects of fenfluramine, a substituted amphetamine derivative, in the management of hyperglycaemia in diabetes mellitus. In short-term experiments, fenfluramine has been shown to increase glucose uptake by skeletal muscle and to accelerate the disappearance of glucose injected intravenously. There is no increase in blood lactate during fenfluramine administration and lactic acidosis has not been reported in patients who have been treated with fenfluramine for obesity. In view of the marked effect of fenfluramine on glucose uptake by muscle, the therapeutic efficacy of this drug has been assessed in maturity-onset diabetics who had been maintained with diet alone, or a combination of a diet plus sulphonylurea.

Patients and Methods

Nineteen patients were used in this study. All had maturity-onset diabetes mellitus on the basis of an abnormal oral glucose tolerance test using the criteria of the American Diabetes Association. Of the 19 patients, nine had been previously maintained on diet plus a sulphonylurea, but had achieved inadequate control of hyperglycaemia. Ten were maturity-onset diabetics presenting to the clinic for the first time. All patients were within 10% of the ideal weight for height and age. Patients outside this range were not included in the study. Four studies were undertaken:

1. One hundred gramme oral glucose tolerance tests were performed in 10 maturity-onset diabetics on presentation. In 9 patients, glucose tolerance tests were performed after three weeks on a supervised diet containing 25 - 30 cal/kg of ideal body-weight and 35 - 40% carbohydrate. These 9 patients were given fenfluramine 40 mg twice daily, 30 minutes before breakfast and the evening meal. After three months the glucose tolerance tests were repeated in 7 patients and also in 3 patients who had been maintained on diet alone.

2. Nine maturity-onset diabetics had been marginally controlled on diet and a sulphonylurea (tolbutamide 1 - 3 g daily or chlorpropamide 500 - 750 mg daily). An oral glucose tolerance test was performed whilst the stabilized dietary regime and former dose of tolbutamide were maintained. Subsequently, these patients were given fenfluramine 40 mg twice daily, 30 minutes before breakfast and the evening meal. After three months on fenfluramine, the oral glucose tolerance tests were repeated. During the period of fenfluramine therapy the dietary regime was not altered.

3. In 3 maturity-onset diabetics the acute effects of fenfluramine on glucose tolerance were evaluated. Two glucose tolerance tests were performed on each patient 24 hours apart. The second glucose tolerance test was preceded by an oral dose of 40 mg of fenfluramine 30 minutes before the test.

4. In 15 maturity-onset diabetics, 7 of whom had been maintained on sulphonylureas, blood glucose was estimated two hours after the patients had eaten their usual breakfast. This was then repeated on a different day when the same breakfast had been preceded by an oral dose of 40 mg of fenfluramine taken 30 minutes before the meal.

All oral glucose tolerance tests were performed with 100 g of glucose given as a 50% solution. Repeated blood samples were obtained from an indwelling venous cannula for the estimation of blood glucose and serum immunoreactive insulin. Glucose was measured by the alkaline ferricyanide method using an Auto-Analyzer and serum immunoreactive insulin was measured by a double antibody precipitation radioimmunoassay. Insulin secretion was expressed as the insulinogenic index, in which the area subtended by the insulin response curve was related to the corresponding glucose curve during a glucose tolerance test. Using this technique, an expression was obtained for the insulin response in terms of the glucose load.

DISCUSSION

Dr Galton: When you are measuring glucose uptake, into muscle using fenfluramine or insulin, or anything else, how do you make a correction for an increase of intercellular muscle space?

Professor Butterfield: I think the only way we can arrive at this is at the end of two and a half hours or so.

METABOLIC EFFECTS OF S992 IN MAN

DR GASTON L. S. PAWAN, *London*

The fenfluramine derivative, S992 (N-(2-benzoyloxy)-norfenfluramine), was shown by Duhault and Malen (1970) to produce an elevation in plasma free fatty acids and glycerol and a loss in body weight in rats. The LD50 of S992 in several animal species is higher than that of fenfluramine, and in addition, this substance has a greater lipid solubility than fenfluramine. For these reasons, it was considered worthwhile to investigate the effects of S992 in human subjects.

A preliminary trial was carried out on 5 subjects, 89 - 132% of ideal body weight while eating a normal diet, *ad libitum*. S992 was administered orally to each subject in the following daily dosage: week 1, 150 mg; week 2, 300 mg; week 3, 600 mg; week 4, 900 mg. At the end of the 4-week period on the drug, the subjects had lost a mean of more than 3 kg, but all five subjects reported increased sleepiness during the experiment with the higher doses.

A second study was made on the effects of oral S992 in 40 volunteers (aged 21 - 62 years, 10 men and 30 women, 88 - 157% ideal body weight) over a 6-week period. Attention was particularly focused on blood lipid changes, body weight, and side-effects. The experimental procedure was as follows: week 1, a control week; week 2, 150 mg/day; week 3, 300mg/day; week 4, 450 mg/day; week 5, 600 mg/day; and week 6, a final control week. During the experiment the subjects were weighed twice weekly, in the morning before breakfast, immediately after emptying the bladder. On the first and last days of each week, fasting blood samples were obtained in the morning after an overnight fast with the subjects at rest for analysis of blood plasma free fatty acids, free glycerol, triglycerides, ketones, cholesterol, total lipids, and glucose, by methods previously described (Pawan, 1969). Thirty of the volunteers completed the trial, 5 stopped the experiment for reasons unconnected with the drug, and 5 others discontinued the experiment as they felt unwell. In the group as a whole, the mean weight loss was 3·4 kg at the end of the experiment. Glucose, free fatty acids, glycerol, and triglycerides were not significantly altered, but ketones were elevated (mean 57%), and particularly with the 450 mg/day dose of S992, cholesterol levels were decreased. During the experiment the following subjective effects were reported by some of the volunteers (numbers in parentheses): dry mouth and thirst (2), depression (3), irritability (5), sleepiness (13), insomnia (1), reduction in cigarette consumption (7), reduction in alcohol consumption (5).

In 5 other subjects (2 normal and 3 obese) the effect of an intravenous infusion of S992 (150 mg over a 60-minute period) produced a slight increase in free fatty acids (+22%) and free glycerol (+18%) at 2 - 3 hours after the infusion in one normal and one obese subject, but induced no change in the other 3 subjects.

Further experiments are in progress to study the effects of different dose levels of S992, both orally and intravenously on metabolism of subjects on control diets and on constant diets, and a double-blind study is under way to evaluate the effects of the drug over several months, in a group of normal and a group of obese subjects.

DISCUSSION

Dr Silverstone: Did you attempt to assess the calorie intake at all during this study?

Pawan: Unfortunately, no. But with myself as subject, I

did attempt to eat roughly the same, but I certainly felt less hungry, so my calorie intake was reduced.

Professor Wilson: You proved a difference between female subjects and males, didn't you?

Pawan: It was not significant.

Professor Wilson: But wasn't there one female you talked about?

Pawan: Yes, bnt only one. In some other females, this did not happeh. I would rather not say anything definite about that yet.

Dr Oswald: May I ask about the side effects? Did the subjects that you were studying know that they were on increasing doses?

Pawan: They did know, yes.

Dr Oswald: What I am specially interested in is the timing of the course of subjective unpleasant effects, and not only while the drug is being given but before and after it has been withdrawn. Did you look for or receive reports of anything unpleasant in the week after the drug was stopped?

Pawan: I must say that we have no definite evidence that in the week after the drug was stopped there were any unpleasant effects.

GENERAL DISCUSSION

Chairman: I think we should discuss three things: The first is this word that Professor Jackson asked about—glycolyptic. Dr Silverstone raised the question of the anorectic action of fenfluramine, and I think we shall have to discuss this again, and finally there is the question of the base of this drug in the management of diabetics.

Professor Jackson: I think the question has been partially answered now. It appears that there is some sort of effect on glucose uptake, but maybe less effect if taken by mouth.

Chairman: Mr Santer, how did you first define the word glycolyptic. Do you feel that it needs perhaps some re-evaluation in the light of this?

Mr Santer: Well, I believe that the definition arose as we observed the effect of the glucose and lipid metabolisms. I still believe that we have a lot to learn on the subjects. I think that one of the interesting things that has been raised by a number of speakers is the time we spend in looking for these effects, and I believe that Dr Turtle's work demonstrated this, and I think some of the workers will possibly have to readjust their thinking on the methodology of the experimental work. Some of the data given this morning, and some that we shall see later in the week, will bear out that the definition is still valid, but it may require a little extension.

Chairman: The observation that weight loss did not occur or was not seen, does not of course mean that fenfluramine does not act in this way. It could mean that in fact when the patient does not respond by weight loss when on fenfluramine, then for some reason or other they do not show these metabolic effects. Professor Butterfield, what is your feeling on this?

Professor Butterfield: I must say that I am not quite sure what the word glycolyptic means, unless it means that when the drug has been given there are profound changes in lipid and glucose metabolism, which is what I suppose Neville meant by this term he has coined, but [illegible]. When we first started working, we knew that obese people were very badly taking up sugar in their peripheral tissues, and after they had lost weight that this improved, and this certainly improved after oral Ponderax. That is a change which is probably mediated through what I think Blundell called 'hoarding mechanism' on his rather nice model he put up yesterday morning. That is my view. I do not think there is any doubt that in fairly high doses in plasma water going into an isolated preparation, that something happens to sugar metabolism for a short time. I think that the $64 000 dollar question for me at this moment of time in this Congress is whether fenfluramine has this effect for a short time and norfenfluramine has the opposite action. It seems to me that that might explain the changes that Turtle shows with improved glucose assimilations soon after taking Ponderax by mouth and an impaired one later. So I think the necessary experimentations for me is perfusions of forearms with norfenfluramine to see whether that might account for Turtle's swingover, and perhaps even account for his fatty-acid release.

Dr Lawson: I was wondering whether your question was a semantic one, really. I wonder whether this is a word that we ought to use? It seems to me to have no sort of reasonable root in the Greek, and it seems to me that there is no point in adding medical jargon to what is already a very difficult subject by inventing a term that really has no exact meaning. I should want to refer to glycolysis and lypolysis.

Dr Anderson: I was just a bit worried about the term 'increased glucose utilization by muscle' I can conceive of a human being being loaded with calories and having to do something with these, but in the majority of us they are deposited as fat. Now, if a muscle is presented with more than its usual requirement of glucose, what does it do with it?

Professor Butterfield: At the end of a tolerance test in lean people, you will find that a lot of sugar has gone in and some lipid comes out. This has caused a certain amount of consternation amongst some of the lipid chemists, but we have repeatedly found in lean people with muscles at rest, an efflux of non-esterified fatty acids at the end of, or during, the glucose tolerance tests. Lipid efflux comes 15 minutes, or 15 - 30 minutes, after the peak glucose uptake. This may be what happens with the people who took fenfluramine, but I can't answer it.

Chairman: Professor Yudkin, we have not heard from you on this subject. Would you like to say anything on this?

Professor Yudkin: No, I don't think so. I find this extremely confusing. Like, I suppose, many of us here.

Dr Turtle: I am getting terribly worried about this situation. If David Galton's findings in adipose tissue and in the intestine and the liver, are correct we probably expect it to be so in muscles, so with glucose being taken up, it doesn't appear to be going to glycogen, and I just don't know where its going to. It can't just sit there. (Interjection from unknown: 'It could be burned'.) Well, is there any evidence that complete glucose oxydation of CO_2 is increased in the muscle?

Professor Butterfield: We do know in our preparations that O_2 consumption has gone up after weight reduction and whether or not it is associated with Ponderax.

Professor Moore: Some of Butterfield's points, of course, are difficult to interpret because of the lack of distinction between the deep and superficial sampling.

Miss Wichelow: I did not go into the details of our preparation, but our chemicals were always placed in deep veins and we were always satisfied throughout that any studies in which we were not quite satisfied, that we had, to the best of our knowledge, got the tip of our catheter right deep down in the muscle and were sampling dark venous blood.

Professor Butterfield: You obviously checked that the blood goes darker with 6 or 7 squeezes of the forearm.

Chairman: I think as pharmacologists we don't use therapeutic concentrations, and we have got to face that fact and we cannot, I think, go straight and extrapolate to therapeutic mechanisms of action from the concentrations that we use in our experiments. This does not mean to say that they are not important experiments. When we eventually learn how fenfluramine acts then we shall be able to explain its effects in pharmacological concentrations just as much as in therapeutic, and I think therefore that the effect on enzymes and fat cells are important experiments for us to do, but I don't think we should be particularly worried if we cannot, from those experiments, relate.

Dr Silverstone: There is a question of the appetite here. I was very interested when the original literature on fenfluramine was published, to note that it was, in its screening procedure, considered to be an appetite depressant drug in the same way as amphetamine. It has been quite clear that most workers when asked about it, or even upon hearing it, suggest that it has a direct appetite depressant effect. This to me is a most interesting comment. Now, Modell suggested not so long ago that all appetite depressants are appetite depressants entirely by virtue of their central stimulant activity. This is not so. I think fenfluramine could well prove the most useful tool in the unlocking of the appetite regulating mechanism in the hypothalamus, and I think that Dr Blundell has already begun to assess this work.

Chairman: Dr Sedgwick, I think, has some evidence that without dietary control, fenfluramine still produces a loss of weight.

Dr Sedgwick: One of the problems in general practice is getting people to stick to diets. I use a fairly high dosage of fenfluramine, with a step-by-step increase in the dose, and I see the patients regularly. In an effort to get them to reduce their weight, they were specifically asked not to diet (this is all in the paper I am reading on Friday). Now, this is not routine, but I have had, I think, 70 patients reporting and as they start to lose weight, which does take time, then one can start to encourage them to decrease their calorie intake.

Chairman: But do they decrease their calorie intake spontaneously as a result of this anorectic action, do you think?

Dr Sedgwick: I believe they do, although I only in fact take random checks, and call in at their houses at mealtimes uninvited and unexpected and see what they were eating. Certainly, most of them still seemed to eat plenty.

Dr Rainer: May I ask a very fundamental question. Do most of these patients overeat? I accept that the most generally accepted way to lose weight is to reduce one's calorie intake, but are we necessarily dealing with the same problem in obesity?

Professor Garattini: I think there is need to have more studies on balance of absorption and feeding and excretion because when we talk about food intake this may have no meaning if there is this absorption. Perhaps this is something which should be added to our material.

Dr Pawan: May I put in a plea for maintaining the metabolic aspects of fenfluramine. In our experience, at least in mice, given a 60% calorie diet, which the animals will eat well, fenfluramine-treated animals show a greater weight loss and fat loss than control animals eating an identical food intake, and this change cannot be explained as a result of decreased bowel absorption, so there must be some other effect.

Professor Yudkin: There is no experiment with any sort of drug in ordinary people that does not have some degree of absorption. Is there any evidence whatever that there is a diminished utilization, that is to say, a diminished faecal excretion?

Professor Garattini: Well, we just don't know.

Chairman: Well, this could be the first drug to show this. In other words, we ought to look for it.

Professor Jackson: Surely, it has been shown quite clearly that one of the effects of fenfluramine is to reduce the carbohydrate intake in the intestine.

Dr Blundell: I would just like to make one comment on the methodology so far, I have been absolutely amazed at the scarcity of those responsible for presenting this subject. I feel it is dangerous to draw conclusions from a single dosage.

Chairman: I think that this is very important. Now, I would like to pass on if we may to the question of the uses of fenfluramine in diabetes. Dr Turtle, you were suggesting that perhaps fenfluramine might be suitable as an alternative to diguanide.

Dr Turtle: Well, all we have done is to test a small group of untreated diabetics several hours after treating them with fenfluramine, and it does improve the K value once you have got lipolysis occurring.

Chairman: Professor Butterfield, would you like to comment on the use of fenfluramine in diabetes?

Professor Butterfield: Well, we don't have very much experience, but I suspect that it is going to be used more and more as time goes on, partly due to Chris Flint in America putting a great deal of propaganda about on the dangers of certain oral antidiabetics. The other part of that study which makes me think that fenfluramine will be used a lot is that most of the American diabetics in that study were very much overweight. Now when oral treatment for diabetes appeared on the scene, everybody, Derek Dunlop, Duncan, ourselves, every diabetologist, wrote two things: We must not use these drugs instead of losing weight and dieting, and we must wait 10 or 15 years to see if they influence the course of diabetic complications, and in the intervening 15 years, very, very few patients are really successfully and actively dieted when they are really overweight diabetics, and instead, after a period of a month or two, in general, people put them on one or other of the oral preparations. I would have thought that in the present state of knowledge, there would be a

strong case for people trying to get their diabetics to lose weight and if they fail on the diet then I think they will have their weight stripped off them using fenfluramine.

Mr Bliss: In answer to the question on K values in a small number, only about 15 cases, over six weeks of oral therapy, we have shown an increase in the K value.

Professor Wilson: We have been talking about this in relation to oral agents, and perhaps we should discuss this later, but I should like to enquire if from Dr Turtle's work whether there is any justification in using fenfluramine when the patients can be treated with insulin?

Dr Turtle: I suspect that we may have some hazards, particularly in patients who are prone to ketosis because if we put up their ketones any more, we may increase their instability.

Dr Dykes: I have got some evidence and experience on giving fenfluramine to diabetics, and I shall present some evidence this afternoon mainly involving one particular group of maturity-onset diabetics.

Dr Sedgwick: Going back to the anorectic activity, I wondered if other people have noticed if it is common in their patients that they have put on fenfluramine, in the first week or so, that they complain of increased appetite? In fact, this is not an uncommon complaint in the first week or ten days.

Dr Darey: Our experience is somewhat to the contrary. In about 10% of the patients we found that the appetite is increased in the first 2 or 3 days, but in the majority of them—about 50%—the appetite goes down, and by about the 5th or 6th day, their intake of food drops down to about 40%.

Professor Sapeika: In view of what Dr Turtle mentioned, that fenfluramine does not cause an increase in lactic release, I am just wondering whether fenfluramine might possibly be useful in the management of patients with lactic acidoses, including diabetics.

Chairman: We look forward to hearing about experiments with specific reference to the anorectic action of fenfluramine over long periods of time.

SESSION II PART 2

TUESDAY AFTERNOON

CHAIRMAN: PROFESSOR J. YUDKIN

GLUCOSE TOLERANCE AND THE METABOLIC RESPONSE TO EXERCISE IN OBESE PATIENTS TREATED WITH FENFLURAMINE

BARBARA K. BROCKIE, PATRICIA BROWN, NASR-EL-DIN AHMED, D. SHIRLING AND PROFESSOR J. A. STRONG, *Edinburgh*

The studies to be described were prompted by two sets of observations. The first of these by Pawan (1969) was concerned with the effect of fenfluramine on raising the circulating levels of NEFA. The other, by Butterfield and Whichelow (1968), indicated that fenfluramine could be shown to increase the uptake of glucose by muscle, and by inference, to divert glucose away from the fat depots. This would then serve to reverse the process occurring in obesity, where glucose is stored in excess as fat in these depots.

The data to be presented will be confined to 5 obese patients. They were aged between 21 and 36 years, and were overweight to an extent varying between 157% and 209%. Their thyroid function was normal, and their adrenocortical function, as judged by plasma 11-OHCS levels and cortisol secretion rates was normal.

On the day following admission to the metabolic ward, where the patients remained throughout the period of study, a glucose tolerance test (GTT) was carried out, with the intention of confirming that the patient's carbohydrate metabolism was normal. For the next two weeks the patient was maintained on a diet which provided 2 500 kcal *per diem*. Three of the patients were shown by energy balance studies to be expending as much as 4 400 kcal per diem. The diet was a conventional mixture of carbohydrate, protein and fat. Throughout the period of study, the patients were encouraged to take at least 2 hours' exercise walking daily.

At the end of 7 days a further GTT extended to 6 hours, was undertaken. On the following day, a 2 hours' walk was undertaken on a treadmill under close observation. After periods of walking for 20 minutes, they were allowed to rest for 5 minutes, during which time a sample of blood was taken, and a sample of expired air for alveolar acetone.

In the second week of the study, while the diet remained unchanged, fenfluramine was given in a dose of 40 mg 4 times daily.

At the end of the second week of the study, a further extended GTT and a similar exercise study were undertaken. For the third week, fenfluramine therapy continued at the same dose of 40 mg 4 times daily, and the diet was reduced to 800 kcal daily. At the end of this third week, the extended GTT and exercise study were repeated once more.

In those extended GTTs, after the administration of an oral dose of 50 g of glucose, blood was taken at intervals of 30 minutes for 3 hours, and thereafter hourly until 6 hours had elapsed. The mean blood level of glucose in 5 subjects was significantly raised at 1 hr, 2½ hr, and at 3 hr during the period when fenfluramine was being given. This effect did not appear to be influenced by the differences which might have arisen on account of the caloric content of the diet.

The plasma insulin concentrations found in the course of each of the GTTs did not differ significantly when the three regimens are compared with each other.

Likewise the values for plasma NEFA concentration showed no difference in the readings obtained throughout the extended GTTs, when the 3 regimens were compared.

The plasma glycerol readings obtained showed a very wide range of response with the GTTs, but the mean figures noted did not differ significantly between the 3 regimens.

As regards plasma HGH readings, the readings obtained were low throughout with each of the 3 regimens studied, and no significant differences were found.

In the exercise studies, after walking for 20 minutes on the treadmill at approximately 3 mph the patient rested for 5 minutes, during which a sample of blood was taken, as well as a sample of alveolar air for estimation of acetone. At the end of 6 periods of exercise of 20 minutes each, a rest was taken for 2 hours, and final samples were then taken. There was no significant change in the blood glucose concentrations throughout the period of study on each of the 3 regimens, nor in the concentration of plasma insulin throughout this period of the investigation.

Plasma NEFA concentrations were noted to rise consistently while the exercise continued, and fell again during the final period of rest. Concentrations of plasma glycerol were much more consistent during exercise than they had been during the glucose tolerance tests, but there was no statistical difference in the plasma concentrations of NEFA or glycerol within each of the 3 periods of study.

Plasma HGH concentrations, by contrast, showed striking increments with exercise, and the differences between the mean values found on the diet of 2 500 kcal, and the same diet when fenfluramine was added, were statistically significant at 1½, 2½, and 4½ hrs after the start of the period of exercise. It is striking that when the dietary intake was reduced, and with continuing treatment with fenfluramine, the values obtained reverted towards those noted initially.

In general, the observations on alveolar acetone concentrations indicated that the main differences were to be found between the full diet and the reducing diet, while there was

SESSION I PART 1

MONDAY MORNING

CHAIRMAN: PROFESSOR S. GARATTINI

THE METABOLISM AND DISTRIBUTION OF FENFLURAMINE AND N-(2-BENZOYLOXYETHYL) NORFENFLURAMINE (J.P.992) IN MAN

PROFESSOR A. H. BECKETT, *London*

Fenfluramine is de-ethylated to norfenfluramine in man; the drug and its metabolites are re-absorbed from urine in the kidney tubules under normal conditions and thus fluctuations in their rates of excretion occur as the pH of the urine fluctuates. Gas chromatographic techniques have facilitated the analysis of the drug and its metabolites in biological fluids.

When the urine is kept acidic at 4·8 - 5·0 pH by the administration of ammonium chloride, smooth curves of rate of excretion of the drug and its metabolites plotted against time are obtained, and under these conditions there is a direct relationship between plasma concentrations and rates of excretion. Also it is then possible to study the absorption, metabolism and excretion of fenfluramine, using a biological model.

Oxidation of J.P.992 N-(2-benzoyloxyethyl)norfenfluramine in urine by alkaline $KMnO_4$ to m-trifluorobenzoic acid has been used to give a quantitative assay of the drug and its main metabolites. The acid is extracted into ether and converted into its methyl ester with diazomethane which is then analysed by gas-liquid chromatography.

J.P.992 in man is metabolized into N-2-hydroxynorfenfluramine which is excreted as such and as the sulphate and glucuronide, and to norfenfluramine. A further water-soluble metabolite (metabolite A) which yields norfenfluramine upon treatment with zinc and hydrochloric acid is also present in the urine. Another metabolite (metabolite B) which accounts for approximately 20 - 30% of the drug can be extracted into ether from the urine.

No unchanged drug either with intact structure or the rearranged product which is produced in alkaline solution was recovered in the urine. The above bases were determined by gas-liquid chromatography.

Under conditions of acidic urine in man, metabolites with the intact m-trifluoromethylbenzyl moiety equivalent to 85 - 100% of the administered dose were excreted in the urine. Peak levels of these metabolites (total) were obtained 1 - 2 hours after the oral dose and then the rate of their excretion fell exponentially. The drug, as indicated by total m-trifluoromethylbenzyl moiety had a very short biological half-life (approx. 2 hours).

The metabolite of J.P.992, norfenfluramine, is extensively metabolized in man, as is the metabolite N-2-hydroxyethylnorfenfluramine.

The above results indicate that J.P.992 is absorbed quickly and completely from the gastro-intestinal tract and is then metabolized quickly and extensively to give products which are excreted quickly via the kidney.

The Effect of Mono N Substitution on the Metabolism and Excretion of Norfenfluramine

Methyl substitution has little effect on the excretion of the unchanged drug; only small amounts of norfenfluramine, the metabolites, are excreted. The introduction of the ethyl group reduces the amount of unchanged drug excreted but leads to much more norfenfluramine than in the case of methyl substitution. The introduction of a terminal OH group in the ethyl group leads to extensive metabolism of the compound so that a negligible amount of unchanged drug and norfenfluramine are excreted. Benzylation of the terminal OH group also leads to extensive metabolism of the drug so that no unchanged drug is excreted and only very small amounts of N-hydroxyethylnorfenfluramine and norfenfluramine.

DISCUSSION

Professor Wilson: Has anybody examined the effects of circadian rhythm on drug metabolism in the human body?

Beckett: No.

Professor Wilson: At what time of day was the drug administered?

Beckett: Always at 8.00 a.m. following an overnight fast.

Dr Turner: Some of the experimental points were not very close to the computer-calculated lines, and how did speaker actually assess the closeness of the fit of the points to the line?

Beckett: For fenfluramine this can be predicted very accurately from the computer but for norfenfluramine the excretion was volume-dependent.

Professor Offermeier: Is speaker aware of the problem of giving an isomer mixture?

Beckett: Yes, with ethylamphetamine there was a difference in the metabolism of the plus and minus isomers but this was not present with fenfluramine, presumably due to the transferral methyl substitution.

Professor Moore: Had the renal flow been examined, due to the great variation as a result of various factors such as meals and exercise?

Professor Butterfield: Does anybody know in which tissue or tissues does de-alkalation occur?

Professors Beckett and Garattini: Primarily in the liver.

Dr Turner: Had anybody investigated the protein binding of fenfluramine?

Mr Campbell: Yes, by equilibrium dialysis. For fenfluramine it was 32% and for norfenfluramine 16%, but as this was a loose binding it would not interfere with kinetics.

Mr Kündig: How did Professor Beckett control the urine pH and within what range?

Beckett: Normally with ammonium chloride, holding it at 4·8—5·0, but if the subjects experienced difficulty with ammonium chloride, methionine was added and if the urine flow was minimal a diuretic sometimes had to be added.

ABSORPTION, DISTRIBUTION AND METABOLISM OF FENFLURAMINE

MR D. B. CAMPBELL, *London*

This study of the blood and urine levels of fenfluramine and norfenfluramine show their similarity to other lipid-soluble drugs which are mainly eliminated from the body metabolically, as there appear to be subject variations in their rates of biotransformation. This becomes clinically important after a regular dosage regimen with differences in the rate of accumulation and magnitude of plateau plasma levels. Side-effects attributed to 'Ponderax', such as diarrhoea, headache, and drowsiness may be a result of elevated levels of fenfluramine or norfenfluramine, in a few subjects with a slow drug metabolism. The role of the metabolite norfenfluramine, in the therapeutic action of 'Ponderax' has not as yet been assessed and although it may not necessarily be the pharmacologically active substance it may contribute to the overall metabolic changes seen in patients treated with this drug. Certainly this work has demonstrated that the magnitude of the concentrations of norfenfluramine are comparable to those of fenfluramine at the steady-state level.

The ability to predict plateau drug levels in subjects from simple kinetic data has far-reaching possibilities and perhaps when further work has been conducted to correlate plasma fenfluramine and norfenfluramine concentrations with the degree of weight loss, dosage regimens can be tailor-made to suit the patients' drug metabolism and weight.

DISCUSSION

Dr Anderson: Did you test sufficient subjects to be able to decide a bimodal or trimodal response which would speak for a pharmacogenetic action here?
Campbell: No.
Professor Beckett: There are no examples of bimodal distribution for de-alkalation, but these are known for hydroxylation processes.
Dr Prime: Is there a correlation between subjective effects and high blood levels?
Campbell: In the few subjects examined, yes, it seemed to be so.
Dr Roscoe: Had he noticed any difference in the half-lives of patients who were young or old in cases of overdose?
Campbell: In the two children investigated the half-lives were shorter.

STUDIES IN PRIMATES ON THE MANIFESTATIONS AND TREATMENT OF FENFLURAMINE INTOXICATION

MR H. KÜNDIG, *Johannesburg, South Africa*

During the past few years a number of instances of fenfluramine poisoning in children and adults have been reported. These case reports stimulated the present study, the objective of which was to find an effective and safe treatment. Experiments were undertaken using mainly unanaesthetized and anaesthetized primates (vervet monkeys and baboons—Papio ursinus) to attempt to elucidate the possible mechanism(s) responsible for the manifestations described in the literature.

Fenfluramine was administered parenterally and only very large doses (50 mg/kg or more i.m. or s.c.) proved to be lethal. (This is 50 - 80 times the recommended therapeutic *oral* dose.) It was found that even after large doses (25 - 35 mg/kg) the animals recovered uneventfully within 24 - 48 hours, often exhibiting a residual tranquillization.

The animals appeared heavily sedated and in a drunken-like stupor during the acute intoxication phase. Convulsions were readily precipitated by excessive stimulation (noise, disturbance, etc.) A noteworthy phenomenon observed in all primates intoxicated with fenfluramine was the distinct 'taming' effect, i.e. the ease with which the animals could be handled, suggesting that the tranquillization was of the major type. Both central nervous system stimulant (as exhibited by tremor and clonic-tonic convulsion) and depressant (sedation and loss of righting reflexes) effects were observed. The central nervous system stimulation observed may, however, be due to inhibition of inhibitory mechanisms, as in the case of pentylenetetrazole. After lethal doses (more than 50 mg/kg s.c. or i.m.) the onset of intoxication and pattern of symptoms were little changed, except that the symptoms were more intense. Death occurred in these latter animals after 90 - 240 minutes (largely dependent on the dose) during repeated clonic-tonic convulsions with respiratory impairment.

The central nervous system effects were probably partially or entirely responsible for the effects observed on the cardiovascular system in anaesthetized animals, namely, the alteration of the P-R and Q-R-S complexes or severe ventricular arrhythmias after very large lethal doses. These arrhythmias were usually associated with a simultaneous respiratory arrest, and may

DISCUSSION

Professor Anand: Could the taming effect be ascribed to sedation?
Kündig: The small doses used were given to animals already anaesthetized.

THE EFFECT OF FENFLURAMINE ON ALCOHOL CONSUMPTION

PROFESSOR C. W. M. WILSON, *Dublin*

The fact that fenfluramine promotes the uptake and metabolism of glucose in cells and influences appetite suggested that it might also affect alcohol consumption and metabolism. An investigation has accordingly been carried out to investigate the effect of 2 doses of fenfluramine on the consumption of various concentrations of alcohol presented to rats with a simultaneous choice of water. Male rats were divided into 2 sets of 4 groups each of 5 animals. The rats were caged individually and the experiment was conducted over three successive time periods of 12 days each. Three of the groups in each set received water and 4, 6 or 8% alcohol and the fourth set received water in each vessel in the cages. During the first period all the rats received intraperitoneal saline daily. During the second period, the animals in the first set received 20 mg fenfluramine per kg daily, and those in the second set received 40 mg/kg fenfluramine daily, in place of the saline. During the third period all the rats received saline by intraperitoneal injection. Daily fluid consumption by each rat was recorded.

There was no significant difference in the water consumption by the control group, which received two containers of water in their cages, during the course of the experiment. The rats preferentially consumed 6% alcohol. Those receiving 4% alcohol drank the second largest volumes, and the rats to whom 8% alcohol was administered drank less of this mixture than the control rats to whom water alone was given. Both doses of fenfluramine caused a significant reduction in consumption of 4% alcohol from days 18 - 22 during the second period. Both doses of fenfluramine caused a significant reduction in consumption of 6% alcohol from days 18 - 24 during the second period. This effect continued during the first 4 days of the third period in those which had received 40 mg fenfluramine, but only for the first 2 days in the rats which had received 20 mg. Neither dose of fenfluramine had significant effects on the consumption of 8% alcohol.

It can be concluded that fenfluramine significantly reduces the consumption of alcohol in rats, but this effect is related to the concentration of alcohol which is being consumed, and to the dose of fenfluramine administered. In rats a dose of 20 mg/kg fenfluramine significantly reduces consumption of alcohol at the preferred concentration.

Experiments are being carried out to discover whether this is a metabolic or centrally mediated action of fenfluramine in rats. Initial results suggest that it is centrally mediated as has been shown to be the case with metronidazole.

EFFECT OF P-CHLOROPHENYLALANINE AND FENFLURAMINE ON ALCOHOL AND SACCHARIN CONSUMPTION IN RATS

PROFESSOR K. OPITZ, *Munster*

The observation of Myers and Veale (1968) that alcohol preference in the rat is greatly reduced by p-chlorophenylalanine (pCPA) led us to the finding that fenfluramine which also lowers

visable to give fenfluramine intermittently. Previous experiences have shown that in spite of millions of patient-doses, with apparent lack of serious side-effects, there still remains the possibility of ultimate long-term toxicity.

Mr Santer: Servier do most carefully keep records and obtain all available information as to the use of fenfluramine in all countries where it is marketed. In spite of thousands of tablets dispensed, there have been no reports of abuse or of dependence. Even amphetamine addicts who have taken fenfluramine because of its chemical similarity, have not become addicted to fenfluramine, nor have they experienced any of the amphetamine-induced sensations.

Professor Wilson: We will now have the opportunity of looking at S992 prospectively.

THE ROLE OF NORFENFLURAMINE IN FENFLURAMINE ACTIVITY

DR J. C. LE DOUAREC

We have had the privilege 10 years ago to be among the first few pharmacologists having carried out the initial investigations on trifluoromethyl substituted phenethylamines. We very soon became extremely interested in the unique properties of these new compounds.

In fact the CF^3 group induced a dissociation between the stimulant and anorectic properties of the amphetamines. In the first extensive pharmacological report presented in 1962, we emphasized the differences between the fluorine substitution which increased the stimulant effect and the CF^3 substitution which affected oppositely the basic CNS properties of amphetamines. The first compounds synthesized were primary amines substituted on the benzene ring with CF^3 in different positions o, m, n. Norfenfluramine was among them.

Norfenfluramine is more *toxic* than fenfluramine in the mouse, in standard conditions. Norfenfluramine is as an *anorectic* as active as amphetamines in the rat and twice less active in the dog. Fenfluramine in this respect is twice less active in the cat and 3 times in the dog. The *hypertensive* effect of norfenfluramine is comparatively less than those of amphetamines—one half in the rat, 10 times in the dog—but fenfluramine is still less potent on the blood pressure, between 1/5 and 1/10 in the rat and one half in the dog.

There are only quantitative differences between the two compounds, they only differ in their level of activity on different systems. Fenfluramine a number of times is less active than norfenfluramine. Norfenfluramine is certainly involved in the pharmacological effect of fenfluramine since we have evidence that it is its major active metabolite in animal and in man as well. May I add that norfenfluramine was discarded years ago from clinical trials in France because of prominent side-effects, namely nausea, vomiting, diarrhoea and dizziness. Thus norfenfluramine may be responsible for some side-effects of fenfluramine in man.

DISCUSSION

Professor Butterfield: Is there any conversion of norfenfluramine into fenfluramine, as there is conversion of fenfluramine to norfenfluramine?

Le Douarec: There is a difference in gut flora in different parts of the world due to national diets, and this can have an effect on the incidence of diarrhoea caused by norfenfluramine.

Mr Santer: It may be of interest to note that JP.992, the methyl-ethyl derivative of fenfluramine does not appear to produce norfenfluramine.

Dr Blythe: Is there any difference in the half-lives of norfenfluramine and fenfluramine?

Le Douarec: No.

Mr Kündig: How much fenfluramine is converted into norfenfluramine?

Le Douarec: There is a great variation, and under normal circumstances about one-third of the fenfluramine in the body exists in the form of norfenfluramine, but one cannot be more precise than that.

Dr Blundell: Is there a common metabolite of amphetamine and fenfluramine?

Le Douarec: No. There are no common metabolites, but there are common metabolic pathways for fenfluramine and amphetamine. The important point is that the CF^3 radical of fenfluramine is not split off with a resultant conversion to amphetamine or any of its metabolites.

Mr Santer: The results of work done in Prof. Beckett's laboratory proved that there were no alterations in fenfluramine-norfenfluramine ratio after repeated doses for six months.

Le Douarec: That is correct, and after prolonged use of fenfluramine the administration could be stopped and restarted without any change in the metabolic pathways.

Professor Opitz: Is there any effect on the pulmonary blood pressure in humans or animals?

Le Douarec: In animals there is evidence of pulmonary hypertension, but the clinical work stopped years ago, and we have no data.

Professor Garattini: In statistical terms we must realize that although in a clinical trial with about 1 000 patients only one or two withdrawal incidences may occur; this would mean that millions of users may eventually produce hundreds of thousands of cases of withdrawal symptoms. In other words, continued monitoring is essential.

AN INTEGRATED THEORY INVOLVING THE HYPOTHALAMUS TO EXPLAIN THE PHARMACOLOGICAL EFFECTS OF FENFLURAMINE

PROFESSOR B. K. ANAND AND DR J. E. BLUNDELL

In monkeys and cats we observed the following two types of electrophysiological and behavioural changes, depending upon the dosage of fenfluramine used: Smaller dosages of fenfluramine result in 'specific' changes restricted to the hypothalamic satiety and feeding centres. The activity of the satiety centre increases with a corresponding inhibition of the feeding centre, while no changes are observed in the rest of the hypothalamus and the adjoining areas of the brain. This is also accompanied by anorexia which appears to have some relation to increased level of glucose utilization.

When relatively larger dosages of fenfluramine are used, or when fenfluramine has been used continuously for a few days even in smaller dosages, there is a generalized inhibitory effect on the hypothalamic regions, which also spreads to the other adjoining areas of the brain. This is accompanied by drowsiness. It is not clear how fenfluramine produces its generalized inhibitory effects.

Drives from the Hypothalamus

In various presentations clinical observations have been made which may be due to influencing the 'drives' which result from the activities of certain specific areas in the hypothalamus.

Anorexia. This results from the 'specific' effects of the drug in increasing the excitability of the satiety centre and inhibiting the feeding centre, thus inhibiting the feeding (hunger) drive.

Thirst. In none of the presentations made at this conference has any mention been made concerning the effects of fen-

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Chronic Anorexic and Behavioural Effects of the Fenfluramine Derivative SE 780* in Rats

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Abstract. The behavioural and anorexic effects of the fenfluramine derivative "SE 780" in rats were studied after chronic administration over 35 days. Behavioural effects of the compound were assessed by "time sampling" behavioural categorisation, on days 1, 14 and 28 of administration. An initial sedative effect observed after acute administration was absent on days 14 and 28 of observation, when the drug had no behavioural effects at all. The anorexic properties of the drug were investigated in two ways. Firstly, by measuring daily body weights; and secondly by measuring intake of food over a 2 h period on observation days. The drug appeared to be a highly potent anorexiant in that tolerance to its effects built up very slowly. It is suggested that SE 780 may be an anorexic agent which is superior to Fenfluramine in two ways; firstly, it lacks stimulant properties after chronic administration, and secondly it is active over longer periods of time; as such it merits further study in humans.

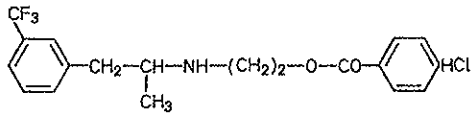
Key words: Anorexia — Time Sampling — Fenfluramine — SE 780.

Introduction

Most contemporary anorexiants are derived from a phenylethylamine base and possess two major therapeutic limitations. Firstly, they are usually C. N. S. stimulants and potentially addictive, and secondly tolerance to their anorexic effects is established very quickly. Fenfluramine is generally considered to be the anorexiant of choice, in that it has minimal amphetamine-like properties. Previous papers from this laboratory have reviewed the evidence for C. N. S. stimulant effects of fenfluramine (Taylor *et al.*, 1973; Goudie and Taylor, 1973). It is clear that Fenfluramine may possess C. N. S. stimulant properties, which differ from those of other phenylethylamines. The present paper reports on the pharmacologic properties of "SE 780", a novel fenfluramine derivative which is lacking in stimulant properties in rats, and which is an active anorexic agent for a longer period of time than other phenylethyl amines.

* This compound has also been referred to as "S 992".

The structure of SE 780 is as below:



Methods

Subjects were 24 male hooded rats weighing between 200 and 250 g at the start of the experiment. They were randomly divided into three groups: those receiving 3 and 9 mg/kg I. P. of SE 780 suspended in Tween 80 and sterile water, and those receiving injections of the control medium. They were adapted for a week to a 22 h food deprivation schedule and always injected 30 min prior to food access. Observations of exploration in an open field were made on days 1, 14 and 28 of chronic administration, 30 min post injection. A "time sampling" procedure of behavioural categorisation was used, with hierarchically arranged categories in the order Rearing, Walking, Sniffing, Grooming and Immobility. Each subject was observed every 2.5 sec for 100 observations. The procedure and rationale behind its use was essentially identical to that described in Taylor *et al.* (1971, 1973) and Goudie and Taylor (1973). In addition, food intake was measured for individual subjects on observation days.

Results

Fig. 1 A shows the cumulative sum of the daily differences between the mean body weights of the treated groups and that of controls. Tolerance to the effects of the drug on body weight appear around Days 20 and 30 of chronic administration for the low and high doses

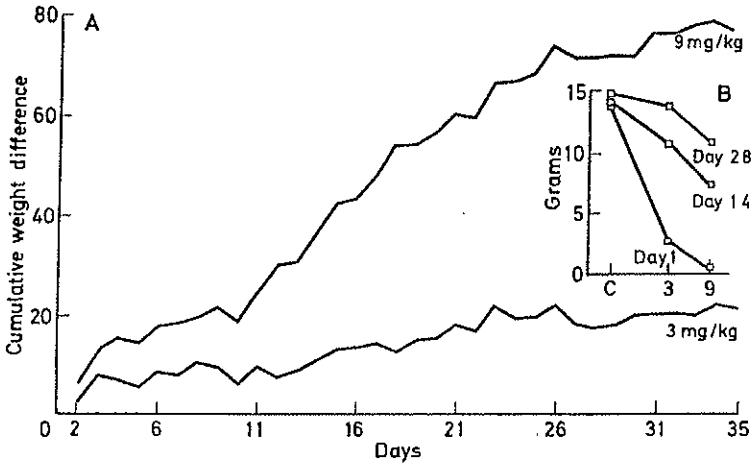


Fig. 1. (A) Cumulative sum of the daily differences, in g, between mean body weights of subjects receiving 3 and 9 mg per kg of SE 780, and that of controls. (B) Mean amounts of food eaten on days 1, 14 and 28 of chronic administration for controls (*C*), and subjects receiving 3 and 9 mg per kg of SE 780

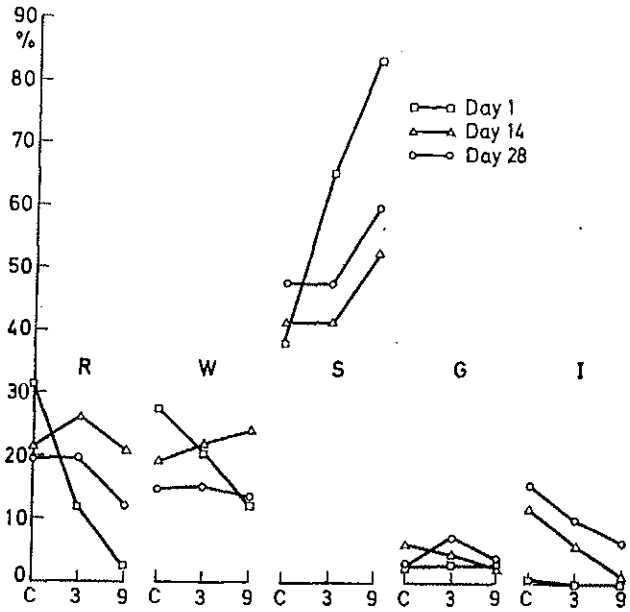


Fig. 2. Mean percentage incidence of Rearing (*R*), walking (*W*); Sniffing (*S*); Grooming (*G*) and Immobility (*I*) after the 1st, 14th and 28th day of chronic administration of control medium (*C*); 3 mg per kg (3) and 9 mg per kg (9) SE 780

respectively. Fig. 1 B shows the mean amounts eaten on observation days and shows that *even* on the 28th day of administration SE 780 still exerts a potent anorexic effect, at the 9 mg/kg dose. However, considered together the data presented in Fig. 1 A and 1 B demonstrate the gradual progressive development of tolerance.

Behavioural observations after acute administration indicated a significant sedative effect (Fig. 2) in that the incidences of rearing and walking were reduced at very high levels of significance (Table 1). The effects on sniffing behaviour are considered to be secondary to those on categories higher in the hierarchy, as described for fenfluramine by Taylor *et al.* (1973). Behavioural observations on Days 14 and 28 failed to show any significant effects of SE 780 on behaviour after chronic administration (Fig. 2).

Discussion

a) Weight Data. Comparable data for Fenfluramine (Taylor *et al.*, 1973) indicates a much more rapid development of tolerances; in this study the effects of SE 780 were so potent that administration was discontinued after 35 days because subjects receiving the high dose of the drug at the same doses became generally debilitated and suddenly be-

Table 1. Statistical comparisons between the three experimental groups (Mann Witney U Test) for all behavioural categories

	Controls vs 3 mg/kg	Controls vs 9 mg/kg	3 mg/kg vs 9 mg/kg
Rearing	$P < 0.001$ ↓	$P < 0.001$ ↓	$P < 0.01$ ↓
Walking	$P < 0.025$ ↓	$P < 0.002$ ↓	NS
Sniffing	$P < 0.001$ ↑	$P < 0.001$ ↑	$P < 0.005$ ↑
Grooming	NS	NS	NS
Immobile	NS	NS	NS

(↓ indicates reduction, ↑ indicates increase, NS = not significant).

gan to lose weight rapidly. (This effect is *not* thought to be due to toxicity of the drug, since the compound has been shown to have a high LD_{50} in chronic studies.) Pawan (1971a) has reported that in mice Fenfluramine causes greated *total* weight loss over a 42 day period than SE 780 when drugs are injected on alternate days. However, this procedure will delay development of tolerance to fenfluramine and so fails to illustrate the superiority of SE 780 as an anorexiant over fenfluramine.

Pankseep and Booth (1973) have suggested that tolerance to the anorexic effect of amphetamine is attributable at least partly to accruing deprivation rather than to the development of true pharmacological tolerance. If this result can be generalized to all phenylethylamine derivatives, (i. e. including SE 780 and Fenfluramine), then the comparison between the results reported here and those for fenfluramine in Taylor *et al.* (1973), becomes even more significant since the subjects in both studies were all between 200 and 250 g at the start of the experiments. The greater duration of action of SE 780 was definitely not due to subjects in *this* study being at a higher initial body weight. Rather, *in spite of* the effects of accruing deprivation, injected subjects continued to lose weight until many of them became greatly debilitated.

b) Behavioural Data. The marked acute sedative effects of SE 780 are in agreement with the findings of Weischer and Opitz (1972) that the drug reduces aggression in isolation reared mice. The sedative effects of acutely administered SE 780 (and its methanesulphonate salt SE 1513) have already been reported on in undeprived subjects (Goudie and Taylor, 1973), and were confirmed in unpublished studies with an ultrasonic motion recorder, in which significantly less gross motor activity was recorded in treated subjects than in controls over a 17 h period. The acute effects of SE 780 on behaviour in deprived subjects appear to be almost identical to those deseribed with fenfluramine (Taylor *et al.*, 1971, 1973).

However, the effects of chronic administration differ markedly in that no stimulant effects are noted. This indicates that tolerance to the *behavioural* effects of SE 780 has clearly developed rapidly.

In rats, SE 780 appears to be a potent anorexic agent to which tolerance is established slowly, and in which an important dissociation between the behavioural and anorexic effects of a phenylethylamine derivative is observed. Since acutely administered SE 780 has a therapeutic margin seven times that of fenfluramine (Unpublished Internal Report of Servier Laboratories) and since it has been shown to be active in humans when given orally (Pawan, 1971 b), it is suggested that further study of its anorexic properties in humans is merited.

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Peripheral and metabolic effects of fenfluramine, 780SE, norfenfluramine and hydroxyethylnorfenfluramine—A review

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Summary

In pharmacological aud clinical studies fenfluramine enhances glucose uptake by muscle and reduces plasma lipids and fat stores. 780SE, a fenfluramine analogue, appears to have similar effects in animals. Both compounds are weak indirect sympathomimetic agents when compared with amphetamine; the effects they elicit on responses to stimulation of sympathetic pathways differ from those evoked by amphetamine.

Introduction

Anorectic agents should ideally decrease body weight, have an effect on glucose and lipid metabolism, and possess minimal side effects.

Fenfluramine was derived from amphetamine by means of a trifluromethyl substitution of the third carbon atom of the phenyl ring of amphetamine by Beregi *et al.* (1970) at Les Laboratoires Servier. The effects of the parent compound which, though it was the drug of choice for the treatment of obesity in 1962, had a number of unacceptable side effects, were thus modified.

Fenfluramine, 780SE and the metabolites norfenfluramine and hydroxyethyl norfenfluramine are frequently classed as amphetamines since they contain a phenylisopropylamino group in their structure (Fig.). However, pharmacological and biochemical effects of the trifluoromethyl substituted compounds differ from those of amphetamine. This paper summarizes the recent findings with respect to the effects of amphetamine and the CF_3-substituted compounds on glucose and lipid metabolism, the cardiovascular system and the peripheral adrenergic system in animals and man.

Action on metabolism with particular reference to lipids and glucose

It is now universally accepted that obesity can be a complex metabolic disorder and that, with obesity, food ingested is selectively synthesized into lipids with a subsequent growth of adipose tissue. In addition, there is a decrease in glucose uptake by muscle and a decrease in fat mobilization.

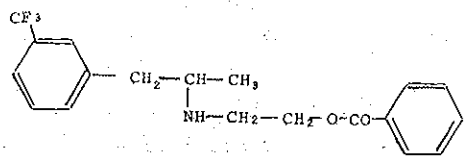
Fenfluramine has been shown in pharmacological and clinical investigations to reduce fat stores, to alter fat metabolism by the release of catecholamines, to decrease the serum levels of triglyceride and to increase the uptake of glucose by muscle. Thus Bizzi, Veneroni and Garattini (1973) found that the rise in plasma and lymph triglycerides which is usually seen after an olive oil load was prevented in rats by pre-treatment with fenfluramine (20 mg/kg i.p.). The same dose of fenfluramine when administered to rats in a post-absorptive state produced a decrease in plasma and lymph triglyceride levels and a decrease in lymphatic flow. The authors therefore have postulated that fenfluramine inhibits the intestinal absorption of triglycerides. One explanation for the mode of action is that fenfluramine *in vivo* decreases the release of pancreatic lipase and *in vitro* (Dannenburg and Ward, 1971) and inhibits palmitoyl-CoA : mono-olein acyl transferase activity in the microsomal fraction of the intestinal walls of rats (Dannenburg, 1973; Dannenburg, Kardian and Norrell, 1973). In these studies fasting was found to reduce or eliminate the effects of fenfluramine. This finding has been confirmed by Bizzi *et al.* (1973). However, Evans *et al.* (1975) could find no evidence of a reduction in the absorption of fat in normal volunteers taking either fenfluramine or 780SE.

In clinical studies fenfluramine has been shown to lower serum triglyceride levels (Chremos, Dannenburg and Noble, 1971, Mace *et al.*, 1972) although Balasse (1973) could only demonstrate weight loss.

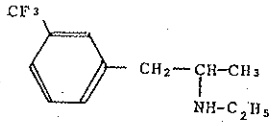
Wilson and Galton (1971) have shown that in man fenfluramine, 780SE and 1513 inhibit lipogenesis in adipose tissue *in vitro*. Only fenfluramine had an inhibitory effect on both the incorporation of T-palmitate and ^{14}C-glucose into neutral lipid. The same workers examined the effects of fenfluramine and 1513 on a broken cell preparation of human adipose tissue. Fenfluramine produced a significant inhibition of lipogenesis from glycerol phosphate and ^{14}C palmitate at a concentration of 1mM while

Abbreviations
Fenfluramine: 1 - (meta - trifluoromethyl - phenyl) - 2-ethylamino propane hydrochloride
Norfenfluramine: 1 - (meta - trifluoromethyl - phenyl) - 2-amino propane hydrochloride
Hydroxyethylnorfenfluramine: 1 - (meta - trifluoromethyl-phenyl)-2-hydroxyethyl amino propane
780SE (meta - trifluoromethyl - phenyl) - 2 - [benzoyloxy-ethyl]-amino-2-propane hydrochloride
1513 (meta - trifluoromethyl - phenyl) - 2 - [n - benzoyloxy-ethyl]-amino-propane methanesulphonate

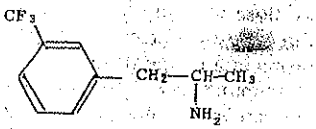
780 SE



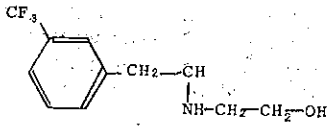
Fenfluramine

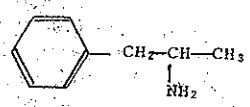


Norfenfluramine



Hydroxyethylnorfenfluramine





Amphetamine

FIG. The structural formulae of fenfluramine, 780SE, norfenfluramine, hydroxyethylnorfenfluramine, (trifluromethyl substituted beta phenylisopropylamines) and amphetamine.

1513 was found to exert a significant inhibitory effect at a concentration of 0·4mM. A similar effect has been observed *in vivo* with fenfluramine (Pawan, 1969; Mace *et al.*, 1972). Duhault (1973) has suggested that lipid synthesis reduces the coenzyme $NADPH_2$ obtained in a reaction catalysed by glucose-6-phosphate dehydrogenase, and has shown that the activity of this enzyme is decreased in fat pads and in the liver of fenfluramine treated rats.

Marsh and Bizzi (1972) demonstrated *in vitro* that d-amphetamine, dl-fenfluramine and dl-norfenfluramine inhibit triglyceride release from rat liver slices. *In vivo*, the drugs increased liver triglyceride, decreased plasma triglyceride and inhibited net synthesis of triglyceride, but did not significantly affect very low density lipoprotein-triglyceride release. Brindley and Bowley (1975) have shown that fenfluramine, norfenfluramine, hydroxyethyl-norfenfluramine and 780SE inhibit *in vitro* triglyceride synthesis by rat liver homogenates. Bliss, Kirk and Newall (1972) found that fenfluramine treatment significantly reduced fasting cholesterol and β-lipoprotein levels in 60% of 25 patients, although no consistent effect on fasting non-esterified fatty acids, triglycerides or pre-beta lipoprotein was seen.

In fasting rats fenfluramine has been shown to prevent glycogen depletion of the liver (Duhault, 1973). A comparison of the effects of an acute oral dose of fenfluramine, 780SE and amphetamine on blood glucose and liver glycogen in rats fasted for 18 hr is shown in the Table. No significant differenee was demonstrated between the pair fed control animals and those treated with amphetamine.

The first step in the formation of glycogen from glucose-6-phosphate is catalysed reversibly by phosphoglucomutase, an enzyme which Zwarenstein and Sapeika (1970) found to be inhibited by fenfluramine in *in vitro* studies with mouse heart and muscle; it is possible that fenfluramine could reduce glycogen formation *in vivo* by inhibiting this enzyme. Duhault and Boulanger (1965) reported that in dogs, an intravenous injection of fenfluramine (2·5 mg/kg) produced an increase in the peripheral uptake of glucose, as determined by measuring the Conard coefficient of carbohydrate utilization. The same authors found

TABLE. Effect of acute oral dose of 780SE, fenfluramine, and amphetamine on blood glucose and liver glycogen levels in rats fasted for eighteen hours. From Duhault and Malen (1969)

Treatment (number of animals)	Food consumption g/24 hr	Liver glycogen content wet tissue mg/g (mean ± S.E.)	Blood glucose mg/100ml (mean ± S.E.)
Controls (18)	24	39·3 ±2·7	78 ± 1·4
Pair-fed controls (17)	4	3·08 ± 1·13	48 ± 1·6
780SE 50 mg/kg (19)	4	*11·6 ±1·79	*74 ± 4·7
Fenfluramine 30 mg/kg (6)	4	**11·25 ± 2·57	*74 ± 2·8
dl-amphetamine 10 mg/kg (12)	4	*** 0·69 ± 0·23	53 ± 1·4

* $P < 0·001$ ** $P < 0·01$ *** $P < 0·10$ compared with pair-fed controls.

that neither 780SE (5 mg/kg p.o.) nor amphetamine produces this effect.

Kirby and Turner (1974) found that in the presence of insulin (100 μu/ml) fenfluramine and norfenfluramine produced a significant increase of glucose uptake by the isolated rat diaphragm. In the absence of insulin, the mean glucose uptake by the diaphragm did not change significantly. The authors have suggested that fenfluramine and norfenfluramine in therapeutic concentrations influence peripheral glucose uptake in rats.

Turtle and Burgess (1973) reported that fenfluramine had a biphasic effect on glucose removal by skeletal muscle during forearm perfusion. The initial early increase in glucose uptake by skeletal muscle which lasts 90–120 minutes disappeared with the release of free fatty acids. There was no increase in lactate release suggesting that there is complete oxidation of glucose by skeletal muscle. The same workers assessed the effects of fenfluramine on plasma glucose levels in maturity onset and insulin requiring diabetics and concluded that the drug was most effective as a hypoglycemic agent when taken before a meal. Fenfluramine consistently lowered plasma glucose levels for a minimum of 2 hr in maturity onset diabetics, and in insulin-requiring diabetics had similar but less marked effects. The authors also found that fenfluramine lowered plasma glucose levels in diabetics maintained on diet alone, or diet plus tolbutamide without risk of lactic acidosis and without a direct effect on insulin secretion.

Dykes (1973) studied glucose tolerance and insulin secretion in twenty-three maturity onset diabetics on a low calorie diet with and without fenfluramine. There was a significant improvement in glucose tolerance only, after the patients had been on the diet for 10 weeks. Those patients who continued with diet alone maintained the improvement in glucose tolerance; patients who received fenfluramine on the diet not only maintained the improvement in glucose tolerance but also, in the case of the high insulin secretors, showed a significant decrease in insulin secretion.

Bliss *et al.* (1972) investigated the effects of fenfluramine on glucose tolerance, insulin, fasting lipid, and lipoprotein levels in 25 patients with peripheral arterial disease. They found that fenfluramine significantly improved glucose tolerance though this was not as a result of an increase in insulin production.

It is possible to conclude from the results obtained in the four studies just described that fenfluramine does have an effect on glucose metabolism in man and in animals and may be useful in the treatment of maturity onset diabetes.

Action on the cardiovascular system

In 1966 Le Douarec, Schmitt and Laubie demonstrated that fenfluramine produced a slight fall in blood pressure in rats, cats, dogs and rabbits. This was followed by a rise in blood pressure in all animals except the rabbits. Berry, Poyser and Robertson (1971) confirmed this effect in anaesthetized cats at doses of 0·3 to 3·0 mg/kg i.v.

At doses of 1–10 mg/kg i.v. Sipes, Ziance and Buckley (1971) produced a biphasic blood pressure response in rats, cats and dogs, characterized by an initial depressor response followed by a prolonged pressor response. Administration of fenfluramine did not significantly affect the blood pressure response to 30 sec carotid occlusion or 1 μg/kg noradrenaline, adrenaline or isoprenaline. They also found that the pressor components of the blood pressure response to fenfluramine could be eliminated by administration of cocaine 10 min before, reserpine 24 hr before or phenoxybenzamine just before the start of the experiment. Sipes *et al.* (1971) therefore concluded that fenfluramine produces its effects by an indirect sympathomimetic action, and that this hypertensive effect is consistent with stimulation of alpha-adrenergic receptors. The same investigators found that the initial transient depressor response was enhanced by treatment with reserpine 24 hr prior to the experiment, and since the same treatment abolishes the response to intraventricular fenfluramine they concluded that the response is a direct effect of the compound.

Berry *et al.* (1971) reported that the depressor

responses to (+) amphetamine (0·01–0·3 mg/kg) were reduced by fenfluramine and subsequently higher doses of (+) amphetamine produced a prolonged and dose related fall in blood pressure. No explanation has yet been found for this reversal of the (+) amphetamine effect on blood pressure. These workers also found that in cats prior administration of amphetamine reduces the pressor response to fenfluramine and also that the tyramine pressor response was unaltered or potentiated by fenfluramine. However, Bocknik and Kulkarni (1973) found that in dogs fenfluramine at doses of 1·0–4·0 mg/kg has a pressor effect on the blood pressure. In addition, they found that fenfluramine potentiates the tyramine pressor response and that it also potentiates the depressor response produced by acetylcholine. Intravenous injection of 780SE in propylene glycol/saline (in the rat, cat and dog) produced no effect on the heart rate. In all 3 species 780SE in doses exceeding 30 mg/kg caused a transient fall in B.P., but unlike fenfluramine produced no pressor response. Intravenous injection of 1513, at doses of 5 mg/kg in the dog produced a slight fall in blood pressure.

It is possible therefore to suggest that fenfluramine, and 780SE, like amphetamine exert their effects on the cardiovascular system by acting as indirect sympathomimetic agents, but that their activity is less marked than that of amphetamine.

Action on the peripheral autonomic nervous system

The effects of fenfluramine hydrochloride on the peripheral autonomic system have been studied by Sipes *et al.* (1971). Intravenous fenfluramine (1, 2, 5 and 10 mg/kg) produced a dose related contraction of the nictitating membrane of the anaesthetized cat. Pre-treatment of cats with reserpine (24 hr prior to the experiment) or phenoxybenzamine (10 min before the administration) eliminated the 2 mg/kg i.v induced contraction. Ganglionic blockade, with chlorisondamine or removal of the superior cervical ganglion did not significantly alter the contraction. As the membrane responses to stimulation of pre- and post-ganglion fibres were not altered; fenfluramine was not affecting ganglionic transmission under these conditions. Fenfluramine has a direct effect on the membrane, whilst 780SE, at i.v. doses between 100 μg and 30 mg/kg, did not cause the membrane to contract. However 780SE is similar to fenfluramine, in that it does not affect ganglionic transmission.

Initial studies by Duhault and Verdavainne (1967) suggested that fenfluramine did not affect catecholamine stores, but subsequent work including that of Sipes *et al.* (1971) has shown that high doses of fenfluramine deplete peripheral and central stores. The latter workers found that fenfluramine reduced the noradrenaline content of both the rat myocardium and the perfused cat spleen, inhibited the uptake of noradrenaline by isolated guinea pig atria and accumulated in noradrenaline storage sites. This accumulation was not inhibited by cocaine. On the basis of this work, Sipes *et al.* (1971) concluded that fenfluramine acts initially as an indirect sympathomimetic agent, and that unoccupied α receptors and noradrenaline are prerequisites for the activity of fenfluramine. They have also suggested that fenfluramine releases noradrenaline from adrenergic nerve endings and that it exerts its effects intraneuronally.

Babulova *et al.* (1972) compared the effects of dl-fenfluramine and d-amphetamine on the adrenergic system using a number of *in vitro* and *in vivo* preparations. Amphetamine potentiated the duration of contraction of the inferior eyelid at a dose ten times lower than that needed with fenfluramine. Blocking of adrenergic transmission by guanethidine was completely reversed by amphetamine at a dose of 30 μmol/kg while fenfluramine only partially reduced the blockade at a dose of 40 μmol/kg. Amphetamine weakly potentiated the increase in blood pressure produced when the posterior hypothalamus was stimulated electrically; this effect was inhibited by 30% in 5 minutes after intravenous fenfluramine. They found that fenfluramine was 50 times less effective than amphetamine in increasing the rate of spontaneously beating isolated atria of the rat, while forty times the dose of amphetamine was required before fenfluramine would induce a contraction of the isolated tail artery of the rat. They also found that fenfluramine was less effective than amphetamine in inducing a contraction of the isolated vas deferens of rats and potentiation of the contraction of the guinea pig vas deferens elicited by electrical stimulation of the hypogastric nerve.

Jespersen and Bonaccorsi (1969) found that both 780SE and fenfluramine blocked the vasoconstrictor effects of amphetamine on the isolated tail artery of the rat and that the drugs did not produce a contraction when added alone or in the presence of tetrabenazine.

In human saphenous vein Coupar (1970) showed that fenfluramine produced contractions, which could not be blocked by phenoxybenzamine or thymoxamine, but which could be blocked with methysergide (Kirby and Turner, 1971). In isolated human uterine tissue fenfluramine also produced responses dependent on the concentration of calcium present and the hormonal status of the tissue (Kirby and Turner, 1971).

In conclusion, fenfluramine has sympathomimetic properties, but its activity is much less than that of amphetamine. The effects of fenfluramine on the responses elicited by stimulation of the sympathetic

pathway seem to differ from those evoked by amphetamine. This may be due to a difference in the modes of action. 780SE is a weaker sympathomimetic agent than fenfluramine.

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A review of the CNS effects of fenfluramine, 780SE and norfenfluramine on animals and man

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Summary

The changes in body functions arising from alterations produced by fenfluramine derivatives in metabolism, storage and release of brain monoamines are reviewed. These include feeding, drinking, behaviour, sleep, body temperature regulation, pain perception, neuroendocrine effects and mood.

Central drug interactions with fenfluramine, which may have an important bearing on clinical usage are summarized.

Introduction

The family of substituted phenylethylamines included in this review are fenfluramine, its benzoyloxyethyl derivative 780SE (992) and a metabolite common to both, norfenfluramine. Their structural relationships are shown in the Figure.

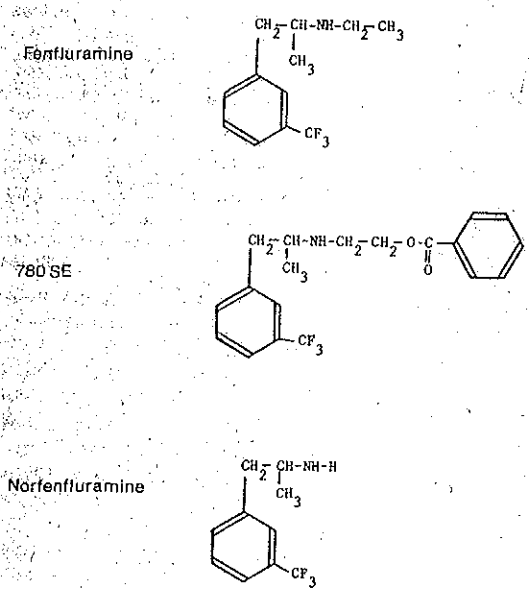

FIG. Chemical relationship.

Effects on brain monoamines

1. Serotonin (5HT)

Table 1 summarizes the studies which have been carried out in several animal species on the alterations in brain 5HT and 5-hydroxyindole acetic acid (5HIAA). The results are in good agreement and show that all three derivatives produce a dose related depletion of brain 5HT following acute administration, characterised by a rapid onset (within 1 hr), a 60–70% depletion lasting up to 48 hr, and the effect being selectively confined to the teldiencephalon in the rat.

For fenfluramine, radioactive studies to estimate turnover show this to be increased (Costa, Groppetti and Revuelta, 1971; Garattini, 1972), whereas brain 5HIAA has been reported to be both increased (Tagliamonte and Tagliamonte, 1970) and decreased (Duhault and Verdavainne, 1967; Garattini; 1972). Brain tryptophane is increased (Tagliamonte *et al.*, 1970; Garattini, 1972). Norfenfluramine has been found to increase 5HT turn over in teldiencephalon and brain stem and 5HIAA levels are raised up to 1 hr, but thereafter return to normal (Costa and Revuelta, 1972); 5HT depletion is comparable to that with fenfluramine, but is of longer duration (Costa *et al.*, 1971, 1972).

Sensitivity to 5HT depletion varies with the animal species. Rat and cat are more sensitive than the mouse, which in turn is more sensitive than the rabbit, whose 5HT appears to be almost unaffected by fenfluramine (Funderburk *et al.*, 1971a). Slight stereospecific differences in the 5HT depleting potency have been reported; the dextro (d) isomer has been found to be slightly more potent than the racemic (dl) or laevo (l) (Duhault and Verdavainne, 1967), but other workers have found no statistically significant differences (Garattini, 1972; Ghezzi *et al.*, 1973). To assign a precise neuropharmacological action for these derivatives on serotonergic pathways has been difficult in the absence of inhibition *in vitro* and *in vivo* on tryptophane hydroxylase or 5HTP-decarboxylase (Duhault and Verdavainne, 1967). It has been suggested that fenfluramine inhibits 5HT uptake at nerve terminals (Garattini, 1972).

fenfluramine (Garattini, 1972) and to antagonize anorexia (Ghezzi *et al.*, 1973; Jesperson and Scheel-Kruger, 1973).

Table 10 details the interactions which have been reported with amphetamine. These interactions are complex and unpredictable in animals; in some instances amphetamine induced activity is antagonized, whilst in others potentiation is found.

Conclusion

Fenfluramine and 780SE appear to share qualitatively similar effects on the brain amines, anorexia, behaviour and sleep. Norfenfluramine, however, differs quantitively with a more pronounced and prolonged effect on central catecholamine pathways. In man, its sympathomimetic potency has been reported to be responsible for the mydriatic effect of fenfluramine (Kramer, Rubicek and Turner, 1973). Norfenfluramine has a greater thermogenic potency and is more toxic.

Stereospecificity with fenfluramine and norfenfluramine appear to be parallel, the d-isomers being more potent on anorexia, and possibly slightly on 5HT depletion, mydriasis, hyperthermia and toxicity, whereas the l-isomers are more active on central catecholamine turn over and analgesia. The activities of the racemic mixture, the marketed form, are intermediate between the d and l.

The drug interaction studies in animals suggest that the anorectic activity of these compounds may be impaired, especially with some tricyclic antidepressants and that careful dosage titration may be necessary in combination with other sedatives and narcotic analgesics.

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Postgraduate Medical Journal, 1975, 51 (Suppl. 1), 56–65.

SESSION II

Chairman: PROFESSOR S. GARATTINI

Comparisons between the behavioural and anorexic effects of 780SE and other phenylethylamines in the rat

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Summary

The behavioural and anorexic effects of fenfluramine, norfenfluramine, and 780SE have been studied in the rat. Behavioural Activity analysis of these compounds indicates that acutely after intraperitoneal administration they all possess sedative properties but that 780SE and the related compound 1513 are much less active when administered subcutaneously. Chronically, fenfluramine and norfenfluramine possess possible stimulant properties, the latter being more potent; in contrast 780SE has been found to be totally devoid of stimulant properties.

Anorexic effects of these compounds were assessed by body weight recording in chronic studies. All were found to have a pronounced permanent dose related effect on body weight. 780SE was found to be a highly potent anorexiant in rats in that tolerance to its effects on body weight built up slowly in comparison to equivalent studies of fenfluramine and norfenfluramine. All three compounds have been found to induce abnormal behaviour at high doses, the characteristic behavioural pattern elicited being that of Backward Walking. 780SE was found to be much less potent in eliciting such behaviour than fenfluramine and norfenfluramine. The behaviour elicited by all three compounds differs from that characteristically induced by amphetamine at high doses which is commonly referred to as stereotypy. Both fenfluramine and 780SE were found to antagonize d-amphetamine induced excitation. However, fenfluramine was found to potentiate amphetamine toxicity whilst 780SE did not at the doses used. The results show that 780SE possesses a number of properties which make it a potentially attractive anorexic agent. Firstly, it appears to be devoid of any possible stimulant properties; secondly it is active anorexically over long periods of time; thirdly much larger doses are required to elicit abnormal behaviour than fenfluramine and norfenfluramine. Further study of 780SE seems merited.

Introduction

Most anorexic agents such as phenmetrazine, phentermine, diethylpropion and the amphetamines possess two major therapeutic limitations. Firstly, they have pronounced stimulant effects and are potentially addictive. Secondly, tolerance to their anorexic effects is established rapidly, thus considerably reducing their usefulness in the treatment of obesity. In evaluating any anorexic agent, the two major dimensions to be considered would consequently seem to be those of duration of action, and drug-induced C.N.S. changes which are reflected in behavioural stimulation. The present paper reports on the anorexic and behavioural effects of a number of phenylethylamines with reference to these dimensions. Emphasis is placed on comparisons between fenfluramine, norfenfluramine and 780SE.

A wide variety of methods exist for the assessment of drug effects on activity (e.g. Boissier's hole board, jiggle cages, photocell cages, Y mazes, open fields, sensory contingent bar pressing, activity meters). Measures obtained from these techniques have frequently been shown to be correlated at very low levels (Tapp *et al.*, 1968; Gross, 1968). The use of the mutually exclusive labels 'sedative' and 'stimulant' with respect to psychotropic agents may be misleading unless the exact behavioural or neurophysiological variables involved are specified. Furthermore, if the terms sedative and stimulant are to be meaningful any one particular method of assessing drug effects on activity needs to be validated by the use of drugs which are universally accepted to be sedatives or stimulants themselves within the specific experimental situation under consideration.

The present paper reports on a number of studies, both acute and chronic, in which activity analysis involved time sampling behavioural categorization (Bindra and Spinner, 1958); an advantage of this system over other techniques is that it allows both

Anorexic effect

Figures 10, 11 and 12 present the effects of chronic fenfluramine, norfenfluramine and 780SE on body weight, and in addition in the case of 780SE, amounts of food eaten. It is clear that in the case of all three compounds, there is a sustained and maintained weight loss, which was greatest for 780SE. An effect on amounts of food eaten after 28 days is also apparent, suggesting that 780SE is anorexically active for long periods of time.

Conclusions

The above results suggest that 780SE, in comparison with fenfluramine and other phenylethylamines, is a potent anorexic agent with a number of important properties. It appears to be devoid of either acute or chronic stimulant properties; it is active over long periods of time; and it requires much larger doses than either fenfluramine or norfenfluramine to elicit abnormal behaviour. It demonstrates an important dissociation between behavioural and anorexic effects. Since acutely administered 780SE has a therapeutic margin seven times that of fenfluramine (Unpublished internal report of Servier

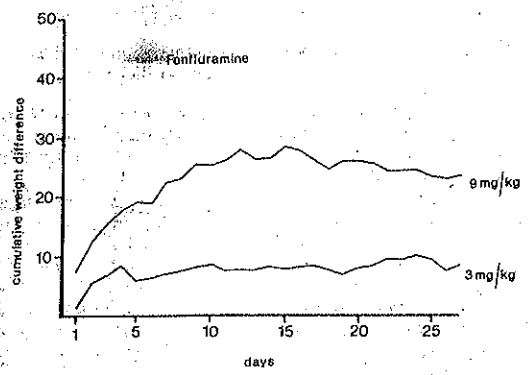

FIG. 10. Cumulative sums of the daily differences, in grams, between mean body weights of subjects receiving 3 and 9 mg/kg of fenfluramine.

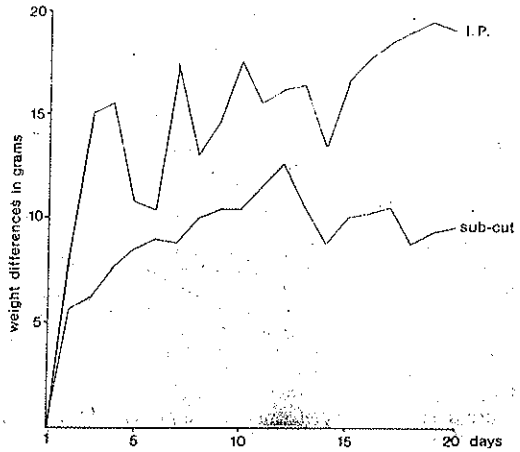

FIG. 11. As for Fig. 10. Norfenfluramine (3 mg/kg) given by two routes: I.P. = intraperitoneal. SUB-CUT = subcutaneous.

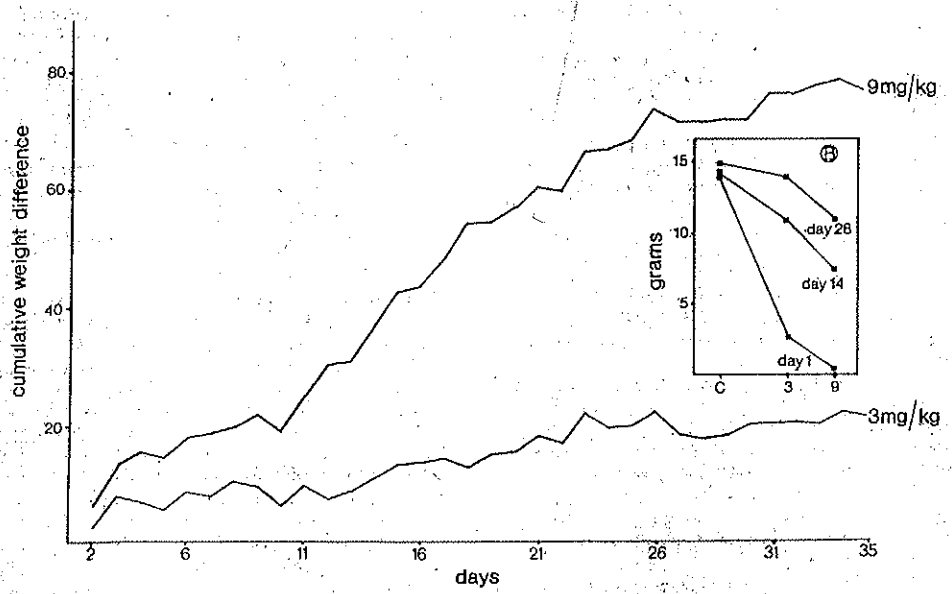

FIG. 12. As for Fig. 10 after 780SE. A = weight difference. Inset B = food intake. C = control.

Laboratories), and since it has been shown to be active in humans when given orally (Pawan, 1971) it is suggested that further study of its anorexic properties in humans is merited.

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The mechanism of action of fenfluramine

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Summary

Fenfluramine and amphetamine exert different actions on central biogenic amines. Neither drug alters the concentration of dopamine (DA) in the rat striatum but both drugs increase striatal homovanillic acid levels with opposite stereoisomeric specificity and by different mechanisms. The evidence presented suggests that fenfluramine blocks the DA receptors, whereas amphetamine acts indirectly presynaptically to stimulate the release of DA from dopaminergic terminals. Thus a similar biochemical effect is achieved by completely opposite mechanisms.

Neither fenfluramine nor amphetamine change the concentration of acetylcholine in whole brain. Fenfluramine and norfenfluramine though not amphetamine lower brain 5-hydroxytryptamine(5HT) and 5-hydroxyindole acetic acid. The results with fenfluramine on release and uptake of ^{14}C 5HT in platelets suggest that this drug acts on 5HT stores by 2 different mechanisms, these being a release of 5HT and inhibition of 5HT uptake.

The results of brain amine manipulations on the anorectic actions of fenfluramine and amphetamine suggest that these two drugs induce anorexia in animals by different mechanisms. An intact serotonergic system appears to be necessary to permit fenfluramine

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On the *in vivo* and *in vitro* actions of fenfluramine and its derivatives on central monoamine neurons, especially 5-hydroxytryptamine neurons, and their relation to the anorectic activity of fenfluramine

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Summary

The effects of fenfluramine, norfenfluramine and N-(2-benzoyloxyethyl) norfenfluramine (780 SE, 1513) have been studied on ^{3}H-dopamine(DA), ^{3}H-noradrenaline-(NA) and ^{3}H-5-hydroxytryptamine (5HT) uptake and release *in vitro*, on 5-HT receptor activity in the spinal cord, on behaviour and on food intake.

Fenfluramine was found to be a powerful granular releaser of ^{3}H-5-HT in cerebral cortex, but much less active on ^{3}H-NA and ^{3}H-DA release in the hypothalamus and the neostriatum respectively. Fenfluramine also caused a marked blockade of ^{3}H-5-HT uptake in the cortex cerebri. This effect cannot be secondary to its 5-HT releasing action, since the 5-HT depleting action of fenfluramine is blocked by pretreatment with chlorimipramine, a 5-HT membrane pump blocker. Thus fenfluramine probably utilized the membrane pump to enter the 5-HT neurons.

In agreement with the demonstrated 5-HT releasing action, fenfluramine enhanced the 5-HT depletion caused by a tryptophan hydroxylase inhibitor.

The functional studies on the spinal cord also produced evidence that fenfluramine is a releaser of granular 5-HT stores and a blocker of the 5-HT membrane pump. Thus, fenfluramine increased spinal 5-HT receptor activity and this action was increased by nialamide and reduced by reserpine, tryptophan hydroxylase inhibition and chlorimipramine. Studies on 5-HT denervated spinal cord obtained by intraventricular 5,7-DHT injections revealed that the activity of fenfluramine was paradoxically increased, probably due to the development of 5-HT receptor supersensitivity. Thus, fenfluramine can release 5-HT from the few remaining 5-HT nerve terminals to reach the supersensitive 5-HT receptors. It is important to stress that monoamine oxidase was inhibited in these experiments. This result makes it easier to explain the finding that the lever pressing for food reward was more reduced when fenfluramine was given to rats with 5,7-DHT induced lesions of the 5-HT ascending pathways than to intact rats. When studying the effects of fenfluramine on the food intake in rats on a food deprivation schedule, however, the anorectic effects of fenfluramine were reduced in the rats with a 5,7-DHT induced degeneration of the ascending 5-HT pathways.

These results are difficult to interpret but the speculative hypothesis is advanced that motivational control of food intake mainly involves the limbic system whereas the basal control of food intake mainly involves the hypothalamus. Norfenfluramine and its derivatives were less potent than fenfluramine on uptake and release of 5-HT but had similar weak actions like fenfluramine on ^{3}H-NA and ^{3}H-DA release in the hypothalamus and neostriatum respectively. The cortical NA nerve terminals however appear to be more sensitive to the releasing action of norfenfluramine and

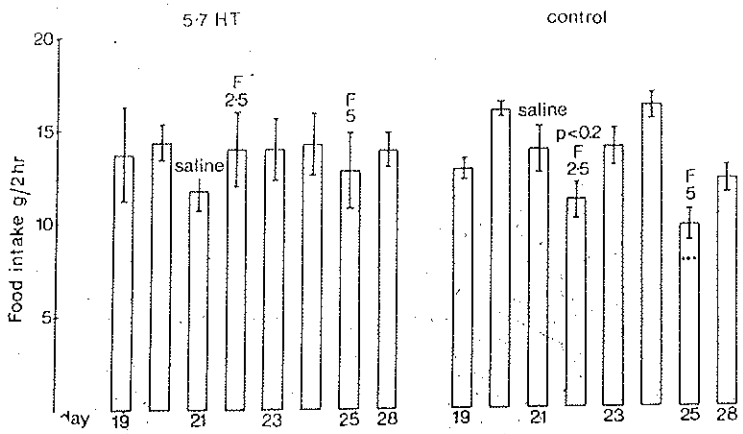

FIG. 6. *Effect of fenfluramine (F) on food intake in animals which had received 5,7-HT in the median raphe* (4 µg/4 µl) 3 *weeks earlier.* Control group received the solvent of 5,7-HT into the raphe. The animals were on a food deprivation schedule receiving food between 1 and 3 p.m. every day. The experiment started 19 days after the operation. Food intake was measured in g/2 hr. Means ± s.e.m. out of 5 rats in each group. Statistical significance according to Student's t-test. *** = $P < 0.001$.

operation, and when the scores are summed for both days there was a significant decrease of both the ambulation and rearing scores ($P < 0.1$ two sample rank test).

This difference could not be seen 14 days after the operation and seems to be time dependent.

Effects of fenfluramine on the rate of lever pressing in sham-operated and 5-HT lesioned animals (Table 7). Neither the sham-operated or 5,7-DHT lesioned animals showed any decrease in response rate on the FR-30 schedule after the operation. Furthermore, there was no significant difference between the two groups and their response rate after saline which ranged between 300 and 500 responses per 5 min.

Injection of fenfluramine (5 mg/kg i.p.) completely inhibited the lever pressings for food in both sham-operated and 5,7-DHT lesioned animals. Lower doses (2·5 and 1·25 mg/kg i.p.) partially blocked the response-rate of the sham-operated animals but strongly inhibited the response-rate of the 5,7-DHT lesioned animals.

The experiment was repeated the next day. There was a marked tolerance to fenfluramine in both sham-operated and 5,7-DHT lesioned animals.

There were no signs of overt sedation with the doses of fenfluramine used. The body temperature showed a slight drop of 0·5°C in some animals in both groups after fenfluramine.

Although the animals received a constant amount of food there was a significant lowering of the body weight after fenfluramine (Table 8), suggesting also the importance of metabolic effects of fenfluramine (Le Douarec and Neveu, 1970).

Discussion

The 5-HT neurons have been postulated as playing an important role in the mediation of the pharmacological actions of fenfluramine and its derivatives. The results from the present investigation further support this view.

Fenfluramine and norfenfluramine have been found *in vitro* to cause a marked release of stored 5-HT in cerebral cortex slices. Also there is a marked inhibition of 5-HT uptake.

However, since fenfluramine and norfenfluramine were very active on 5-HT release, it is difficult to know if the reduction of 5-HT uptake occurs secondary to a reduced 5-HT accumulation.

On the other hand, the biochemical studies *in vivo* and the functional experiments on the extensor reflex suggest that fenfluramine and norfenfluramine can act both on the 5-HT granules to cause release and at the nerve cell membrane to reduce 5-HT uptake. Thus, *in vivo* fenfluramine causes a 5-HT depletion as found in this and previous studies (Duhault and Verdavainne, 1967; Opitz, 1967), and it also enhances the depletion caused by H 22/54. These findings can be explained from the *in vitro* findings which showed a releasing action on the 5-HT granules. The mechanism for the 5-HT release is probably a displacement by fenfluramine and norfenfluramine of the 5-HT, since the functional

TABLE 8. Effect of fenfluramine on the body weight of sham-operated and 5,7-dihydroxytryptamine lesioned animals. Each figure represents the mean and S.E.M. of 5 animals

Treatment	Average body weight (g) before fenfluramine (7 days after operation)	P	Average body weight (g) after fenfluramine (14 days after operation)
Saline	266·0±2·9	<0·001	237·0±3·0
5,7-dihydroxytryptamine	277·0±4·6	<0·001	241·0±1·9

experiments suggest increased 5-HT receptor activity after fenfluramine, making a reserpine-like action unlikely. An action at the 5-HT nerve cell membrane is indicated by the fact that chlorimipramine, a potent 5-HT uptake blocking agent (Carlsson *et al.*, 1969), can block the fenfluramine and norfenfluramine induced increase in spinal 5-HT receptor activity. Also chlorimipramine antagonizes the 5-HT depletion caused by fenfluramine (Garattini *et al.*, 1975), and the anorexic action of fenfluramine (Jespersen and Scheel-Krüger, 1973). It thus seems that fenfluramine and norfenfluramine utilize the 5-HT membrane pump in order to get into the 5-HT neuron and displace the 5-HT stores. The studies on the extensor reflex further underlined the importance of the presynaptic actions of fenfluramine, since the increase in 5-HT receptor activity caused by fenfluramine was blocked by pretreatment with reserpine and H 22/54 and potentiated by nialamide, a monoamine oxidase inhibitor. The potentiation by nialamide can be due to several mechanisms, one being that under normal conditions the 5-HT released from the granules by fenfluramine will be attacked by intraneuronal monoamine oxidase, and therefore large amounts may be broken down before 5-HT can diffuse out of the cell and reach the 5-HT receptors. It has in fact been shown by Ziance and Rutledge (1972) that the NA released by fenfluramine has increased access to monoamine oxidase.

It may be pointed out that the fenfluramine derivatives, 780SE and 1513 were much less potent than fenfluramine and norfenfluramine on 5-HT release and uptake. These results were in agreement with the functional experiments on the spinal cord which suggested only weak increases of 5-HT receptor activity with high doses.

The studies on DA and NA uptake and release *in vitro* showed that fenfluramine and norfenfluramine had relatively weak effects on NA and especially on DA terminals. The cortical NA terminals appeared to be more sensitive to norfenfluramine and its derivatives (data not shown) than the hypothalamic NA terminals. Thus, it may be that the NA and DA granules are less sensitive to the releasing action of fenfluramine and/or it is not taken up as efficiently in these terminals as in the 5-HT terminals. In agreement with this view, the histochemical findings revealed no changes in DA and NA stores following fenfluramine and norfenfluramine treatment in a dose of 10 mg/kg. The histochemical findings further suggested that the cortical NA terminals were more sensitive to fenfluramine and norfenfluramine than the hypothalamic NA nerve terminals since the H 44/68 induced NA disappearance was enhanced in the cortex cerebri but not in the hypothalamus. Also the studies on the turning behaviour in experimental animals indicated that fenfluramine and norfenfluramine were only weak DA releasing agents and are thus in agreement with the biochemical and histochemical findings. It should be noted that 780SE had about the same potency as fenfluramine and norfenfluramine on NA release in hypothalamus in contrast to the findings with 5-HT release in the cortex cerebri. It is also of interest that the methane sulphonate of 780SE but not the hydrochloride, caused a significant reduction of 5-HT uptake and a significant release of 5-HT at concentrations as low as 10^{-7}M. It can be speculated that even if the experiments are performed *in vitro* 780SE and 1513 could partly act by being a precursor to hydroxyethylnorfenfluramine. Thus, it is possible that esterases in the slices could remove the benzoyloxy part of the molecule.

In view of the available evidence that fenfluramine acts by releasing granular stores of 5-HT (see above) it may seem paradoxical that the action of fenfluramine in the spinal cord was potentiated by treatment with 5,7-DHT which results in disappearance of the majority of the spinal cord 5-HT nerve terminals. However, it has been shown that the 5-HT receptors rapidly become supersensitive following degeneration of the 5-HT terminals (Fuxe *et al.*, 1974; Daly *et al.*, 1974; Nygren *et al.*, 1974), and recent findings suggest (Nygren *et al.*, 1974) that 5-HT can leak out from the remaining 5-HT nerve terminals to reach the supersensitive 5-HT receptors. It should also be pointed out that monoamine oxidase was inhibited in the present experiment which will protect the diffused 5-HT from being broken down before it reaches the 5-HT receptors. This explanation is also supported by the fact that when a complete 5-HT denervation is obtained, there are no signs of supersensitivity following nialamide-chlorimipramine treatment (Nygren *et al.*, 1974). It is

therefore assumed that the enhancement of the fenfluramine induced inhibition of food reward observed in the present experiment after 5,7-DHT induced lesion of the subcortical 5-HT pathway is best explained in a similar way, although no monoamine oxidase inhibitor was used. However, it may seem difficult to reconcile this hypothesis with the fact that inhibition of food intake in a free-feeding situation by fenfluramine was significantly reduced by the same type of lesion, which has been previously reported (Samanin *et al.*, 1972; Clineschmidt, 1973). It must be remembered that this lesion causes a 70% loss of 5-HT nerve terminals in the hypothalamus and a 30—50% loss of 5-HT terminals in the cortex cerebri (Fuxe and Jonsson, 1974; Everitt, Fuxe, Jonsson and Hökfelt, unpublished data). The CA neurons are relatively unaffected. Therefore, since extrahypothalamic influences mainly from the limbic cortex probably also play a role in the control of food intake (Grossman, 1973), it is possible to propose the following speculative explanation of the present results. The limbic and other cortical 5-HT terminals may mainly control the *motivational* aspects of food intake. Therefore, since the majority of these terminals still remained, 5-HT released by fenfluramine may easily reach the supersensitive limbic 5-HT receptors, and an enhancement of inhibition of food drive is obtained.

This mechanism also explains the rapid development of tolerance found, since the 5-HT stores even if only little depleted may not reach the supersensitive 5-HT receptors in sufficient quantities after fenfluramine. The hypothalamic 5-HT terminals, on the other hand, could be involved in the *basic* control of food intake regulated *e.g.* by glucostatic mechanisms. Therefore, since most of the hypothalamic 5-HT nerve terminals have degenerated, the fenfluramine induced inhibition of food intake in deprived animals is lost. This is in contrast to the case in the studies on the spinal 5-HT receptors where monoamine oxidase inhibition was performed. Had this been done in the study on food intake, an opposite result might have been expected according to the present hypothesis which must be tested by further experiments. Finally, it should be pointed out that lesions of the sub-cortical 5-HT pathway did not result in hyperphagia although this has recently been reported to occur following lesions of the ventral NA pathway to the hypothalamus and other subcortical structures (Ahlskog and Hoebel, 1972). This lesion was found by these workers to counteract amphetamine-induced anorexia.

The subcortical 5-HT pathway may also be involved in control of exploratory behaviour. Thus, rearing and ambulation may be reduced during the first 2–4 days following the operation.

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The mechanism of action of fenfluramine

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Summary

Fenfluramine and amphetamine exert different actions on central biogenic amines. Neither drug alters the concentration of dopamine (DA) in the rat striatum but both drugs increase striatal homovanillic acid levels with opposite stereoisomeric specificity and by different mechanisms. The evidence presented suggests that fenfluramine blocks the DA receptors, whereas amphetamine acts indirectly presynaptically to stimulate the release of DA from dopaminergic terminals. Thus a similar biochemical effect is achieved by completely opposite mechanisms.

Neither fenfluramine nor amphetamine change the concentration of acetylcholine in whole brain. Fenfluramine and norfenfluramine though not amphetamine lower brain 5-hydroxytryptamine(5HT) and 5-hydroxyindole acetic acid. The results with fenfluramine on release and uptake of ^{14}C 5HT in platelets suggest that this drug acts on 5HT stores by 2 different mechanisms, these being a release of 5HT and inhibition of 5HT uptake.

The results of brain amine manipulations on the anorectic actions of fenfluramine and amphetamine suggest that these two drugs induce anorexia in animals by different mechanisms. An intact serotonergic system appears to be necessary to permit fenfluramine

anorexia by a release of 5HT, whilst the catecholaminergic pathways appear to be involved in amphetamine anorexia.

Introduction

Fenfluramine is an anorectic drug which, being different from amphetamine at the biochemical, pharmacological and behavioural levels, has represented a useful research tool for unmasking the complex mechanisms involved in the regulation of food intake.

Previous work from these laboratories has shown several effects of fenfluramine at the central as well as the peripheral level (Bizzi *et al.*, 1970; Garattini *et al.*, 1974a). This review is devoted to summarizing the present knowledge of the action of fenfluramine on brain monoamines with particular reference to dopamine (DA) and serotonin (5HT).

Table 1 shows that fenfluramine and amphetamine exert different effects on central biogenic amines. While neither drug affects the concentration of DA in the striatum or of acetylcholine in the whole brain, an opposite effect can be seen on noradrenaline (NA) and 5HT levels. In fact, amphetamine, but not fenfluramine, lowers brain NA, while fenfluramine but not amphetamine decreases brain 5HT.

Studies on striatum dopamine

The fact that the concentration of a given biogenic amine is not affected by a given drug does not necessarily mean a lack of activity. Both amphetamine and fenfluramine (Jori and Bernardi, 1969, 1972) have been shown to increase the concentration of the major metabolite of DA in the striatum, namely homovanillic acid (HVA). However, the actions of the two drugs do not appear comparable according to a number of observations, which may be summarized as follows:

(a) In the case of fenfluramine, the effect on striatum HVA is higher for the l- than for the d-isomer, whereas the opposite is true for amphetamine (Jori *et al.*, 1973). These differences in action do not appear to be related to major differences in the availability of the two drugs to the dopaminergic structures in the striatum. In this respect it should also be mentioned that fenfluramine does not appear to act on striatum HVA through the formation of its major metabolite, norfenfluramine, because norfenfluramine appears to be less active at equal concentrations (Jori *et al.*, 1973).

(b) Repeated treatments with d-amphetamine induce a tolerance to the increase of striatum HVA (Jori and Bernardi, 1969), whereas fenfluramine is still able to elicit a rise of striatum HVA, suggesting that it may act at a different site (Jori and Bernardi, 1972). Conversely, rats pretreated with l- or dl-fenfluramine are still able to respond to d-amphetamine as far as HVA in the striatum is concerned. These findings are summarized in Table 2.

(c) Previous studies from these laboratories have indicated that C3H mice are relatively insensitive to the stimulant action of amphetamine (Dolfini, Garattini and Valzelli, 1969; Dolfinini *et al.*, 1970) although these mice react to this drug with a decrease of food intake (Jori and Garattini, 1973). Amphetamine does not show in this strain of mice any effect on striatum HVA at doses effective in the CD_1 strain (Caccia *et al.*, 1973). As shown in Table 3, fenfluramine however increases the level of striatum HVA in both strains of mice. Other drugs, such as chlorpromazine and haloperidol which increase the levels of striatum HVA by inhibiting dopaminergic receptors and, therefore, eliciting an increased turnover of DA by a feedback mechanism (Da Prada and Pletscher, 1966), are also effective in both strains of mice.

(d) The difference in the mechanism by which fenfluramine or amphetamine raise striatum HVA can also be studied by the interaction with dopaminergic stimulant drugs. It is known that apomorphine (Ernst, 1967; Andén *et al.*, 1967) and piribedil (Corrodi, Fuxe and Ungerstedt, 1971; Jori *et al.*,

TABLE 1. Effect of amphetamine and fenfluramine on rat brain monoamines

Treatment	Dose (mg/kg ip)	Brain level (μg/g ± S.E.)			Striatum dopamine μg/g ± S.E.
		Noradrenaline	Serotonin	Acetylcholine	
Saline		0·40 ± 0·01	0·60 ± 0·02	2·4 ± 0·1	8·2 ± 0·5
d-amphetamine sulphate	15	0·24 ± 0·02*	0·58 ± 0·03	2·5 ± 0·1	7·5 ± 0·3
dl-fenfluramine-HCl					

TABLE 2. Effect of repeated treatment on the increase of HVA concentration induced by amphetamine and fenfluramine in rats

Pretreatment (5 mg/kg i.p.) on 4 days	Treatment (15 mg/kg i.p.)	Striatum HVA (ng/g ±S.E.)
—	saline	204 ± 4
—	d-amphetamine	416 ± 9
—	l-fenfluramine	620 ± 12
—	dl-fenfluramine	403 ± 14
d-amphetamine	d-amphetamine	181 ± 2*
l-fenfluramine	d-amphetamine	430 ± 21
dl-fenfluramine	d-amphetamine	425 ± 7
d-amphetamine	l-fenfluramine	698 ± 57
d-amphetamine	dl-fenfluramine	479 ± 59

* $P < 0.01$ versus the corresponding acute treatment.
Animals were sacrificed 1 hr after the treatment.
HVA was measured according to Korf *et al.* (1971).

1974a; Garattini *et al.*, 1974b) by stimulating dopamine receptors reduce, by a feedback mechanism, the synthesis of DA and therefore the level of striatum HVA. Table 4 summarizes the results obtained by combining apomorphine or piribedil with either amphetamine or fenfluramine. While the increase of HVA induced by fenfluramine is antagonized by dopaminergic agents, the effect of amphetamine remains unchanged (Jori *et al.*, 1974b). These studies suggest that only fenfluramine may interact with DA receptors while amphetamine is acting only indirectly through its well-known capacity to release DA from presynaptic dopaminergic terminals.

(e) More direct proof that fenfluramine may interact with dopaminergic receptors is offered by studies showing that this drug antagonizes the stereotyped behaviour induced by agents currently believed to induce this behaviour through stimulating DA receptors directly (Ernst, 1967; Andén *et al.*, 1967) as well as indirectly (Glowinski, 1970) by releasing DA at the presynaptic level. Table 5 shows that fenfluramine inhibits the stereotypy induced by apomorphine, piribedil and amphetamine at a dose similar to the one effective in increasing striatum HVA. Due to the variety of chemical structures involved, it is unlikely that the interaction observed is occurring unspecifically. It should also be remembered that, if anything, fenfluramine is known to increase the brain levels of amphetamine (Jonsson, 1972; Jonsson and Gunne, 1972). These and other data available in the literature permit a tentative interpretation of the action of amphetamine and fenfluramine on the striatum. According to the scheme suggested in Fig. 1, amphetamine increases the levels of HVA by releasing DA and therefore inducing a compensatory increase in synthesis of DA in the striatum. Thus amphetamine is considered to be a stimulant of the dopaminergic system (Glowinski, 1970). Fenfluramine however acts by a mechanism common to the neuroleptic drugs (Jori *et al.*, 1974b), because the increase of striatum HVA would be the consequence of the blockade of dopaminergic receptors which elicits, by a feedback action, an increase of dopamine synthesis. Fenfluramine should, therefore, be considered as an inhibitor of the dopaminergic system (Jori *et al.*, 1974b). It is of interest to observe how compounds with a similar chemical structure eliciting a similar biochemical effect (increase of striatum HVA) may eventually act in a completely opposite manner.

Studies on brain serotonin

It is well known that fenfluramine lowers the level of brain 5HT (Duhault and Verdavainne, 1967; Opitz, 1967; Costa, Groppetti and Revuelta, 1971) by a mechanism which is not yet fully elucidated and, in any case, it appears to be different from the action exerted by other drugs. In fact, fenfluramine decreases not only brain 5HT but also the major metabolite of 5HT, namely 5-hydroxyindoleacetic acid (5HIAA) (Garattini, 1973). Chase and Shoulson (1975) have also observed that fenfluramine

TABLE 3. Effect of various drugs affecting the HVA concentration in the striatum of CD_1 and C3H mice

Treatment	mg/kg i.p.	Striatum HVA (ng/g ±S.E.) CD_1 mice	C3H mice
Saline	—	248 ± 12	252 ± 9
d-amphetamine sulph.	7·5	432 ± 20	295 ± 0·5*
	15·0	729 ± 19	526 ± 43*
N-methyl amphetamine HCl	7·5	495 ± 37	226 ± 28*
	15·0	403 ± 32	430 ± 14
l-fenfluramine HCl	7·5	669 ± 67	739 ± 31

TABLE 4. Effect of piribedil and apomorphine on the levels of HVA after amphetamine and fenfluramine

Treatment mg/kg i.p.		Striatum HVA (ng/g ± S.E.)	
		d-amphetamine (15 mg/kg i.p.)	l-fenfluramine (15 mg/kg i.p.)
Saline		487±32	676±19
Piribedil	240	416± 9	247± 7*
Apomorphine	10	469±11	385±15*

Piribedil was given 1 hr before amphetamine and fenfluramine. Apomorphine was given twice (5 mg/kg i.p.) 20 min and 10 min respectively before drugs.
* $P<0.01$ versus the corresponding saline group.

reduces by about 50% the levels of 5HIAA in the cerebrospinal fluid of neurological patients. The effect on brain 5HT and 5HIAA is dose-dependent in rats (Garattini, 1973) and occurs in all the parts of the brain (Ghezzi *et al.*, 1973) although quantitative regional differences have been reported (Costa *et al.*, 1971). No major difference exists between the d- and the l-isomers of fenfluramine in lowering brain indoleamines (Garattini *et al.*, 1974). Also the metabolite of fenfluramine, norfenfluramine, has the capacity to decrease brain 5HT (Morgan, Löfstrandh and Costa, 1972; Garattini *et al.*, 1974) and it may contribute to the long-lasting effect of fenfluramine. However, fenfluramine acts *per se*, shown by the fact that equal lowering of brain 5HT may be obtained when the N-deethylation of fenfluramine is blocked by a previous treatment with SKF525A, a known inhibitor of liver microsomal enzymes (Axelrod, Reichentral and Brodie, 1954; Stitzel, Anders and Mannering, 1966) (Table 6).

As previously mentioned, the mechanism of action of fenfluramine on brain 5HT remains unknown since there is no simple mechanism to explain its action. The only compounds known to lower simultaneously 5HT and 5HIAA in the brain are the inhibitors of 5HT synthesis, such as p-chloroamphetamine (Sanders-Bush and Sulser, 1970a, b) and p-chlorophenylalanine (Koe and Weissman, 1966). However, there is no proof that fenfluramine inhibits 5HT synthesis. On the other hand it has been shown that although the levels of 5HT are lowered, the turnover of 5HT is increased (Costa *et al.*, 1971). Consistent with this finding is the observation that fenfluramine does not block tryptophan hydroxylase (Morgan *et al.*, 1972), while it does increase the brain levels of tryptophan (Tagliamonte *et al.*, 1971; Morgan *et al.*, 1972) which are believed to be rate limiting for 5HT synthesis.

Work on isolated platelets, as a possible model for nerve-endings with respect to their serotonin uptake system (Pletscher, 1968; Todrick and Tait, 1969) has shown that fenfluramine rapidly inhibits the uptake of ^{14}C–5HT. Fig. 2 shows that d-fenfluramine, particularly in the first few minutes, is a strong inhibitor, although the concentrations required are considerably higher than for chlorimipramine, a well-known inhibitor of 5HT uptake (Carlsson *et al.*, 1969; Todrick and Tait, 1969; Lidbrink, Jonsson and Fuxe, 1971). In addition, Tables 7 and 8 show that the effect of fenfluramine is dose-dependent and that fenfluramine is more effective than its metabolite, norfenfluramine. The inhibition of the 5HT uptake may explain why fenfluramine lowers brain 5HIAA since it is currently believed that most of the oxidative deamination of 5HT occurs intraneuronally (Blaschko and Levine, 1966).

However, other experiments indicate that, unlike chlorimipramine, fenfluramine is able to release 5HT from platelets which have previously been incubated with ^{14}C–5HT. These results, summarized in Table 9, taken together with the inhibition of 5HT uptake,

TABLE 5. Effect of dl-fenfluramine and chlorpromazine (CPZ) on the stereotypy induced by amphetamine, apomorphine and piribedil in rats

Treatment (mg/kg i.p.)		Stereotypy (mean score±SEM) induced by Amphetamine	Apomorphine	Piribedil
Saline		3·3±0·2	3·7±0·1	2·2±0·2
dl-fenfluramine	10	0·5±0·2**	0·8±0·2**	1·0±0·001*
CPZ	5	1·6±0·5**	1·0±0·3**	1·2±0·2*

Each figure is the mean score±SEM of 4–6 animals.
dl-Fenfluramine and CPZ were injected 30 min before d-amphetamine

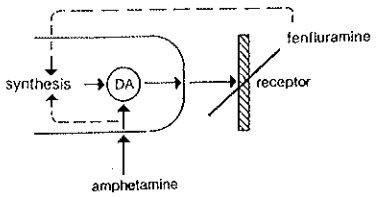

FIG. 1. Proposed mechanism of action of fenfluramine or amphetamine on the dopaminergic system. Amphetamine releases dopamine from nerve terminals by acting directly at the presynaptic level, whereas fenfluramine would produce an increase of dopamine synthesis through a feed-back mechanism due to the blockade of postsynaptic dopamine receptors.

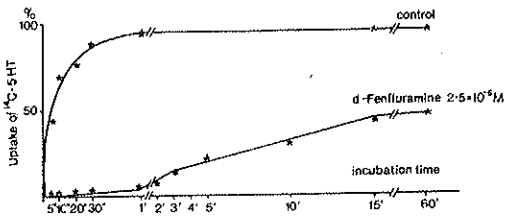

FIG. 2. Influence of d-fenfluramine ($2{\cdot}5 \times 10^{-5}$M) on the uptake of ^{14}C-serotonin (0·5 μg) by rat blood platelets.

suggest that fenfluramine decreases the stores of 5HT by two different mechanisms, i.e. release of 5HT and inhibition of 5HT uptake. Similar data have been obtained by Fuxe *et al.*, (1975) working with brain slices of rats. The following further data may help to elucidate the action of fenfluramine. It was observed that chlorimipramine prevents the effect of fenfluramine on the brain 5HT stores (Ghezzi *et al.*, 1973). The fact that this interaction may be related to the capacity of chlorimipramine to block 5HT uptake is suggested by the following findings:

(a) Chlorimipramine does not induce major changes in the levels of fenfluramine or norfenfluramine in the brain (Ghezzi *et al.*, 1973).

(b) Chlorimipramine does not inhibit the increase of striatum HVA induced by fenfluramine (Garattini, 1973).

(c) Other tricyclic antidepressant agents (imipramine and desipramine) which are more effective inhibitors of NA than 5HT uptake do not prevent the action of fenfluramine on brain 5HT (Ghezzi *et al.*, 1973).

It is, therefore, suggested that chlorimipramine may prevent the access of fenfluramine to the serotonergic terminals, inhibiting in this way the depletion of brain 5HT.

Significance of the effect on serotonin to explain the anorexic effect of fenfluramine

Several data indicate that by manipulating brain monoamines it may be possible to affect the anorectic action exerted by amphetamine or fenfluramine.

Table 10 reports three experimental conditions which are able to affect selectively the various monoaminergic pathways. The lesion of the midbrain raphe (MR) induces degeneration of the serotonergic projections (Andén *et al.*, 1965) to the forebrain (Kostowski *et al.*, 1968). This effect is consistent with the marked lowering of forebrain 5HT occurring without any change of brain NA or DA (Samanin *et al.*, 1972). The intraventricular administration of 6-OH-dopamine (6-OH-DA), on the other hand, induces a degeneration of the noradrenergic terminals and a partial degeneration of the dopaminergic ones (Samanin *et al.*, 1972), leaving the levels of brain 5HT unaltered. When the treatment with 6-OH-DA is preceded by the administration of the monoamine oxidase inhibitor, pargyline, there is a destruction of both noradrenergic and dopaminergic terminals (Breese and Taylor, 1971) without any effect on 5HT.

Table 11 shows that fenfluramine-induced anorexia does not occur in rats with MR lesions, while it is fully present in the other two experimental conditions where the noradrenergic and/or dopaminergic systems were degenerated. On the contrary, amphetamine partially loses its capacity to decrease food intake in animals treated with pargyline and

TABLE 6. Effect of SKF 525-A on the depletion of brain 5HT and 5HIAA induced by d l-fenfluramine in the rat

Time after injection (hr)	dl-fenfluramine		SKF+dl-fenfluramine	
	5HT	5HIAA	5HT	5HIAA
	μg/g±SEM		μg/g±SEM	

TABLE 7. Dose-response values for the inhibitory activity of d-fenfluramine on ^{14}C-5HT uptake by rat platelets. For each drug concentration, mean ± S.E. for 4 duplicated experiments is reported as per cent of control experiments. d-Fenfluramine was preincubated at 37°C with platelet-rich plasma (600,000/μl) for 15 minutes before an additional incubation period of 15 minutes with 0·2 μg ^{14}C-5HT. The reaction was stopped by rapid cooling of the sample, platelets were sedimented by centrifugation (4,000 g for 20 minutes at 4°C) and the radioactivity in the supernatant measured in a liquid scintillation counter.

concentration	$1{\cdot}0\times10^{-5}$M	$1{\cdot}25\times10^{-5}$M	$2{\cdot}5\times10^{-5}$M	$5{\cdot}0\times10^{-5}$M	10^{-4}M
Mean ± S.E. (% control values)	22·2 ± 4·3	32·5 ± 2·5	52·0 ± 9·1	76·0 ± 5·4	94·0 ± 0·0

TABLE 8. Effect of fenfluramine on the uptake of serotonin (5-HT) by platelets

Drug $2{\cdot}5\times10^{-5}$M	% Inhibition 5HT uptake PRP*
l-fenfluramine	26·3 ± 5·7
l-norfenfluramine	3·1 ± 0·6
d-fenfluramine	52·0 ± 9·1
d-norfenfluramine	27·3 ± 3·4
chlorimipramine	89·0 ± 3·6

*=platelet-rich plasma.

TABLE 9. Percent release of platelet bound ^{14}C-5HT after different incubation periods of platelet-rich plasma with d-fenfluramine (10^{-4}M). Mean values ± S.E. for four duplicated experiments are reported. Platelets were first preincubated at 37°C with 0·2 μg ^{14}C-5HT for 15 min, then with the drug. The reaction was stopped at different time intervals by rapid cooling of the samples

	Incubation time (min)			
	15	30	60	120
Control	< 1	< 1	< 1	< 1
d-fenfluramine	29·5 ± 1·0	45·5 ± 2·1	47·2 ± 0·5	61·0 ± 0·6

6-OH-DA while it is still effective in animals with MR lesions or following the intraventricular administration of 6-OH-DA. These data again show that amphetamine and fenfluramine induce anorexia by different mechanisms suggesting that fenfluramine may act via a release of 5HT.

In Table 12 it is shown that the anorectic effect of fenfluramine is also inhibited by chlorimipramine and by methergoline, a blocker of serotonergic receptors (Ferrini and Glässer, 1965). While chlorimipramine inhibits the lowering effect of fenfluramine on brain 5HT, methergoline, as expected, does not show any action on this biochemical effect (Table 13). These last results are in agreement with a number of data reported in the literature. In fact, several 5HT antagonists inhibit the anorectic effect of fenfluramine (Funderburk *et al.*, 1971; Jespersen and Scheel-Krüger, 1973), but do not affect the action of amphetamine (Jesperson and Scheel-Krüger, 1973). Furthermore, another agent known to destroy the serotonergic central terminals, 5,6-dihydroxytryptamine (Baumgarten and Lachenmayer, 1972), has been reported to abolish the anorectic effect of fenfluramine (Clineschmidt, 1973).

All these findings strongly suggest, although they do not conclusively prove, that fenfluramine induces in animals a reduction of food intake by a mechanism which is different from the one currently ascribed to amphetamine. It is possible that 5HT is somewhat involved in the action of fenfluramine and that, in any case, an intact serotonergic system is necessary to permit the anorectic effect of this drug. If this hypothesis should be confirmed by future studies, it will become apparent that the regulation of food intake is under the control of several systems not necessarily involving only the ventromedial nucleus and the lateral hypothalamus (Rabin, 1972) or the

TABLE 10. Forebrain levels of noradrenaline (NA), dopamine (DA) and serotonin (5HT) in midbrain raphe (MR)-lesioned, 6-hydroxydopamine (6-OH-DA) treated or pargyline + 6-OH-DA treated rats

	Brain amines (μg/g ± S.E.)

TABLE 11. Effect of fenfluramine or amphetamine on food intake of midbrain raphe (MR)-lesioned, 6-hydroxydopamine(6-OH-DA)-treated or pargyline + 6-OH-DA-treated rats

Treatment	mg/kg i.p.	Control	Experimental
MR Lesion			
Saline	—	8·0 ± 0·4	8·7 ± 0·6
Fenfluramine	5	2·1 ± 0·3*	7·2 ± 0·8*
Amphetamine	2·5	2·0 ± 0·4	2·4 ± 0·6
6-OH-DA			
Saline	—	9·2 ± 0·6	9·3 ± 0·6
Fenfluramine	5	2·3 ± 0·5**	1·6 ± 0·5**
Amphetamine	2·5	1·7 ± 0·4**	2·3 ± 0·7**
Pargyline + 6-OH-DA			
Saline	—	8·1 ± 0·5	8·7 ± 0·9
Fenfluramine	5	1·5 ± 0·3	0·8 ± 0·2
Amphetamine	2·5	1·6 ± 0·4***	3·5 ± 0·5***

Each figure represents the mean of 2-hr food intake (g/rat ± S.E.) of 6 animals.
The data for each experiment were analysed as 2 × 3 factorial, using Fisher's F ratio for significance testing in the analysis of variance.
* MR lesioning has a significant effect on the fenfluramine-treated group only ($P < 0·001$).
** The 6-OH-DA treatment showed no significant effect for any of the treatment groups.
*** The pargyline + 6-OH-DA treatment has a significant effect on the amphetamine-treated group only ($P < 0·05$).

TABLE 12. Effect of chlorimipramine (Cl-IMI) and methergoline on food intake reduction induced by dl-fenfluramine in rats

Treatment	Dose mg/kg i.p.	Food intake (g/rat ± SEM)
Saline	—	10·0 ± 0·6
dl-fenfluramine	5	3.6 ± 0·5**
Cl-IMI	10	7·8 ± 0·9
Methergoline	3	6·4 ± 1·4
Cl-IMI + dl-fenfluramine	10 + 5	5·5 ± 0·5*
Methergoline + dl-fenfluramine	3 + 5	6·3 ± 0·4*

Each figure represents the mean ± SEM of two-hour food intake of 6–8 animals.
Cl-IMI and methergoline were injected respectively 30 and 60 min before dl-fenfluramine.
Food intake was evaluated immediately after d l-fenfluramine.
Analysis of variance and the extension of Duncan's multiple range test for group means with unequal numbers of replications have been used for the statistical evaluation of the data.
** $P < 0·001$ in respect to saline-treated rats.
* $P < 0·05$ in respect to d l-fenfluramine-treated rats.

TABLE 13. Effect of chlorimipramine (Cl-IMI) and methergoline on the depletion of brain serotonin (5HT) induced by dl-fenfluramine in rats

Treatment	Dose mg/kg i.p.	Brain levels 5HT (μg/g ± SEM)
Saline	—	0·32 ± 0·02
dl-fenfluramine	15	0·15 ± 0·01°
Cl-IMI	10	0·36 ± 0·02
Methergoline	3	0·30 ± 0·02
Cl-IMI + d l-fenfluramine	10 + 15	0·28 ± 0·02*
Methergoline + d l-fenfluramine	3 + 15	0·16 ± 0·01

Each figure represents the mean ± SEM of 6 animals.
Cl-IMI and methergoline were injected respectively 30 and 60 min before d l-fenfluramine.
Biochemical determinations were performed 2 hr after d l-fenfluramine administration.
Analysis of variance and Duncan's new multiple range test have been used for the statistical analysis of the data.
° $P < 0·01$ in respect to saline-treated animals.
* $P < 0·001$ in respect to d l-fenfluramine-treated animals.

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the effect of fenfluramine derivatives was not simply due to liver damage.

It is therefore concluded that fenfluramine derivatives significantly diminish the output of triglycerides by the liver, or from the splanchnic region, of the rabbit as measured by the plasma triglyceride response to protamine sulphate injection in the fed animal. This raises the possibility that the fenfluramine induced lowering of plasma triglycerides in man may be due to an effect on secretion by the liver. Unlike triton WR 1339, protamine sulphate, which is used therapeutically as an anti-heparin agent, may be administered to humans. Work is in progress to study the protamine response in humans in relation to hypertriglyceridaemia.

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Pharmacological effects of 780SE (992) on hyperlipidaemic and obese rats

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Summary

The effect of 10 days oral administration of 780SE, a fenfluramine analogue, was evaluated in four rat models of hyperlipidaemia. The models used were rats fed high lipid diet and high carbohydrate diets for three weeks, rats with alloxan induced diabetes for three weeks and 16-week-old genetically obese rats.

In both types of dietary induced hyperlipidaemia (neither of which were associated with obesity) the rats were markedly hypertriglyceridaemic, especially the high lipid diet animals. 780SE, in oral doses of 25 and 50 mg/kg significantly lowered triglyceride levels and free fatty acids, the effects being more pronounced at the higher dose level. Drug treated rats showed a slower weight gain.

In the alloxan diabetic rats, 780SE (25 mg/kg) lowered the raised serum triglycerides, free fatty acids and blood glucose.

In the genetically obese rats, 780SE (25 and 100 mg/kg) significantly reduced plasma triglycerides, and total lipids, especially at the higher dose. Cholesterol levels did not change significantly and plasma free fatty acids increased.

780SE orally administered for 10 days was thus associated with a reduction in plasma triglycerides to near control concentrations in each of the four experimental models. The effects on serum cholesterol were slight. The hyperlipidaemic action of 780SE does not appear to depend upon the amount of exogenous fat. Whether the mechanism of action is a decrease in lipid synthesis and/or an increase in lipid utilization requires further elucidation.

Introduction

Disorders of lipid metabolism are now well established as playing a role in the pathogenesis of

many forms of cardiovascular disease, although only one of many factors. From a pharmacological aspect, it is however the one which is most easy to study. In a previous paper (Duhault and Malen, 1969), we have shown that a new compound, 780SE, is able to lower plasma triglyceride levels in normal rats and to modify the composition of plasma free fatty acids. Because of this, the effect of 780SE on blood lipids has been further studied in four animal models of hyperlipidaemia using high lipid diets, high carbohydrate diets, rats with experimental diabetes and genetically obese rats.

An increase in the carbohydrate content of the diet of normal humans and rats produces a progressive rise in the serum triglycerides, possibly due to an increase in hepatic lipogenesis. Since hyperlipidaemia frequently accompanies diabetes mellitus, the diabetic rat model, which has been shown to have endogenous and exogenous types of hyperlipidaemia was used (Schnatz, Formaniak and Chlouverakis, 1972; Duhault *et al.*, 1972b). The raised free fatty acids and triglycerides in the diabetic rat are probably of endogenous origin and represent an indispensable substrate for the formation of triglyceride and cholesterol in the liver (Feigelson *et al.*, 1961).

Rats homozygous for the mutant gene (fa) have genetically determined metabolic disorders such as obesity, hyperlipidaemia and hypercholesterolaemia (Zucker and Zucker, 1961), It has been reported that 'fatties' have a lipid distribution like that in human hyperlipidaemia (Zucker, 1965). Obesity and hyperlipidaemia seen in the fatty rat may more closely parallel certain types of human obesity in which adiposity is related to increased cell numbers and cell size, than does experimental obesity produced by hypothalamic lesions. Thus these rats also seem to be a suitable model for the investigation of anti-obesity and hypolipidaemic drugs.

Materials and methods

Male Sprague-Dawley rats delivered by caesarian section and weighing 175–200 g were fed *ad libitum* for three weeks either with a standard diet, a high lipid diet or a high sucrose diet (Table 1).

Male Sprague-Dawley rats weighing 150 g were made diabetic by subcutaneous injection of alloxan monohydrate as previously described (Duhault and Lebon, 1972a). Daily insulin injection was adjusted for glycosuria ++ or +++ (Tes-tape) and stopped eighteen hours before sacrifice. The diabetic animals were killed three weeks after the alloxan injection. All the rats had free access to food. In the drug treated animals, oral 780SE was given in doses of 25 and 50 mg/kg daily at 4.30 p.m. for ten days and the animals killed at 10.00 a.m., one hour after an additional dose.

Genetically obese male and female rats ('fatties') (Zucker and Zucker, 1961) were also studied. The 'fatties', sixteen weeks old, were trained to eat their food in a seven hour diurnal period. In order to eliminate the anorectic effect, 780SE was given orally after feeding in doses of 25 and 100 mg/kg for 10 days. Tap water was allowed *ad libitum*.

Chemical analyses were performed on individual blood samples obtained by decapitation of all the unanaesthetized animals. Blood glucose (Hoffman, 1937) and free fatty acids (FFA) (Dole, 1957) were measured using a Technicon auto-analyser. After removal of phospholipds with 'zeolith' (hydrated alkali-aluminium silicate), serum triglycerides were measured according to Van Handel and Zilversmit (1965) and serum cholesterol by the procedures of Lieberman-Burchard, modified by Huang *et al.* (1961) and adapted for the Technicon autoanalyser by Levine, Morgendtern and Ulastelica (1967). Total blood lipids were determined by a precipitation method using dextran sulphate on the Technicon auto-analyser. Serum insulin was assayed by a radio-immunoassay technique (Wide and Porath, 1966).

Epididymal fat pads were excised and weighed. In some experiments, the diameter of fat cells from perirenal adipose tissue (or the proximal part of the epididymal fat pads) was measured according to the

Table 1. Composition of diets (%). (U.A.R. Manufactured diet)

	Standard diet	High-lipid diet	High-carbohydrate diet
Protein	24	33 (casein)	20 (casein)
Vitamin mixture	—	4	1
Salt (USP XIV)	6	5	4
Lard	—	10	—
Glycerol	—	43	—
Cellulose	3	5	10
Sucrose	—	—	60
Corn oil	8	—	4
Starch	47	—	—
Moistness	12	—	1

histological method of Sjörnström, Björntorp and Vrana (1971).

Results

1. *Dietary induced hyperlipidaemia* (*Table* 2)

Control rats fed the high lipid diet or the carbohydrate diet had somewhat smaller fat-pad weight than normal controls fed the standard diet. The difference was not statistically significant, but could be related to a somewhat slower weight gain shown by these rats. This may be a consequence of an unbalanced diet as the rats on these diets were consuming less protein than rats on control diets. The rats fed the high fat diet were markedly hypertriglyceridaemic with a mean serum triglyceride level of 255 mg/100 ml compared with 73 mg/100 ml for normal controls. Free fatty acids (FFA), always much higher in the fat fed group than in the control group, were probably of alimentary origin. Total blood lipid was also markedly increased but serum cholesterol levels were not changed. Plasma insulin showed a small but non-significant increase.

780SE (Table 3) significantly reduced the triglycerides and FFA, especially at 50 mg/kg. Plasma cholesterol levels were slightly reduced in the high carbohydrate fed group. 780SE treated rats had significantly smaller fat-pad weight and showed a slower weight gain compared with the controls.

2. *Alloxan diabetic rats*

As shown in Table 4, long-term diabetic rats showed a significant increase in plasma glucose, FFA and triglycerides, when compared with normal non diabetic controls. The diabetic rats grew more slowly than the normal group. Oral administration of 780SE (25 mg/kg) for 10 days significantly lowered plasma glucose triglycerides and cholesterol.

TABLE 2. Findings in diet induced hyperlipidaemic rats compared with control animals fed standard diet (mean ± SD)

Diet	Plasma free fatty acids μeq/L	Plasma triglycerides mg/100 ml	Plasma cholesterol mg/100 ml	Blood lipids mg/100ml	Plasma insulin μU/ml	Epididymal fat pads g	Fat cell diameter μ	Change in body weight g
Normal (n = 50)	366 ± 19	73 ± 4	84 ± 2	386 ± 11	25 ± 1	2·2 ± 0·2	65 ± 2	+ 60 ± 3·6
High lipid diet (n = 30)	664 ± 44***	255 ± 20***	85 ± 2	886 ± 70***	31 ± 2	2·1 ± 0·2	63 ± 3	+ 43 ± 8·7
High carbohydrate diet (n = 25)	363 ± 24	110 ± 9***	87 ± 4	474 ± 42**	34 ± 2	2·1 ± 0·2	65 ± 3	+ 27 ± 10·5

** $P < 0.01$.
*** $P < 0.001$.

TABLE 3. 780SE treated rats compared with high lipid and high carbohydrate fed controls (mean % change relative to controls)

Diet	Plasma free fatty acids	Plasma triglycerides	Plasma cholesterol	Blood lipids	Plasma insulin	Epididymal fat pads	Fat cell diameter	Change in body weight g
High lipid (n = 5)								Control + 43
Dose 25 mg/kg po × 10 days	+ 26%	— 52%**	+ 13%	23%	— 20%	— 30%*	0%	+ 36 ± 15
50 mg/kg po × 10 days	0%	— 40%*	+ 8%	— 21%	0%	— 27%*	0%	+ 4 ± 11
High								Control + 27

TABLE 4. Findings in normal and alloxan diabetic rats treated with 780SE (mean ± SD)

	Plasma free fatty acids μeq/L	Plasma triglycerides mg/100 ml	Plasma cholesterol mg/100 ml	Plasma glucose mg/100 ml	Change in body weight g
Normal rats (n = 5)	293 ± 55	69 ± 5	83 ± 1·0	87 ± 2	+ 53 ± 3·4
Control diabetic rats (n = 10) (compared with normal)	614 ± 78**	215 ± 41**	95 ± 5	286 ± 22**	+ 30 ± 9·0
Diabetic rats following 780SE 25 mg/kg po × 10 days (n = 10) mean % change from and comparison with control diabetic rats	488 ± 58 (−21%)	99 ± 7·5 (−54%)***	78 ± 3·6 (−17%)**	213 ± 12 (−26%)**	+ 28 ± 3·0 + 28 ± 3·0

** $P < 0{\cdot}01$.
*** $P < 0{\cdot}001$.

3. *Genetically obese rats* (*Table 5*)

Female 'fatties' were relatively much fatter than male 'fatties'. In the fed state, serum lipids were above normal but triglycerides and total lipids levels were higher in females (respectively 283 ± 69 and 877 ± 222 mg/100 ml), than in males (respectively 247 ± 50 and 535 ± 76 mg/100 ml). This difference was not seen in fasted animals. Plasma insulin was twice as high in the 'fatties' compared with the controls. However, because of the abnormal feeding schedule, the weight gain in the 'fatties' was less than that obtained by free access to food in 24 hr periods.

The degree of obesity is shown by the weight of the abdominal and epididymal fat tissue. As the growth of the fat depots in the non-obese Zucker rat is quite similar to that reported for the Sprague-Dawley animals (Hirsch and Han, 1969), these latter were used as controls because of lack of lean heterozygote (fa-) rats. Perirenal fat cells were significantly larger than those of normal rats.

'Fatties' had a very low sensitivity to the anorectic effects of 780SE. The data presented in Table 6 shows the effect of a 10 day oral 780SE administration (25 and 100 mg/kg) when compared with control fatty animals of both sexes. Plasma FFA were significantly increased in male and female 'fatties', whereas plasma triglycerides and total lipid were decreased. The epididymal fat pads and body weight gain were markedly reduced by 780SE, all these effects being more evident after the higher dose.

Discussion

The data presented in this paper show that after a ten day administration of 780SE, plasma triglyceride levels were reduced to near control concentrations in the four experimental models. It is interesting to note that in genetically obese rats, females were more responsive to the drug than males. The effect of 780SE on serum cholesterol was slight. While a decrease in cholesterol concentration was observed on the high carbohydrate diet and in alloxan diabetic rats, a slight increase was noted in high lipid diet animals and in 'fatties'.

The effects of 780SE on serum lipids suggest that the influence of the drug does not depend only on the amount of exogenous fat. Recent evidence by Garattini and ourselves (unpublished results) suggests that 780SE decreases the absorption of endogenous fat. This effect could be mediated by pancreatic lipase inhibition as described *in vitro* (Bernier, personal communication). Such a mode of action cannot

TABLE 5. Findings in genetic obese rats of both sexes (mean ± SD) compared with normal male rats (see Table 2)

	Plasma free	Plasma	Plasma	Blood		

TABLE 6. Effect on 780SE on genetic obese rats (mean % change ±SD compared with control fatty rats of both sexes)

	Plasma free fatty acids	Plasma triglyceride	Plasma cholesterol	Blood lipids	Plasma insulin	Epididymal fat pads	Fat cell diameter	Change in body weight g
								Control −6g
Fatty males 25 mg/kg po × 10 days	+14%*	0%	−9%	−8%	+10%	−17%***	−10%	−48 ± 7·6
100 mg/kg po × 10 days (n = 5)	+52%***	−30%*	+12%*	+4%	−19%	−25%***	−23%	−56 ± 10·0
								Control +5g
Fatty females 25 mg/kg po × 10 days	+18%	−42%*	0%	−38%**	−25%	—	0%	−33 ± 3·4
100 mg/kg po × 10 days (n = 5)	+94%***	−68%**	0%	−29%*	−25%	no data	−9%	−61 ± 7·8

* $P < 0{\cdot}05$.
** $P < 0{\cdot}01$.
*** $P < 0{\cdot}001$.

explain the simultaneous decrease in FFA and triglyceride noted in diabetic rats, genetically obese rats and in rats on a carbohydrate diet. These data suggest an increase of lipid utilization and/or a decrease of the endogenous lipid synthesis, possibly by inhibition of phosphatidate phosphohydrolase, (Brindley and Bowley, 1974) or by inhibition of liver triglyceride production (Kaye, Galton and Tomlin, 1974). Since FFA represent an indispensable substrate for the formation of triglycerides and cholesterol in the liver, it is important to underline that a ten day administration of 780SE does not induce triglyceride deposition in the liver (Duhault and Malen, 1969). Removal of plasma triglyceride by adipose tissue with high lipoprotein lipase activity might be suggested, but this hypothesis would need an increase of lipid turn-over with subsequent utilization since administration of 780SE reduces fat stores. In this regard, diabetic rats which had low adipose tissue and high lipoprotein lipase activity did not present additional lost weight under treatment. On the other hand a decrease of plasma insulin albeit not statistically significant was noted in 'fatties'. As blood lipids are known to induce insulin resistance (Randle, Garland and Hales, 1966), it seems to us that the decrease in plasma insulin was due to the important blood lipid lowering effect of 780SE.

The hypoglycaemic effect of 780SE, observed in alloxan diabetic rats is however not readily explicable [illegible] not induce insulin secretion as do mechanism of action of 780SE as a hypolipidaemic drug and as a glucose lowering agent needs further elucidation.

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Discussion

Chairman: MR D. B. CAMPBELL

Sessional Secretaries: MISS S. MACRAE, MR. C. H. L. PARKER

DR ASMAL (Natal) said that insulin is known to play a most important role in carbohydrate induced hypertriglyceridaemia, and he wondered therefore if DR BRINDLEY knew whether insulin exerts any influence on the enzyme phosphohydrolase. He suggested that fenfluramine and its analogue 780SE exert their effects by suppressing insulin secretion.

DR BRINDLEY said that we know little about these enzymes, but it is possible that insulin may reduce the synthesis of the phosphohydrolase although there is no direct evidence to support this.

DR BRINDLEY wondered to what extent fatty acid synthesis is governed by the activity of the synthetase and the acetyl-CoA-carboxylase, and to what extent fluctuations of, for example, the levels of citrate and other metabolites might influence the activity of carboxylase.

PROFESSOR LOWENSTEIN (Waltham) said that the enzymes involved in fatty acid synthesis do not respond rapidly in terms of changes of level. The enzymes involved in cholesterol synthesis, in particular HMG-Co-A reductase, show a very rapid response. There is a 50% loss in the total amount of reductase within approximately 4 hr. It is possible therefore that changes in enzyme level play a part in the control of cholesterol synthesis. He said his work with metabolite levels was incomplete and he could not give a definite answer.

DR BALASSE (Brussels) wondered whether Dr Duhault

DR BALASSE said that he had carried out studies which confirmed the results which Dr Duhault had presented and that he was convinced that fenfluramine, 780SE and amphetamine can decrease the absorption of triglyceride from the intestine, though he had been unable to demonstrate a similar effect on the absorption of cholesterol. He believed that there was a small decrease in plasma cholesterol levels when fenfluramine and 780SE are given to both animals and patients.

PROF. GARATTINI (Milan) said that he had seen a decrease in the absorption of triglycerides from the gut and that fenfluramine may inhibit the enzyme pancreatic lipase and the enzyme which re-esterifies the fatty acid with monoglyceride in the intestine.

MR MILLER (London) said that when comparing normal animals with obese, the total metabolic activity would be very different.

PROF. LOWENSTEIN agreed that the obese have a much higher rate of fatty acid production, largely due to their bigger livers.

DR BEREGI (Paris) said he wished to comment on the important difference between obese and normal animals with respect to drug kinetics as in the obese animal there is 50% more fenfluramine in plasma, liver and brain than in the normal animals given the same dose of fenfluramine in mg/kg body weight.

Annexe 1-15

LES LABORATOIRES SERVIER

Neuilly, le 14 Novembre 1977

Monsieur Jean WEBER
Directeur de la Pharmacie et des Médicaments
9 Avenue de Lowendal
75007 - P A R I S -

Objet : Inscription du BENFLUOREX (MEDIATOR) au tableau A des substances vénéneuses. (Arrêté du 1/9/77 publié au Journal Officiel du 29/9/77).

Monsieur le Directeur,

Nous avons pris connaissance avec un certain étonnement de l'Arrêté sous référence qui modifie l'inscription de notre spécialité pharmaceutique "MEDIATOR" au tableau des substances vénéneuses.

Le MEDIATOR dont l'autorisation de mise sur le marché sous les numéros : 317 553.3 - 317 555.6 - 317 556.2 - 317 557.9 - 317 558.5 - 317 559.1 a été accordée le 16 Juillet 1974, est inscrit depuis cette date au tableau C.

Les indications thérapeutiques de notre spécialité étayées par le dossier pharmacologique et clinique soumis lors de notre demande d'A.M.M. et approuvées par le Ministère de la Santé et de la Sécurité Sociale comme l'atteste l'A.M.M. ci-joint (annexe 1) sont les suivantes :

- Troubles métaboliques glucido-lipidiques athérogènes
- Troubles du métabolisme des lipides
- Troubles du métabolisme des glucides.

.../...

Annexe 1-15

Or, nous constatons que le Benzoate de{[méthyl-1 (trifluorométhyl-3 phényl) -2 éthyl] amino} -2 éthyle, chlorhydrate ou BENFLUOREX, Principe Actif de notre spécialité est, d'après l'Arrêté du 1/7/77, classé au tableau A.
N'ayant pas été consultés avant cette prise de position à nos yeux injustifiée, nous nous devons de rappeler à votre haute attention les qualités profondément originales du MEDIATOR qui constituent une véritable découverte sur le plan thérapeutique.

Par la tripolarité de son action

- hypolipémiante
- antihyperglicémiante
- hypouricémiante

dont le mécanisme est brièvement rappelé ci-contre (annexe 2), le MEDIATOR se présente comme la médication de choix d'une pathologie métabolique complexe et sévère.

A cet égard, le MEDIATOR permet de supprimer le recours aux associations thérapeutiques toujours susceptibles d'entraîner des interactions médicamenteuses indésirables et par là même, répond aux soucis bien actuels de pharmacovigilance et d'économie de traitement.

Malgré la parenté relative de sa structure chimique avec celle de la FENFLURAMINE le BENFLUOREX est une molécule originale douée de propriétés métaboliques et cliniques fondamentalement distinctes de cette substance et, par voie de conséquence, dénuée des actions anorexigènes et amphétaminomimétiques reprochées aux autres produits visés par l'Arrêté du 1/9/77.

En tout état de cause, il a été prouvé que les deux substances donnent naissance à des produits de dégradation essentiellement différents.
La FENFLURAMINE est métabolisée par déséthylation en une amine primaire oxydée secondairement en acide métatrifluorométhylhippurique, tandis que le BENFLUOREX est hydrolysé dans cette fonction ester en libérant un alcool primaire ultérieurement oxydé en acide métatrifluorométhylisopropylaminoacétique (annexe 3).

En outre, les analyses spécifiques de nos chercheurs n'ont, à aucun moment du processus de métabolisme du BENFLUOREX, mis en évidence de traces de FENFLURAMINE.

.../...

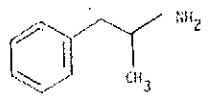
Annexe 1-15

A la lumière de ces informations, nous vous prions de bien vouloir accepter notre demande de recours par laquelle nous sollicitons l'abrogation du Paragraphe VII de l'Article 1 de l'Arrêté du 1/9/77 et la réinscription de notre spécialité MEDIATOR au tableau C des substances vénéneuses.

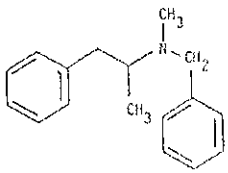
Nous restons à votre entière disposition pour vous fournir tout élément complémentaire de justification, et vous prions de croire,
Monsieur le Directeur, à l'expression de notre haute considération.

Annexe 1-16

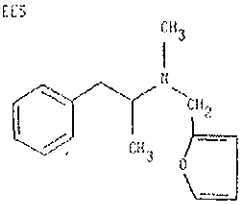
AMPHETAMINE



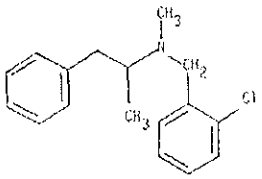
AMPHETAMINES N-SUBSTITUEES



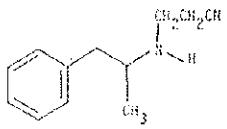
Benzphetamine



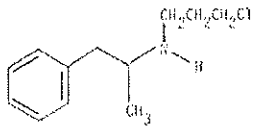
Furfenorex



Clobenzorex



Fenproporex

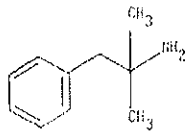


Mefenorex

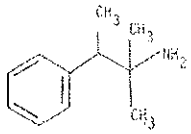
Fig. 1 (*ci-dessus*). — Structures chimiques et noms génériques des amphétamines N substituées.

Fig. 2 (*ci-contre*). — Structures chimiques et noms génériques des phénylisopropylamines substituées sur la chaine latérale.

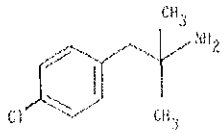
PHENTERMINES



Phentermine

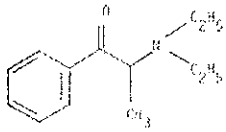


Pentorex

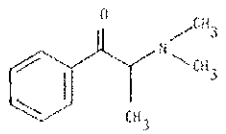


Chlorphentermine

AMFEPRAMONES



Amfepramone



Metamfepramone

c) *Phénéthylamines et phénylisopropylamines cyclisées.*

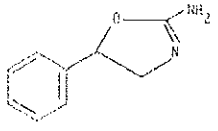
Il y a trois représentants dont deux sont disponibles en France *(figure 3)*.

d) *Phénylisopropylamines halogénées sur le noyau.*

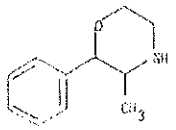
Seule la fenfluramine fait l'objet d'une spécialité pharmaceutique *(figure 4)*.

e) *Autres structures.*

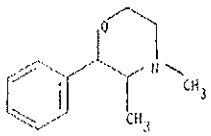
La diphéméthoxidine seule, stimulant central, appartenant à cette catégorie est disponible sur le marché français *(figure 5)*.



Aminoxaphen

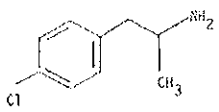


Phenmetrazine

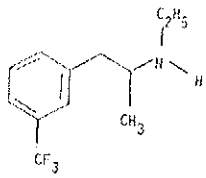


Phendimetrazine

FIGURE 3

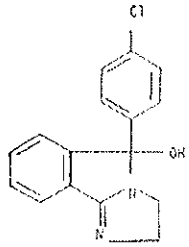


p-chloroamphétamine

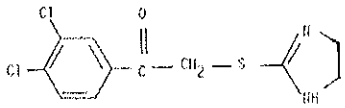


Fenfluramine

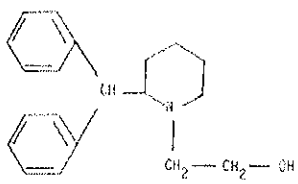
FIGURE 4



Mazindol



Dita



Diphéméthoxidine

FIGURE 5

FIG. 3. — Structures chimiques et noms génériques des phénethylamines cyclisées.

FIG. 4. — Structures chimiques et noms génériques des phénylisopropylamines halogénées sur le noyau.

FIG. 5. — Structures et noms génériques ou de code des structures non amphétaminiques.

2. Classification par les mécanismes d'action.

Les progrès réalisés au cours de la dernière décade dans le domaine des amines cérébrales concernant leur localisation, leur métabolisme et leurs effets, ont tout naturellement été appliqués à l'étude du mécanisme d'action des anorexigènes qui font l'objet de l'article suivant (Prof. H. Schmitt).

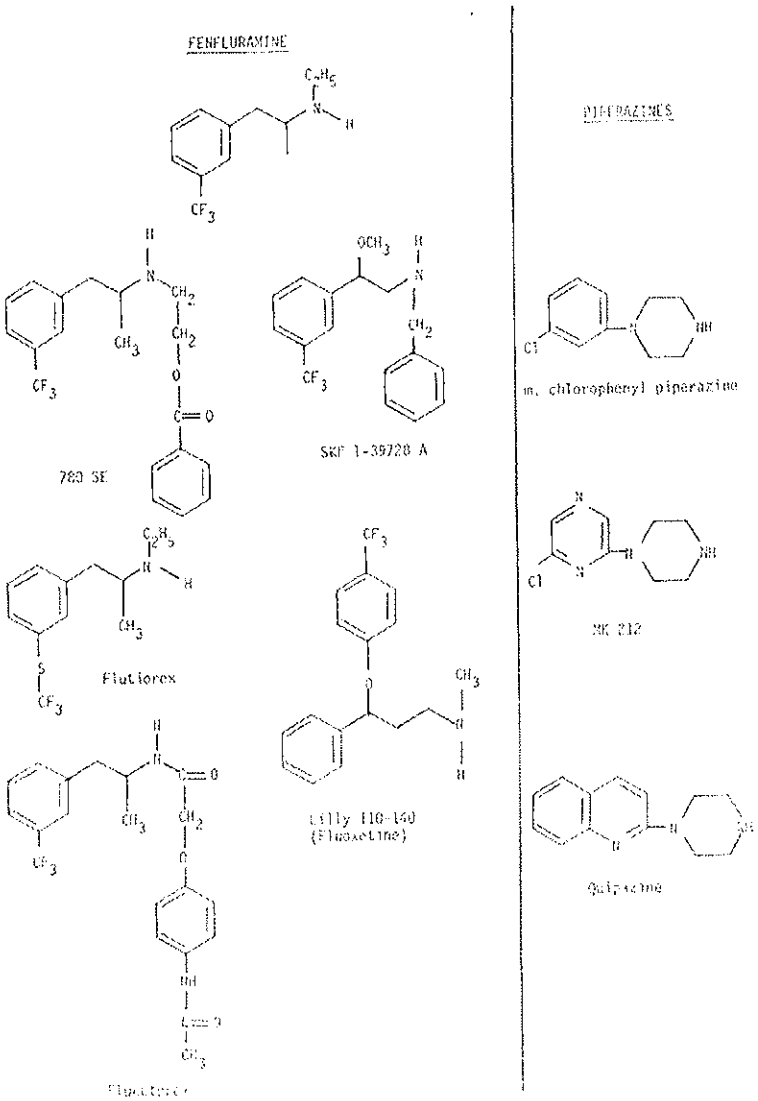


Fig. 6 - Structures et noms génériques ou de code des anorexigènes interférant avec la sérotonine cérébrale

Le Douarec Thérapie 1979 : Méthodes expérimentales d'études , structures chimiques et classification.

Annexe 1-17

SERVIER

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Le 3 décembre 2010

Cher Confrère,

Au nom des collaborateurs des Laboratoires Servier, je souhaiterais vous dire à quel point nous partageons votre émotion et celle de vos malades, devant le déferlement d'une campagne médiatique sans précédent qui vise notre spécialité Mediator® (benfluorex) alors qu'elle n'est plus commercialisée depuis fin novembre 2009. Au-delà des multiples contre-vérités qui ont pu être avancées par certains médias, nous sommes particulièrement sensibles à l'inquiétude ressentie par les malades et leurs familles. Ce d'autant que les atteintes valvulaires sont fréquentes dans la population générale, d'origine dégénérative le plus souvent, et que leur prévalence augmente avec l'âge et le diabète.

Mediator® est un antidiabétique oral mis à la disposition du corps médical depuis 1976. De nombreuses études ont démontré son efficacité : diminution de la glycémie à jeun et baisse d'environ 1 point de l'hémoglobine glyquée HbA1c, associées à un effet favorable sur le profil lipidique (baisse des triglycérides, du cholestérol total et LDLc).

Ces dernières années trois nouvelles études internationales multicentriques randomisées et contrôlées en double aveugle ont permis de confirmer cette efficacité selon les standards internationaux les plus récents et les plus rigoureux chez plus de 1500 patients.

Dans la première étude (1), l'efficacité antidiabétique et la tolérance de Mediator® ont été comparées, à double insu, à celles du placebo et de la metformine chez des diabétiques de type 2 mal équilibrés par le régime seul. Dans une deuxième étude (2), elles ont été évaluées contre placebo, chez des diabétiques insuffisamment contrôlés par des sulfamides hypoglycémiants. Ces deux études ont montré que Mediator® abaissait de 0,8 à 1 point l'HbA1c, diminuait la glycémie à jeun, par rapport au placebo, avec une amélioration du profil lipidique, et une bonne acceptabilité clinique. En particulier, il n'y a pas eu d'hypoglycémie, pas d'acidose lactique, pas d'impact sur la fonction hépatique ou rénale, pas de variation cliniquement signifiante du poids, et pas d'effet indésirable émergent autre que des effets classiquement connus (essentiellement des troubles digestifs).

A la suite des résultats de ces deux études, et dans le but de préciser la place de Mediator® dans la stratégie thérapeutique, en 2005, une troisième étude a été mise en place, REGULATE (3), comparant l'efficacité antidiabétique de Mediator® à celle de la pioglitazone, chez des diabétiques de type 2 insuffisamment contrôlés par des sulfamides hypoglycémiants. Dans le cadre de cette étude, 847 malades ont été recrutés et traités pendant un an. Comme dans tout essai, une surveillance approfondie des événements indésirables a été réalisée, avec notamment un suivi cardiologique comprenant des échocardiographies qui ont été analysées de façon centralisée et en aveugle des traitements.

Cette étude confirme l'efficacité à un an du benfluorex en association aux sulfamides sur le contrôle glycémique, avec une meilleure efficacité de la pioglitazone sur l'équilibre glycémique mais une efficacité supérieure du benfluorex sur le profil lipidique (triglycérides, cholestérol LDL) et sans prise de poids.

Merci d'adresser toute correspondance au : 35, rue de Verdun • 92284 Suresnes cedex
Siège social : 22, rue Garnier • 92578 Neuilly sur Seine cedex • Tél. : 01.55.72.60.00
S.A.S. au capital de 34.596.852 euros • 085 480 796 RCS Nanterre

Les résultats échocardiographiques de l'étude REGULATE, disponibles lors de l'été 2009, ont montré pour leur part :

- que 51 % des patients diabétiques présentaient à l'inclusion, et donc avant la mise en route du traitement par benfluorex ou pioglitazone, des altérations morphologiques valvulaires sans retentissement clinique hémodynamique, et que 84 % présentaient déjà des anomalies valvulaires fonctionnelles (régurgitations de grade 1 dans la majorité des cas) ;

- une incidence des modifications valvulaires fonctionnelles (de grade 1, non symptomatiques), plus importante sous benfluorex que sous pioglitazone (26 % vs 10 %, p<0,0001), essentiellement chez des malades ayant des anomalies pré-existantes. Des régurgitations incidentes de grade >1 ont été détectées chez 2 malades sous benfluorex (0,7 %) et 3 malades sous pioglitazone (1 %). Quant aux altérations morphologiques nouvellement observées, elles ont concerné 8 malades du groupe benfluorex et 4 du groupe pioglitazone.

Ces résultats disponibles et validés par les experts de l'étude (en septembre 2009), ont été communiqués à l'AFSSAPS (à la Commission Nationale de Pharmacovigilance), dans le cadre de la réévaluation du rapport bénéfice/risque du benfluorex. Parallèlement sont apparus les résultats d'études rétrospectives de type pharmaco-épidémiologique, notamment celle de la CNAM (4), aboutissant, sur la base d'hypothèses d'imputations et d'extrapolations, à partir de données des années 2006 à 2008, au calcul d'un risque relatif de valvulopathie de 2,9 chez les malades diabétiques traités par benfluorex.

Bien que les principes actifs de Mediator® et d'Isomeride® soient différents, tant en termes de structures chimiques que d'effets biologiques (en pharmacologie et en clinique) ou en termes de métabolisme, l'existence d'un métabolite commun entre la fenfluramine et le benfluorex avait conduit sur décision de l'AFSSAPS, dès 1998, à rechercher la possible émergence d'hypertensions artérielles pulmonaires et de valvulopathies. Cette surveillance n'a pas objectivé de risque d'hypertension artérielle pulmonaire lié au benfluorex, comme le confirment, depuis cette date, différents rapports de la Commission Nationale de Pharmacovigilance et les conclusions de l'AFSSAPS. Et toujours selon les Autorités compétentes « il n'y a pas eu de signal d'alerte significatif de valvulopathies avant fin 2008-début 2009 » (5).

Dans ce nouveau et récent contexte de signal avéré, la réévaluation du ratio bénéfice/risque a conduit l'AFSSAPS à suspendre en novembre 2009 l'AMM des spécialités contenant du benfluorex (Mediator® ainsi que 2 génériques mis sur le marché en octobre 2009). Nous avons pris acte de cette décision.

Depuis quelques jours, apparaissent dans les médias des chiffres issus, d'une part d'un complément d'études de la CNAM reposant toujours sur des hypothèses concernant les causes de décès, l'imputation, le calcul du nombre de malades exposés à Mediator® à partir de données recueillies entre 2006 et juillet 2010, et d'autre part sur des extrapolations, aboutissant à un nombre de 500 décès « attribuables au benfluorex » en conséquence de valvulopathies, entre 1976 et 2009. A ce jour nous ne disposons toujours pas des rapports des études pharmaco-épidémiologiques ni des précisions nécessaires pour expliquer les calculs réalisés, en l'absence de tout chiffre comparable disponible à ce jour dans les bases de données de pharmacovigilance.

Annexe 1-17

Pour ce qui est de la conduite à tenir aujourd'hui, chez les patients qui ont été traités par Mediator®, elle a été définie dès 2009 par l'AFSSAPS, et précisée ultérieurement par la Société Française de Cardiologie : il est recommandé aux patients de consulter leur médecin traitant pour rechercher une éventuelle symptomatologie fonctionnelle compatible avec une valvulopathie, ou un souffle à l'auscultation. Et si le médecin constate des éléments cliniques évocateurs d'une valvulopathie, il lui appartient d'adresser son patient à un cardiologue qui jugera de l'utilité de pratiquer une échocardiographie.

Pour plus de précisions, nous vous suggérons de vous rendre sur les sites internet (6) de l'AFSSAPS et/ou de la Société Française de Cardiologie, où vous pourrez trouver des éléments complémentaires d'information, utiles dans le cadre de la conduite à tenir face aux malades qui pourraient s'adresser à vous.

Notre Département de l'Information Scientifique et Médicale (Tél. 01 55 72 60 00) se tient à votre disposition pour vous fournir les informations complémentaires, ou la bibliographie, et toute l'aide dont vous auriez besoin.

En espérant vous avoir apporté des précisions utiles, nous vous prions de croire, Cher Confrère, à l'assurance de nos sentiments respectueusement dévoués.

Dr Denys SCHUTZ

Références :

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"Six-month efficacy of benfluorex vs. placebo or metformin in diet-failed type 2 diabetic patients"

2 : *Ph. Moulin, M. André, H. Alawi, L. C. Dos Santos, A. K. Khalid, D. Koev, R. Moore, V. Serban, B. Picandet, M. Francillard ; Diabetes Care, 2006 ; 29:515-520*
"Efficacy of Benfluorex in Combination With Sulfonylurea in Type 2 Diabetic Patients – An 18-week, randomized, double-blind study"

3 : *Ph. Moulin, M André, H. Alawi, L. C. Dos Santos, A. K. Khalid, D. Koev, R. Moore, V. Serban, B. Picandet, M. Francillard ; Diabetes Care, 2006 ; 29:515-520*
"Efficacy of Benfluorex in Combination With Sulfonylurea in Type 2 Diabetic Patients An 18-week, randomized, double-blind study"

4: *A. Weill, M. Paita, Ph. Tuppin, JP. Fagot, A. Neumann, D. Simon, Ph. Ricordeau, JL. Montastruc, H. Allemand ; Pharmacoepidemiology and Drug Safety, 2010 ; DOI:10.1002/pds.2044*

5 : *AFSSAPS : Mediator® (chlorhydrate de benfluorex) – Point d'information – 16 nov. 2010*
www.afssaps.fr

6. *Portails informatiques :*
AFSSAPS : www.afssaps.fr
Société Française de Cardiologie : www.cardio-sfc.org

visable to give fenfluramine intermittently. Previous experiences have shown that in spite of millions of patient-doses, with apparent lack of serious side-effects, there still remains the possibility of ultimate long-term toxicity.

Mr Santer: Servier do most carefully keep records and obtain all available information as to the use of fenfluramine in all countries where it is marketed. In spite of thousands of tablets dispensed, there have been no reports of abuse or of dependence. Even amphetamine addicts who have taken fenfluramine because of its chemical similarity, have not become addicted to fenfluramine, nor have they experienced any of the amphetamine-induced sensations.

Professor Wilson: We will now have the opportunity of looking at S992 prospectively.

THE ROLE OF NORFENFLURAMINE IN FENFLURAMINE ACTIVITY

DR J. C. LE DOUAREC

We have had the privilege 10 years ago to be among the first few pharmacologists having carried out the initial investigations on trifluoromethyl substituted phenethylamines. We very soon became extremely interested in the unique properties of these new compounds.

In fact the CF^3 group induced a dissociation between the stimulant and anorectic properties of the amphetamines. In the first extensive pharmacological report presented in 1962, we emphasized the differences between the fluorine substitution which increased the stimulant effect and the CF^3 substitution which affected oppositely the basic CNS properties of amphetamines. The first compounds synthesized were primary amines substituted on the benzene ring with CF^3 in different positions o, m, n. Norfenfluramine was among them.

Norfenfluramine is more *toxic* than fenfluramine in the mouse, in standard conditions. Norfenfluramine is as an *anorectic* as active as amphetamines in the rat and twice less active in the dog. Fenfluramine in this respect is twice less active in the cat and 3 times in the dog. The *hypertensive* effect of norfenfluramine is comparatively less than those of amphetamines—one half in the rat, 10 times in the dog—but fenfluramine is still less potent on the blood pressure, between 1/5 and 1/10 in the rat and one half in the dog.

There are only quantitative differences between the two compounds, they only differ in their level of activity on different systems. Fenfluramine a number of times is less active than norfenfluramine. Norfenfluramine is certainly involved in the pharmocological effect of fenfluramine since we have evidence that it is its major active metabolite in animal and in man as well. May I add that norfenfluramine was discarded years ago from clinical trials in France because of prominent side-effects, namely nausea, vomiting, diarrhoea and dizziness. Thus norfenfluramine may be responsible for some side-effects of fenfluramine in man.

DISCUSSION

Professor Butterfield: Is there any conversion of norfenfluramine into fenfluramine, as there is conversion of fenfluramine to norfenfluramine?

Le Douarec: There is a difference in gut flora in different parts of the world due to national diets, and this can have an effect on the incidence of diarrhoea caused by norfenfluramine.

Mr Santer: It may be of interest to note that JP.992, the methyl-ethyl derivative of fenfluramine does not appear to produce norfenfluramine.

Dr Prime: Is there any difference in the half-lives of norfenfluramine and fenfluramine?

Le Douarec: No.

Mr Kündig: How much fenfluramine is converted into norfenfluramine?

Le Douarec: There is a great variation, and under normal circumstances about one-third of the fenfluramine in the body exists in the form of norfenfluramine, but one cannot be more precise than that.

Dr Blundell: Is there a common metabolite of amphetamine and fenfluramine?

Le Douarec: No. There are no common metabolites, but there are common metabolic pathways for fenfluramine and amphetamine. The important point is that the CF^3 radical of fenfluramine is not split off with a resultant conversion to amphetamine or any of its metabolites.

Mr Santer: The results of work done in Prof. Beckett's laboratory proved that there were no alterations in fenfluramine-norfenfluramine ratio after repeated doses for six months.

Le Douarec: That is correct, and after prolonged use of fenfluramine the administration could be stopped and restarted without any change in the metabolic pathways.

Professor Opitz: Is there any effect on the pulmonary blood pressure in humans or animals?

Le Douarec: In animals there is evidence of pulmonary hypertension, but the clinical work stopped years ago, and we have no data.

Professor Garattini: In statistical terms we must realize that although in a clinical trial with about 1 000 patients only one or two withdrawal incidences may occur; this would mean that millions of users may eventually produce hundreds of thousands of cases of withdrawal symptoms. In other words, continued monitoring is essential.

AN INTEGRATED THEORY INVOLVING THE HYPOTHALAMUS TO EXPLAIN THE PHARMACOLOGICAL EFFECTS OF FENFLURAMINE

PROFESSOR B. K. ANAND AND DR J. E. BLUNDELL

In monkeys and cats we observed the following two types of electrophysiological and behavioural changes, depending upon the dosage of fenfluramine used: Smaller dosages of fenfluramine result in 'specific' changes restricted to the hypothalamic satiety and feeding centres. The activity of the satiety centre increases with a corresponding inhibition of the feeding centre, while no changes are observed in the rest of the hypothalamus and the adjoining areas of the brain. This is also accompanied by anorexia which appears to have some relation to increased level of glucose utilization.

When relatively larger dosages of fenfluramine are used, or when fenfluramine has been used continuously for a few days even in smaller dosages, there is a generalized inhibitory effect on the hypothalamic regions, which also spreads to the other adjoining areas of the brain. This is accompanied by drowsiness. It is not clear how fenfluramine produces its generalized inhibitory effects.

Drives from the Hypothalamus

In various presentations clinical observations have been made which may be due to influencing the 'drives' which result from the activities of certain specific areas in the hypothalamus.

Anorexia. This results from the 'specific' effects of the drug in increasing the excitability of the satiety centre and inhibiting the feeding centre, thus inhibiting the feeding (hunger) drive.

Thirst. In none of the presentations made at this conference has any mention been made concerning the effects of fen-

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The absorption, metabolism and elimination of (±)-*N*-(2-benzoyloxyethyl)norfenfluramine (JP992) in man

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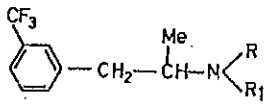
Department of Pharmacy, Chelsea College (University of London), Manresa Road, London, S.W.3, U.K.

The urinary excretion of *N*-(2-benzoyloxyethyl)norfenfluramine (JP 992) was examined in man with normal and acidic urine after oral administration of the drug; 86–100% of the dose was excreted in 48 h as metabolites of the drug having *m*-trifluoromethylbenzyl and benzoyl moieties, but no unchanged drug was detected. Norfenfluramine, *N*-2-hydroxyethylnorfenfluramine, and a metabolite, which on treatment with zinc and hydrochloric acid gave norfenfluramine, were excreted in urine. *N*-2-Hydroxyethylnorfenfluramine and a second unidentified metabolite were also excreted as both sulphate and glucuronide conjugates.

N-(2-Benzoyloxyethyl)norfenfluramine (Id, JP 992) is as potent an anorectic but ten times less toxic in animals as fenfluramine (compound Ib) (Beregi, Hugon & others, 1970). In man with acid urine only 7–10% of the dose of Id was excreted in urine as *N*-2-hydroxyethylnorfenfluramine (Ic) and norfenfluramine (Ia), but no unchanged drug was detected (Brookes, 1968). Pronounced renal tubular reabsorption of Id is probable because it was almost completely absorbed between pH 4 and 9 in the buccal absorption test; its extensive metabolism is also likely.

We have determined by the oxidation method of Beckett, Shenoy & Brookes (1971) the metabolites of Id containing *m*-trifluoromethylbenzyl and -benzoyl moieties excreted in the urine in order to investigate the absorption, distribution and elimination of Id in man, and to determine quantitatively the excretion of various metabolites of the drug.



I

Ia	$R=R_1=H$	Norfenfluramine
Ib	$R=H$; $R_1=Et$	Fenfluramine
Ic	$R=H$; $R_1=C_2H_4OH$	*N*-2-Hydroxyethylnorfenfluramine
Id	$R=H$; $R_1=C_2H_4OCOC_6H_5$;	*N*-(2-Benzoyloxyethyl)norfenfluramine (JP 992)
Ie	$R=COC_6H_5$; $R_1=C_2H_4OH$	*N*-(2-Hydroxyethyl)-*N*-benzoylnorfenfluramine (Rearranged form of JP 992)

MATERIALS AND METHODS

Urinary excretion trials

Three normal healthy males took 60 or 100 mg doses of compound Id hydrochloride (equivalent to 54·31 or 90·52 mg of the base respectively) by mouth in water (the drug was dissolved in 1 ml absolute ethanol and then diluted to 50 or 100 ml

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with water). The urinary pH was kept acid by ingestion of ammonium chloride (Beckett & Brookes, 1967). One subject was also given 2 × 150 mg tablets of compound Id (equivalent to 271·56 mg of the base) and the pH of the urine was not controlled.

In another experiment, two subjects with induced acid urine were given 180 mg base equivalent of Id in solution orally, or on other occasions 8 mg base of Id equivalent (as methane sulphonate) in 2 ml aqueous solution intravenously or 20 mg base equivalent of Ic orally in aqueous solution.

Urine samples were collected at every ½ h or 1 h for the first 4 h, hourly for the next 10 to 12 h and then at longer intervals up to 48 h. In all cases the exact time of urine collection was noted, the pH of the urine and volume was determined shortly after collection, and the urine was stored at 4° until analysis. A "blank" urine sample was collected at the time of drug administration.

Materials

Compounds Ia, b, c, d and e hydrochlorides were obtained from Servier Laboratories Ltd., U.K., as the racemic forms.

Analysis

Total *m*-trifluoromethylbenzyl and -benzoyl metabolites and compounds Ia and Ic were measured (Beckett & others, 1971). After large doses, aliquots of urine high in drug concentration were diluted to contain >50 μg/ml of drug with the subjects "blank" urine before analysis.

Investigations for other metabolites

The urine samples (5 ml) were made alkaline (pH 12) for the extraction of Ia and Ic. They were then made acidic with 6N HCl and zinc powder (about 0·05 g) added. After ½ h, the solution was made alkaline with 20% NaOH, the internal standard (1 ml, 10 μg/ml aletamine hydrochloride in water) added and the solution extracted with freshly distilled ether (3 × 2·5 ml) and analysed for compound Ia by gas liquid chromatography (g.l.c.).

Investigations for conjugated metabolites

(a) With β-glucuronidase (Ketodase, Warner–Chilcott). The following samples were placed on a water bath at 37·5° with constant shaking for 24 h: 1. A "blank" urine (5 ml) adjusted to pH 4·5 with acetic acid, acetate buffer, B.P. 1963 (1 ml) and containing Ketodase (0·5 ml). 2. Aliquots of urine (5 ml) from subjects given oral doses of JP 992; these were adjusted to pH 4·5 with acetic acid and acetate buffer (1 ml) and Ketodase added to some.

(b) With sulphatase (Clarase 300; Takamine). The above experiments were repeated at pH 5·5 using sulphatase (20 mg) instead of β-glucuronidase. After incubation, the samples were analysed by g.l.c. for bases as described.

Thin-layer chromatography

Glass plates (20 × 20 cm) coated with a layer (0·5 mm) of silica gel G (Merck) and activated at 105° for 1 h were stored in a desiccator over silica gel. The reference samples of compounds Ia, Ic, Id and Ie and ethereal extracts of the bases from urine were spotted on plates and the chromatograms developed with the following solvent systems: (a) methanol–acetone (1:1), (b) methanol–chloroform (20:80), (c) methanol–chloroform–ammonia 25% (90:10, 5 drops), and (d) methanol–

chloroform (1:1). Dragendorff's reagent (Stahl, 1962) and a solution of bromothymol blue in ethanol were used to visualize the spots.

Buccal absorption test

The general procedure of Beckett & Triggs (1967) was adopted. Drug solution (0·5 ml) equivalent to 1 mg base of compounds Ia, Ib, Ic and Id was diluted with appropriate buffer solution to 25 ml (pH range 4–9·18) and examined by the test. The expelled solutions were combined, the volume adjusted to 250 ml with distilled water and an aliquot (5 ml) analysed by g.l.c. as for the bases described and the findings were related to calibration graphs prepared from diluted saliva solutions. All curves were plotted as a percentage of the base absorbed against the mean pH of the buffer solution before and after the test.

RESULTS AND DISCUSSION

Total m-*trifluoromethylbenzyl and -benzoyl-containing metabolites*

The drug Id was excreted almost completely after an oral dose under conditions of acidic and uncontrolled urinary pH as *m*-trifluoromethylbenzyl and -benzoyl metabolites (Table 1); unchanged drug was not detected in the urine. These meta-

Table 1. *Urinary excretion in 48 h of total* m-*trifluoromethylbenzyl and -benzoyl-containing metabolites and of norfenfluramine (Ia),* N-*2-hydroxyethylnorfenfluramine (Ic) and other metabolites after oral administration of* (±)-N-*(2-benzoyloxyethyl)-norfenfluramine (Id) hydrochloride to subjects under conditions of acidic urine.*

Subject	Dose (mg)	% dose excreted as† 1	2	3	4	5	Total drug moieties by oxidation to trifluoromethyl benzoic acid as % of dose
1	60	6·2	3·0	19·4	12·3	8·9	101
1	60	—	—	—	—	—	102
2	100	3·2	2·2	4·3	12·7	5·0	87
3	100	5·0	1·5	2·7	7·5	7·5	86
4	300	*4·7	0·3	3·9	5·7	—	101

1. Norfenfluramine (Ia).
2. *N*-2-Hydroxyethylnorfenfluramine (Ic).
3. Norfenfluramine on treatment with Zn/HCl.
4. *N*-2-Hydroxyethylnorfenfluramine as glucuronide.
5. *N*-2-Hydroxyethylnorfenfluramine as sulphate.

* 2 × 150 mg tablets but urine not kept acidic.

† The metabolites constituting the difference between the total of 1–5 and the total drug by oxidation are under investigation.

bolites were excreted rapidly during the first 12 h with a peak at about 2 h (Fig. 1), but small amounts continued to be excreted up to 48 h; smooth rate of excretion: time curves were obtained in subjects with acid urine (Fig. 1) but not when urine pH was uncontrolled. The semi log plots after the maxima showed an exponential decrease and were parallel (Fig. 2); the "apparent" half life of the total drug moieties was about 2 h. Thus, the drug is rapidly and completely absorbed from the gastro-

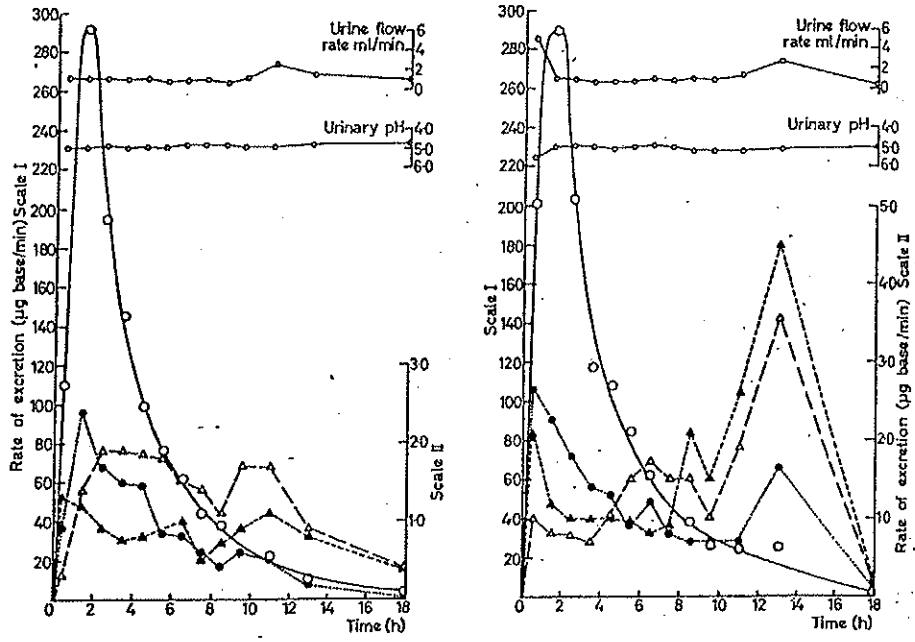

FIG. 1. Urinary excretion of *m*-trifluoromethyl-benzyl and -benzoyl metabolites O—O (scale I), and the metabolites: compound Ic ●---●, Ia ▲---▲ Δ---Δ (all scale II) produced on treatment with Zn/HCl, after the oral administration of 100 mg of compound Id HCl under acidic urine condition to two subjects.

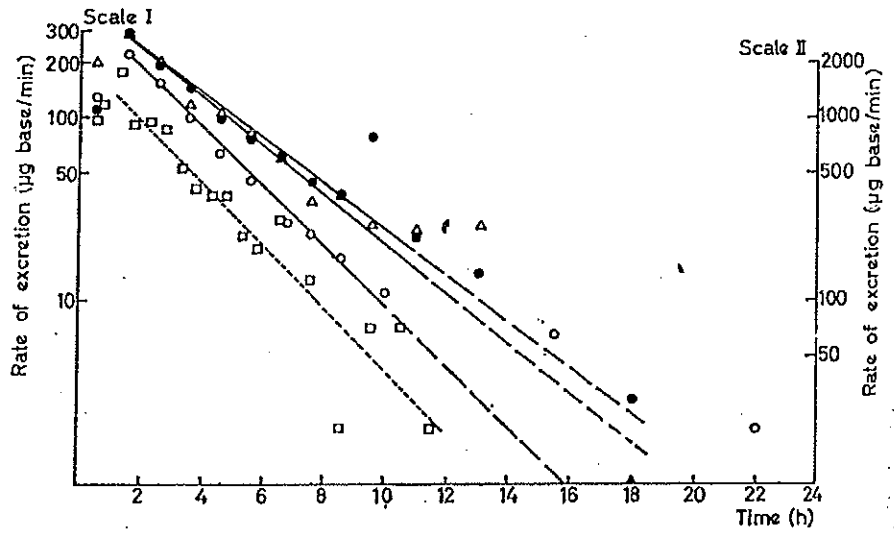

FIG. 2. Urinary excretion of *m*-trifluoromethyl-benzyl and -benzoyl metabolites after oral administration of compound Id HCl. Acidic urine control: Subject 1, 60 mg, O—O; Subject 2, 100 mg, Δ—Δ; Subject 3, 100 mg, ●—●. Fluctuating urinary pH (all scale I): Subject 4, 300 mg (2 × 150 mg tablets) □---□ (scale II).

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intestinal tract and is eliminated rapidly and almost completely via the urine; the predominant metabolites must therefore be highly water soluble compounds and their solubility must be independent of pH since they were recovered from acid and alkaline urine in similar amounts (Table 1). Because virtually quantitative amounts of *m*-trifluoromethylbenzoic acid equivalent to the drug given were obtained after oxidation of total urinary metabolite, a negligible amount of *p*-hydroxylation could have been involved since *p*-hydroxylated metabolites would not give the above acid on oxidation.

Basic metabolites

N-2-Hydroxyethylnorfenfluramine Ic and its dealkylated product norfenfluramine Ia were shown to be present in urine by g.l.c. (see Beckett & others, 1971) and t.l.c. (Table 2); less than 4% of Ic and only about 5% of Ia were recovered after an oral dose of Id under conditions of acid urine (Table 1). By comparison with the oral route, the amount recovered of Ic was doubled (6·7–8·7%) and Ia halved (1–1·7%) when

Table 2. R_F *values for compound Ia, Ic, Id and Ie using various solvent systems.*

Solvent system	R_F values			
	Ia	Ic	Id	Ie
a	0·55	0·45	0·69	0·69
b	0·32	0·29	0·70	0·71
c	0·35	0·46	0·67	0·70
d	0·28	0·51	—	—

Ia and Ic from urine gave similar R_F values to those of authentic samples of Ia and Ic.

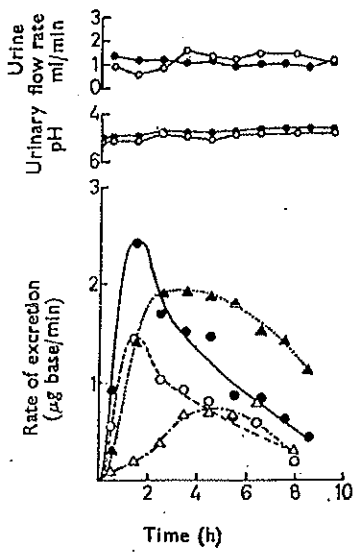


FIG. 3. Comparison of the urinary excretion of compounds Ic –●– and Ia ▲– – –▲ after the oral administration of 100 mg of compound Id HCl, and of compounds Ic ○– – –○ and Ia △–·–△ after the oral administration of 20 mg of compound Ic under acidic urine conditions to Subject 6. (Similar results were obtained with Subject 5.)

a small amount (8 mg base) of Id was administered intravenously to the same subject this was probably a result of a partial bypass of the liver.

The recovery of Ia and Ic in the urine after doses of 180 mg base of Id and 20 mg base of Ic orally were respectively 1·5–3·5 and 1·2–3·7% (5 subjects) and their profiles (Fig. 3) were similar, indicating rapid *in vivo* hydrolysis of Id to Ic; Fig. 4 shows that hydrolysis is virtually complete within 2 h since the semi log rate of excretion:

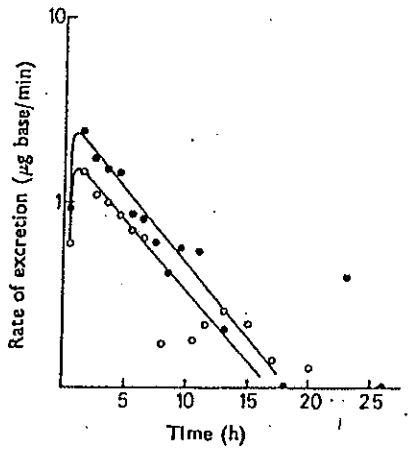


FIG. 4. Comparison of the urinary excretion of compound Ic after the oral administration of 100 mg of compound Id HCl ●—● and 20 mg base of compound Ic ○—○ under acidic urine conditions to Subject 6. (Similar results were obtained with Subject 5.)

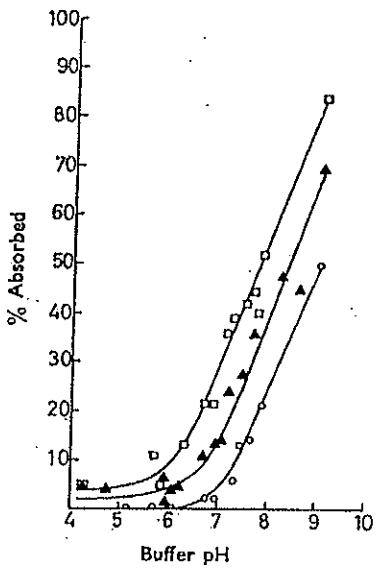


FIG. 5. Buccal absorption of norfenfluramine (Ia) ▲—▲, fenfluramine (Ib) □—□ and *N*-2-hydroxyethylnorfenfluramine (Ic) ○—○.

time plots of Ic from Id and Ic after that time are parallel. The peak excretion rate of Ia occurs later than that of Ic and the urine concentrations remain high for longer (Fig. 3), although Ia is only slightly more lipophilic than Ic in the buccal absorption test (see Fig. 5) at pH 5 and only a slight difference in the kidney tubular reabsorption would then be expected at this urinary pH. The results in Fig. 3 indicate that Ia is produced by metabolism of Ic which itself is formed rapidly *in vivo* from Id.

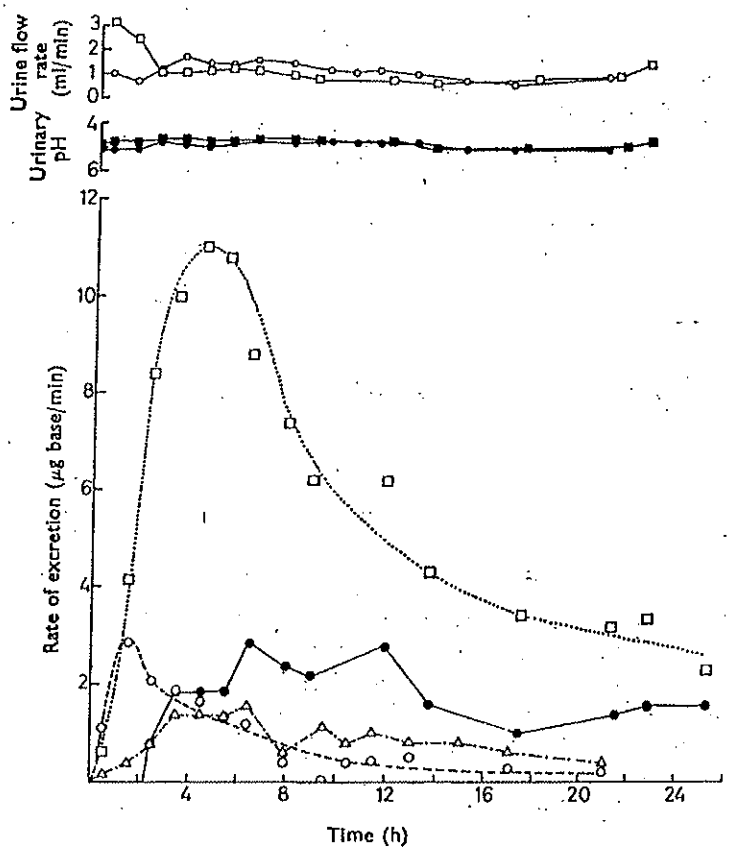
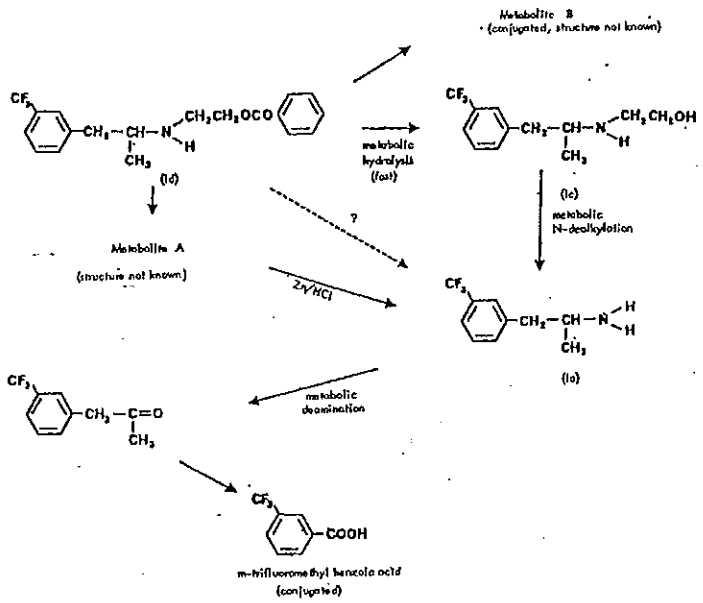


FIG. 6. Comparison of the urinary excretion of (a) unchanged drug □—□ and metabolite compound Ia ●—● after the oral administration of 20 mg of compound Ib HCl and (b) unchanged drug ○- - - ○ and compound Ia △-·-△ after the oral administration of 20 mg of compound Ic under acidic urine conditions to Subject 6.

Under acidic urine conditions, about 25% (19–32·5%, 5 subjects) of an oral dose of compound Ia (20 mg base) was recovered from urine unchanged and about 13% (9·7–19·1%, 5 subjects) of Ia was recovered after an oral dose of Ib (20 mg base), thus indicating about 50% *in vivo* conversion of Ib to Ia. However, only about 3% (1·2–3%, 2 subjects) of Ia was recovered in urine after an oral dose of Ic (20 mg base), indicating about 10% metabolism of Ic by this route; the introduction of the hydrophilic OH group into fenfluramine (Ib) to give *N*-2-hydroxyethylnorfenfluramine (Ic) has thus led to a significant reduction in *N*-dealkylation. Elimination of Ic as

conjugates cannot account for the difference since only about 15–20% of Ic is excreted as combined glucuronide and sulphate conjugates (Table 1). The introduction of the hydroxyl group into the *N*-ethyl group facilitates metabolism of *N*-2-hydroxyethylnorfenfluramine other than by dealkylation since less of this compound as well as of norfenfluramine is excreted when this change is made (see Fig. 6).



Neither compound Id nor its rearranged form Ie (see Beckett & others, 1971) were detected in urine. Two unknown metabolites were excreted. Metabolite A in urine on treatment with zinc and hydrochloric acid give Ia and had an excretion profile similar to that of Ia excreted as free base (Fig. 1). Metabolite B with a g.l.c. retention time of 23 min on Column A (see Beckett & others, 1971) was excreted as glucuronide and sulphate conjugates. Neither the ketone nor the oxime, free or conjugated were excreted in the urine, but conjugated *m*-trifluoromethylbenzoic acid was excreted.

Acknowledgement

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Psychopharmacologia (Berl.) 38, 67—74 (1974)

Chronic Anorexic and Behavioural Effects of the Fenfluramine Metabolite, Norfenfluramine: An Evaluation of Its Role in the Actions of Fenfluramine

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Abstract. The anorexic and behavioural effects of Norfenfluramine were studied in rats. Two separate experiments were conducted involving administration by intra-peritoneal and sub-cutaneous routes respectively. Behavioural effects were assessed by time sampling categorisation on Days 1 and 14 of a 20 day chronic study and anorexic effects by daily weighing. Norfenfluramine was found to be a potent anorexiant, to which tolerance is established fairly quickly. It was also found to possess sedative properties after acute administration, but marked stimulant properties after 14 days chronic administration. These results are similar to those previously reported in a study of Fenfluramine, although the behavioural effects of Norfenfluramine are more marked. The results implicate Norfenfluramine in the anorexic and behavioural effects of Fenfluramine, and provide indirect confirmation of the suggestion made in an earlier paper that Fenfluramine may have chronic stimulant properties.

Key words: Fenfluramine — Norfenfluramine — Anorexia — Activity Analysis.

Introduction

Fenfluramine is known to be metabolized rapidly both in man and in animals, and one of its major metabolites has been shown to be the de-ethylated derivative, Norfenfluramine (Opitz and Weischer, 1966; Beckett and Brookes, 1967; Bruce and Maynard, 1968; Belvedere *et al.*, 1972; Morgan *et al.*, 1972). Campbell (1973) has recently reviewed the literature on the metabolism, absorption and distribution of Fenfluramine; it is clear that whilst Fenfluramine is extensively metabolized to Norfenfluramine, both compounds are eliminated slowly from the body, and only then after being further metabolized. During chronic administration of Fenfluramine blood plasma levels of both compounds plateau for a sustained period. Le Douarec (1971) claimed that "Norfenfluramine is certainly involved in the pharmacological effects of Fenfluramine." However, it is difficult to establish the *precise* role played by Norfenfluramine, (partic

* The work reported here forms part of an M.Sc. thesis to be submitted to the Department of Psychology, U. C. N. W. Bangor.

cularly after chronic administration), because of the simultaneous presence of Fenfluramine, Norfenfluramine *and* other possible metabolites in the body, any of which may have unique pharmacological effects. The situation is made more complex in the study of *chronic* effects by the development of tolerance to these drugs. Taylor *et al.* (1973) have described a possible stimulant effect of Fenfluramine after 14 days chronic administration, in contrast to an acute sedative effect. The present paper reports on the behavioural and anorexic effects of Norfenfluramine with an identical experimental procedure in an attempt to elucidate, at least partially, the role played by Norfenfluramine in the anorexic and behavioural effects of Fenfluramine. The results indicate that Norfenfluramine is a potent anorexiant which acts acutely as a sedative but has a definite chronic stimulant effect. It is concluded that part, at least, of the anorexic effect of Fenfluramine is mediated by Norfenfluramine, and that the stimulant effect noted after chronic administration of Fenfluramine is due either to the build up of high body levels of Norfenfluramine *itself*, or of metabolites of Norfenfluramine.

Methods

The methods used were essentially identical to those described by Taylor *et al.* (1973). In both of the experiments reported here there were 16 male hooded rats weighing between 200 and 250 g at the start of the experiment, which were housed randomly in groups of four. In Experiment One, 8 of the 16 subjects received 3 mg per kg of Norfenfluramine sub-cutaneously, whilst the other eight subjects received saline control injections. In Experiment 2 the drugged subjects received 3 mg per kg of Norfenfluramine by the intra-peritoneal route. Drugs were made up in saline and injected daily for the twenty day chronic studies, all subjects receiving the relevant solution at a volume equivalent to 2 ml per kg body weight. Subjects were adapted to a 22 h deprivation schedule prior to both experiments and fed for two hours daily throughout the studies. Drug injections preceded this feeding period by 30 min. The anorexic effects of Norfenfluramine were assessed by daily weighing, and the behavioural effects by time sampling categorisation 30 min post injection on Days 1 and 14 of the chronic study, according to the procedure described in detail by Taylor *et al.* (1973) and Goudie and Taylor (1974). All behavioural observations were made blind, by a well trained observer. The two experiments were run successively.

Results

a) Weight Changes. Fig. 1 shows the cumulative sum of the daily differences between the mean body weights of the two treated groups and the mean body weights of the saline control groups. Norfenfluramine has a clear permanent effect on body weight, the magnitude of which is proportional to the route of injection, the I. P. route having the greater effect.

b) Behavioural Observations. The behavioural effects observed in the two experiments are shown in Table 1. Acutely, Norfenfluramine pro-

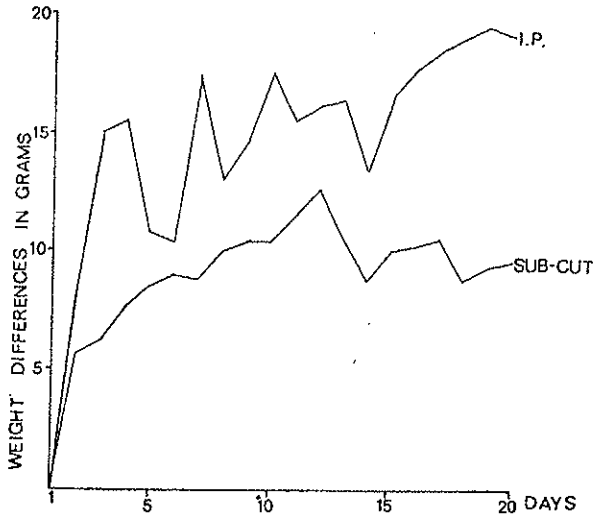

Fig. 1. Cumulative sum of the daily differences between the mean body weights of the sub-cutaneous and I.P. injected groups and the mean body weights of the saline controls

Table 1. Statistical comparisons between controls and drugged subjects on days 1 and 14 of the chronic study for each behavioural category. (Mann Witney U Test)

	Experiment 1		Experiment 2	
	Controls day 1 compared with drugged subjects day 1	Controls day 14 compared with drugged subjects day 14	Controls day 1 compared with drugged subjects day 1	Controls day 14 compared with drugged subjects day 14
Rearing	$P < 0.001$ ↓	NS	$P < 0.001$ ↓	$P < 0.05$ ↑
Walking	NS	$P < 0.05$ ↑	$P < 0.05$ ↓	$P < 0.001$ ↑
Sniffing	$P < 0.05$ ↑	NS	$P < 0.001$ ↑	NS
Grooming	$P < 0.05$ ↓	NS	NS	$P < 0.05$ ↓
Immobile	NS	$P < 0.01$ ↓	NS	$P < 0.01$ ↓

NS = Not Significant ↓ Indicates reduction ↑ increase

duces a significant reduction in the incidence of Rearing and an increase in the incidence of Sniffing when given sub-cutaneously. When given I. P. significant reductions in the incidences of Rearing and Walking and an increase in Sniffing occur. The effects are more pronounced when the same dose is given by the I. P. route than sub-cutaneously. After 14 day chronic administration sub-cutaneous injection causes an increase in the incidence of Walking with a reduction in the incidence of Im-

mobility; I. P. injection again has more marked effect in that the incidence of Walking *and* Rearing are significantly increased whilst the incidences of Grooming and Immobility are decreased. It is clear that the behavioural effects of Norfenfluramine are reversed following chronic administration in both experiments.

Discussion

a) Weight Changes. Norfenfluramine *per se* is a potent anorexic agent to which tolerance is established fairly rapidly in a manner similar to that reported for Fenfluramine (Taylor *et al.*, 1973) but which is not a general feature of the effects of all phenylethylamine derivatives (Taylor and Goudie, 1974). Norfenfluramine, like Fenfluramine (Taylor *et al.*, 1973) exerts a permanent effect on body weight. Magour *et al.* (1974), have shown that Amphetamine exerts a similar permanent effect on body weight in rats, despite the development of tolerance to its effects on food intake, and suggest that "the persistance of body weight loss is probably due to the increased hyperactivity of rats during the experiment". An alternative explanation for the permanent effects of Fenfluramine, Norfenfluramine and Amphetamine on body weight lies in their well known fat mobilising effects (Garratini, 1973). It is difficult to see how the permanent effect of Fenfluramine, in particular, can be attributed to increased locomotor activity since Taylor *et al.* (1973) have presented evidence for such an effect *despite* the development of behavioural tolerance to the drug after sustained chronic administration.

Since Norfenfluramine is an active anorexic agent and is known to be one of the major metabolites of Fenfluramine, it seems clear that at least part of the anorexic effects of Fenfluramine are mediated by Norfenfluramine or its metabolites, as suggested by Le Douarec (1971).

b) Behavioural Observations. The acute behavioral changes induced by Norfenfluramine indicate that it has sedative properties, whilst the chronic behavioural effects are indicative of possible stimulant properties of the compound. Taylor *et al.* (1973) emphasised the difficulties inherent in describing psychotropic agents as either sedatives or stimulants without reference to the behavioural or neurophysiological variables involved. The most obvious example of this problem has been derived from studies on the effects of amphetamine on operant behaviour, which led McKearney (1972) to suggest that "Amphetamine tends to increase responding that normally occurs at relatively low rates . . . at the same doses at which it decreases responding that normally occurs at high rates". The most adequate method of validating a screening test for C.N.S. stimulants or depressants is by studying the effects of drugs which are themselves generally defined as stimulants or sedatives, within the specific expermental situation of the test. Goudie and Taylor (1974) have reviewed the

evidence for the effects of neuroleptics, anxiolytics and stimulants on exploratory behaviours such as those considered here; and concluded that reductions in the incidences of rearing and ambulation are generally indicative of sedative properties of a drug, whilst increases in the incidence of these "active" behaviours are indicative of stimulant properties Norton (1973) has presented evidence that amphetamine at doses of 0.5 and 1.0 mg per kg increases the incidence of rearing and walking in a novel environment, whilst reducing those of sniffing and grooming, in agreement with suggestions made above. As suggested by Taylor *et al.* (1973) and Goudie and Taylor (1974) an increase in the incidence of sniffing observed after acute administration of a phenylethylamine derivative does not necessarily reflect the induction of stereotyped behaviour. Due to the hierarchical, exhaustive nature of the behavioural categorisation system used in these studies a reduction in the incidences of rearing and walking, following administration of a sedative drug, will by definition be accompanied by an increase in the incidences of behaviours lower down the hierarchy. The sniffing observed after injection of 3 mg per kg Norfenfluramine differs in kind from that observed following injection of high doses of Amphetamine. The observed increase in the incidence of sniffing following acute administration of Norfenfluramine is consequently not due to the induction of sterotyped behaviour.

The behavioural effects of Norfenfluramine are similar to those described for Fenfluramine except that they are much more marked; in particular, the chronic "stimulant" effect (reported by Taylor *et al.*, 1973, with 9 mg per kg Fenfluramine sub-cutaneously) is much more marked with Norfenfluramine even at a lower dose. Since Fenfluramine is extensively metabolized to Norfenfluramine in rats and since the latter is known to be metabolized prior to excretion it is suggested that the effects noted after chronic administration of both Fenfluramine and Norfenfluramine are due *either* to the build up of brain concentrations of Norfenfluramine or of its metabolites. Bruce and Maynard (1968) suggested that Norfenfluramine is converted to m-trifluormethylhippuric acid, although this has been questioned by Campbell (1973); any possible active metabolites consequently remain unknown. The marked stimulant effects noted after chronic administration of Norfenfluramine, provide indirect confirmation that under certain conditions Fenfluramine itself has a stimulant effect in accord with reports of such effects in animals (Everitt and Hackett, 1972; Le Douarec *et al.*, 1966; Taylor *et al.*, 1973) and in humans (Oswald *et al.*, 1971; Belvedere *et al.*, 1972). At high doses (between 15 and 30 mg per kg) Norfenfluramine induces abnormal behaviour of a type similar to that induced by Fenfluramine; and it is more potent in this respect than Fenfluramine. The behavioural syndrome induced by both compounds differs from that induced by amphetamine in that,

over a range of doses, it is characterised by a predominance of the behaviour patterns of backward locomotion and circling, whilst the amphetamine induced syndrome is characterised by a predominance of repeated head movement, compulsive gnawing and sniffing (Taylor *et al.*, 1974). Fenfluramine and Norfenfluramine consequently have similar behavioural effects at high doses, just as they do at low doses. The two compounds also have similar neurochemical effects (which differ from those of amphetamine) and which have been shown to be closely linked to their psychopharmacological actions. Both drugs are known to lower brain serotonin concentrations (Duhault and Verdavainne, 1967; Costa *et al.*, 1971; Costa and Revuelta, 1972; Ghezzi *et al.*, 1973); and 5HT has been implicated in the behavioural (Jespersen and Scheel-Krüger, 1970; Southgate *et al.*, 1971) and anorexic (Funderbunk *et al.*, 1971; Samanin *et al.*, 1972; Jespersen and Scheel-Krüger, 1973; Blundell *et al.*, 1973; Clineschmidt, 1973) effects of Fenfluramine. Morgan *et al.* (1972), Costa and Revuelta (1972) and Ghezzi *et al.* (1973) have all suggested that the 5HT depletion observed following Fenfluramine administration may be mediated by Norfenfluramine, and not by the parent compound. Since 5HT has been strongly implicated in the actions of Fenfluramine it is clear that Norfenfluramine and its metabolites may play an important role in the anorexie and behavioural effects of Fenfluramine. Whether or not Norfenfluramine is best characterised as the major compound involved in Fenfluramine's effects remains uncertain. The data reported in this paper provide evidence which implicates Norfenfluramine as a mediator of the actions of Fenfluramine.

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Does fenfluramine act via norfenfluramine?

Goudie, Taylor & Wheeler (1974) recently demonstrated that behavioural and appetite depressant effects of norfenfluramine were strikingly similar to those of fenfluramine. In several species fenfluramine is de-alkylated to norfenfluramine (Bruce & Maynard, 1968; Beckett & Brookes, 1967; Morgan, Cattabeni & Costa, 1972). These findings suggest that the anorectic properties of fenfluramine could be due to its metabolite norfenfluramine.

Samanin, Ghezzi & others (1972) and Clineschmidt (1973) demonstrated that lesions which specifically affect the serotonergic systems in the brain antagonized the anorectic properties of fenfluramine. We have investigated the possible central action of fenfluramine and its metabolite norfenfluramine by injections of small amounts directly into the brain of rats.

For the local injections, the area of the nucleus interstitialis of the stria terminalis was chosen because its involvement in the regulation of food intake is indicated by experiments on the elicitation of feeding behaviour by α-adrenoceptor stimulating drugs (Booth, 1967; Davis & Keesey, 1971; Broekkamp & van Rossum, 1972), and the neostriatum was chosen because it contains the highest synthesizing capacity for 5-hydroxytryptamine and therefore seems to be highly innervated by serotonergic nerves (Mandell, Knapp & Hsu, 1974).

Bilateral implantation of two cannulae was made stereotaxically in male Wistar rats of 200-250 g. In two groups the cannulae were aimed at the nucleus interstitialis of the stria terminalis and in two groups the cannulae were placed into the neostriatum. Post mortem examination of the brains confirmed that the injection sites were in the area A 7·3 ± 0·35, L 2·4 ± 0·7 and D 0·9 ± 0·4 within the neostriatum and A 6·65 ± 0·4, L 0·9 ± 0·4 and D −1·0 ± 0·5 within the nucleus interstitialis of the stria terminalis with reference to the atlas of König & Klippel (1963).

The drugs were dissolved in saline and injected in a volume of 0·5 μl into each hemisphere.

The anorectic effect was measured on the intake of cold cooked white rice in a 30 min period. The injections were made 15 min before the test period began. The animals were housed and tested individually and had laboratory chow and tap water freely available. The rats were made accustomed to the diet and the injection procedure in the week preceding the injections. Injections were made every other day in ascending dosage until an anorectic effect was evident or the dose became unreasonably high. The sequence of doses was concluded with a second saline injection.

Table 1. *Amount of rice eaten in a half hour period following injections of saline, norfenfluramine and fenfluramine.*

Treatment (μg)	Neostriatum		Nucleus interstitialis of the stria terminalis	
	Fenflur. n=7	Norfenflur. n=6	Fenflur. n=6	Norfenflur. n=6
saline	4·7±1	5·1±1·3	5·5±0·8	5·7±1
2 × 2·5	4·6±0·9	6·9±1·2	5·1±1·2	5·6±0·6
2 × 5	4·2±0·8	7·3±1·6	5·9±0·6	5·8±1·3
2 × 10	3·2±0·3	0·7±0·3*	6·2±0·9	2·1±0·9*
2 × 20	3·6±0·4		5·9±0·7	
2 × 40	4·3±0·9		4·9±1·3	
saline	5·0±0·7	4·9±1·3	6·1±1·2	5·1±0·6

The amounts eaten are given in grams ± the standard error of the mean; * = $P<0·05$; two-tailed Mann-Whitney U-Test. Drugs were: (±)-fenfluramine HCl and norfenfluramine HCl.

As shown in Table 1, even high dosages of fenfluramine are inactive when administered via the intracerebral route. Under identical conditions norfenfluramine is active in moderate doses. There was a significant difference in the amount of rice eaten by the rats with nucleus interstitialis cannulae and those with neostriatal cannulae after norfenfluramine administration (Mann-Whitney U-test; two-tailed; $P<0{\cdot}05$).

It is unlikely that fenfluramine is inactive because of a more rapid removal from the brain since Morgan & others (1972) have shown that both fenfluramine and norfenfluramine persist in the brain for up to 24 h after a systemic injection. Our results are comparable to the results of Kramer, Rubicek & Turner (1973) who demonstrated that after topical application only norfenfluramine is effective in inducing mydriasis whereas after systemic injections both drugs are active. Together these findings add substance to the suggestion that the central anorectic properties of fenfluramine are mediated mainly by norfenfluramine.

A further screening of other brain sites with norfenfluramine is necessary before it can be concluded that the neostriatum is the main site of action after systemic administration.

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Psycho-pharmacology

Discriminative Stimulus Properties of Fenfluramine in an Operant Task: An Analysis of its Cue Function

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Abstract. Fenfluramine at a dose of 3.0 mg/kg was found to possess discriminative stimulus properties controlling lever selection by rats in a two-lever operant task. Subjects trained to discriminate the 'Fenfluramine cue' failed to generalize to amphetamine in extinction tests at doses between 0.25 and 1.0 mg/kg. Subjects did, however, generalize to the fenfluramine metabolite, norfenfluramine, at a dose of 2.0 mg/kg. These data provide further evidence for a pharmacological difference between fenfluramine and amphetamine, and support the hypothesis that norfenfluramine is an active metabolite of fenfluramine. The relevance of these findings to theoretical and methodological aspects of drug discrimination studies is considered.

Key words: Fenfluramine – Norfenfluramine – Amphetamine – Drug discrimination – Stimulus properties of drugs – Fixed ratio responding

Fenfluramine is a phenylethylamine derivative whose pharmacological effects reportedly differ from those of amphetamine (for reviews see Garratini et al., 1975; Pinder et al., 1975). Despite evidence for a distinction between these two chemically related compounds, however, there have been reports of amphetaminelike effects of fenfluramine in animals (Everitt and Hacket, 1972; Taylor et al., 1973; Zolovick et al., 1973; Clineschmidt et al., 1975) and in humans at very high doses (e.g., Riley et al., 1969). Moreover, in a recent study from this laboratory we reported that the aversive effects of amphetamine in the conditioned taste aversion paradigm were markedly attenuated by prior drug experience with either fenfluramine or amphetamine (Goudie and Thornton, 1975). While the interpretation of the effects of drug pretreatment on drug-induced taste aversions remains a subject of controversy (Cappell and Le Blanc, 1976), one possible explanation of our finding is that amphetamine and fenfluramine have common stimulus properties in rats. In conjunction with earlier reports of possible amphetaminelike effects of fenfluramine, this result led us to examine both the ability of fenfluramine to act as a discriminative stimulus and the relationship between any such stimulus properties and those of amphetamine. In addition, in an attempt to clarify the role of norfenfluramine in the actions of fenfluramine (Goudie et al., 1974; Broekkamp et al., 1975), we examined the relationship between the stimulus properties of the metabolite and those of its parent compound.

The results reported demonstrate the potential value of studying the discriminative stimulus properties of drugs as one method of predicting the abuse potential of novel derivatives of drugs of abuse. They also provide further information about the pharmacological identity of fenfluramine.

METHODS

Seven female albino rats (230–280 g) were individually housed and run in 30 min operant sessions 5 days a week. One hour after each session subjects received access to food and water for 1 h, but at all other times they were deprived of food and water. On weekends the subjects received access to food and water for 1 h. This deprivation regime allowed subjects to maintain their body weight at approximately 75% of ad lib. body weight.

Standard two-lever operant chambers were used in the study. Reinforcement consisted of 0.02 ml of 20% (v/v) condensed milk presented via a dipper situated between the levers. Secondary reinforcement was available in the form of a light onset in the food chamber during dipper operation. Standard electromechanical programming and cumulative recorders were used to record and control behaviour.

(i) Acquisition of Fixed-Ratio Lever Pressing. Following preliminary shaping subjects were trained for seven sessions during which reinforcement was available on a CRF schedule on both levers. From the eighth session onwards only one lever was operative throughout any one session on an FR 10 schedule of reinforcement. Subjects were run for a further 22 sessions in this phase of the study. Between

sessions the operative lever was varied pseudorandomly with the constraint that the same lever was never operative on more than three consecutive sessions. During these sessions all subjects developed the stable response pattern characteristic of FR schedules of reinforcement.

(ii) Acquisition of a Saline-Fenfluramine Discrimination. The procedure adopted in this study was derived from that described by Colpaert et al. (1975a). Subjects were reinforced for responses on the drug (right) lever on days on which they received injections of fenfluramine and for responses on the saline (left) lever on days on which they received saline injections. After four sessions of alternating saline and drug injections the operative lever was varied according to the two weekly pseudorandom sequence shown:

Week 1: Drug – Saline – Saline – Drug – Drug

Week 2: Saline – Drug – Drug – Saline – Saline.

Injections were administered 30 min before each session. *d,l*-Fenfluramine hydrochloride was administered at a dose of 3.0 mg/kg. All injections were made i.p. at a volume equal to 2 ml/kg body weight of rat.

Each subject was trained to a criterion of ten consecutive sessions of 'correct lever selection.' 'Correct lever selection' was defined as taking place in a session in which the first reinforcement (on an FR 10 schedule) was obtained within the first 12 responses, regardless of which lever was selected (subjects were consequently allowed no more than two responses on the inoperative lever).

(iii) Stimulus Control Test with Fenfluramine. After all the rats could discriminate between saline and fenfluramine, the degree of discriminative control exerted by the training dose of fenfluramine was assessed in a 5 min extinction session in which neither primary *nor* secondary reinforcement was available. This stimulus control test took place (as did subsequent generalization tests) on the last day of the two weekly alternating sequence described above. On this day the saline session was omitted and subjects received a 5 min extinction session only. The test day was consequently preceded by a day on which subjects received saline injections; this procedure was adopted in order to minimise on testing days any residual drug effects that might have influenced the results of the stimulus control test (and subsequent generalization tests).

Two measures of discriminative control and generalization were recorded. The first measure was the total number of responses made (irrespective of which lever they were made on) before ten had accumulated on the drug lever. This measure is subsequently referred to as the CRD 10 index (cumulative responses before ten made on the drug lever), and gives an index of lever selection by subjects. A CRD 10 value of between 10 and 12 was considered to indicate 'perfect' generalization to the training drug, values between 13 and 19 to indicate 'imperfect' generalization, and values greater than 19 to indicate progressively greater discrimination between the drug administered and the training dose of fenfluramine. The second measure recorded was the percentage of total responses made on the drug lever during the extinction session. This index is subsequently referred to as 'Percentage Drug Responding.'

(iv) Generalization Tests with Amphetamine and Norfenfluramine. Following the stimulus control test subjects were tested for generalization to *d*-amphetamine sulphate and *d,l*-norfenfluramine hydrochloride. Generalization tests involved the methods and procedures described above. Generalization to amphetamine was tested at doses of 0.25, 0.5 and 1.0 mg/kg, and to norfenfluramine at doses of 1.0 and 2.0 mg/kg.

(v) Rationale behind Experimental Design and Data Analysis. Overton (1974) has considered in some detail the methodology of cross-drug generalization studies, noting that conventional procedures that employ measures of percentage responding on the training drug lever raise the problem that it is virtually impossible to interpret meaningfully the commonly encountered partial transfer effects (i.e., 50% responding as under training drug). Since it is possible to assess such transfer against either the saline or the training drug baseline, it may seem possible to derive statistically significant results that can be considered indicative of either generalization or discrimination, but in fact they merely reflect random responses. Because it is invalid to assess partial transfer effects against an arbitrarily chosen baseline, it appears that percentage training drug responding scores in cross-drug generalization tests are subject to difficulties of interpretation. If a saline baseline is used, such scores may result in the labelling of drugs as similar when they do in fact differ – a phenomenon termed 'over-inclusiveness' (Overton, 1974). In order to show that two drugs are equivalent, it is necessary to show that 'the test drug causes drug choices just *as frequently* as does the training drug' (Overton, 1974). In this study the fenfluramine stimulus control test consequently provides a baseline for the assessment of the possible stimulus equivalence of other drugs. It should be noted, however, that the statistical techniques required to fulfill the criterion outlined are those that involve acceptance of the null hypothesis; the sophisticated techniques required for such an analysis have not been previously used in this field, nor are they commonly encountered in psychological and pharmacological literature.

Due to the problems of interpretation and analysis of percentage drug responding scores, those reported in this study are interpreted with considerable caution. Such scores are only used to support conclusions drawn from lever selection data (CRD 10 index) and to make tentative inferences when equivocal lever selection data is obtained.

The methodological problems raised by the percentage drug responding scores can be largely resolved by using a procedure that forces the subject to make a binomial choice between the drug and the nondrug responses. A response selection index, such as that used in this and related studies (Colpaert et al., 1975a, b, c, d), consequently provides a more viable measure of the discriminative properties of drugs than the more conventional percentage drug response measure.

RESULTS

(a) Acquisition and Maintenance of Saline-Fenfluramine Discrimination. All subjects were run for 98 operant sessions with six intervening extinction sessions. Table 1 presents data relevant to the acquisition and successful maintenance of discrimination.

After subjects had been trained to criterion, a few "errors" in lever selection were recorded (Table 1), but these occurred in only a very small proportion of sessions postcriterion. Figure 1 shows a typical cumulative record for a session in which an "error" in selection occurred. The cumulative record illustrates how a subject that initially selected the inoperative lever rapidly switched to the operative lever and continued responding on that lever with only rare alternations between levers. In the session shown, 96.7% of the total responses were made on the correct (operative) lever.

(b) Stimulus Control Test with Fenfluramine. Table 2 shows the results of the stimulus control test with fenfluramine (generalization test in extinction).

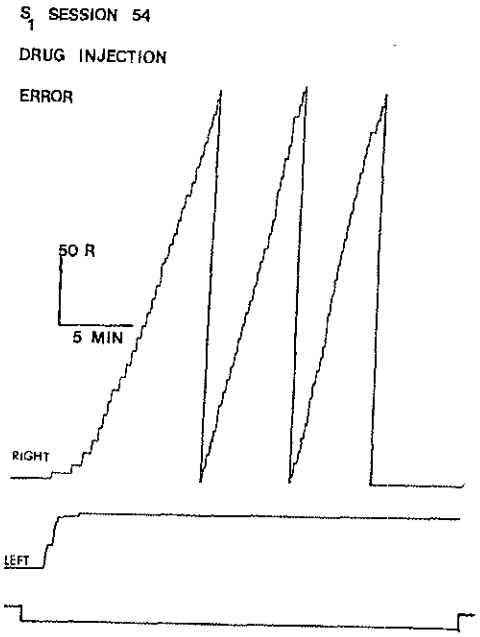

Fig. 1. Sample cumulative records for a session in which an 'error' selection was recorded. Only the right (drug) lever was operative. Cumulative records of responding on both right and left levers are shown

Table 1. Acquisition and maintenance of fenfluramine-saline discrimination (all subjects run for 98 sessions)

	Acquisition	Maintenance (post-criterion)		
	Trial on which criterion was attained[a]	'Partial errors'[b]	'True errors'[c]	Percentage of total sessions post-criterion on which 'correct selection' occured
S_1	50	1	3	91.7
S_2	31	0	1	98.5
S_3	23	0	3	96.0
S_4	36	0	0	100.0
S_5	27	0	1	98.6
S_6	31	1	0	98.5
S_7	10	0	1	98.9
Median	31	0	1	98.5

[a] Last trial in sequence of ten successive 'correct lever selection' sessions

[b] Sessions in which the first reinforcement was obtained after > 12 but < 20 responses

[c] Sessions in which the first reinforcement was obtained after ≥ 20 responses

All subjects selected the drug lever (CRD 10 index). This effect was highly significant ($P < 0.01$, Binomial Test). However, the degree of stimulus control exerted by the drug was variable. Some subjects persisted in responding on the drug lever in extinction (S_6), while others showed a much weaker degree of stimulus control (S_7).

Table 2. Stimulus control test (generalization test in extinction with training drug, fenfluramine at 3.0 mg/kg)

	Total number of responses in 5 min session	Percentage of total responses on the drug lever	CRD 10 Index Cumulative responses before 10 made on drug lever
S_1	90	79	12
S_2	46	65	12
S_3	176	57	10
S_4	77	70	10
S_5	138	51	10
S_6	42	90	10
S_7	27	44	10
Median	77	65	10

Table 3. Generalization tests in extinction with *d*-amphetamine sulphate

	Total number of responses in 5 min sessions			Percentage of total responses on the drug lever			CRD 10[a] Cumulative responses before 10 made on drug lever		
	Dose (mg/kg)			Dose (mg/kg)			Dose (mg/kg)		
	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0
S_1	259	218	195	42	45	38	78	49	26
S_2	262	191	36	76	39	19	10	22	> 36[b]
S_3	165	125	99	36	15	40	81	65	30
S_4	188	99	127	74	26	48	10	53	24
S_5	161	348	336	14	12	9	59	70	42
S_6	203	63	59	52	40	42	10	22	42
S_7	118	133	37	28	7	4	39	132	> 37[b]
Median	188	133	99	42	26	38	39	53	–

[a] A CRD 10 value of < 12 indicates 'perfect' generalization to the fenfluramine cue. A value of > 12 < 20 indicates 'imperfect' generalization to the fenfluramine cue. A value of 20 or more indicates a progressively greater degree of discrimination between the test drug and fenfluramine

[b] Indicates that subject did not make ten responses on the drug lever within extinction

(c) Generalization of Discrimination to Amphetamine. Table 3 shows the results of tests of generalization to *d*-amphetamine sulphate.

At the 0.25 mg/kg dose of amphetamine 3 out of 7 subjects selected the drug lever. There was consequently no consistent pattern of cross-drug generaliza-

Table 4. Generalization test in extinction with *d,l*-norfenfluramine

	Total number of responses in 5 min sessions		Percentage of total responses on the drug lever		CRD 10 Index Cumulative responses before 10 made on drug lever	
	Dose (mg/k)		Dose (mg/kg)		Dose (mg/kg)	
	1.0	2.0	1.0	2.0	1.0	2.0
S_1[a]	53	0	53	0	21	–
S_2	151	102	68	87	22	10
S_3	97	31	21	100	67	10
S_4[a]	30	0	100	0	10	–
S_5	254	31	23	48	69	10
S_6	19	33	58	67	16	17
S_7	42	12	24	83	33	12
Median	53	31	53	83	22	10

[a] Two subjects failed to respond in the 5 min extinction session at the 2.0 mg/kg dose

tion when this measure was used. However, at this dose the subjects showed significantly less Percentage Drug Responding in extinction than under fenfluramine (Randomisation Test for Matched Pairs, $P < 0.05$). Although subjects did not readily discriminate the fenfluramine cue from the amphetamine cue in lever selection, fenfluramine clearly exerted a greater degree of stimulus control than did amphetamine (Percentage Drug Responding index), suggesting that at higher doses the drugs might be discriminated.

At the higher doses of amphetamine (0.5 and 1.0 mg/kg), no subject initially selected the drug lever (the CRD 10 values were all greater than 19). This effect was statistically significant ($P < 0.01$ at both doses, Binomial Test). The CRD 10 values were greater under both higher doses of amphetamine than under fenfluramine ($P < 0.02$ at both doses, Randomization Test for Matched Pairs). Furthermore, subjects made significantly fewer responses on the drug lever (as a percentage of the total number of responses) under amphetamine than under fenfluramine ($P < 0.02$ at both doses, Randomisation Test for Matched Pairs).

The results show that in cross-drug generalization tests rats are able to discriminate the fenfluramine cue from the amphetamine cue.

(d) Generalization Test with Norfenfluramine. Table 4 shows the results of the generalization test with norfenfluramine.

At the lowest dose (1.0 mg/kg), 2 of the 7 subjects selected the drug lever, so that the results obtained from the lever selection (CRD 10) measure were again somewhat equivocal since no clear pattern emerged. However, there was *no* significant difference in the Percentage Drug Responding scores obtained with norfenfluramine at this dose and with fenfluramine at the training dose (Randomisation Test for Matched Pairs). This result contrasts with the findings with amphetamine, since with the latter drug subjects made significantly fewer responses on the drug lever at all doses, suggesting that subjects *might* generalize from fenfluramine to norfenfluramine at higher doses. This conclusion was substantiated by the results of the cross-drug generalization test with the higher dose (2.0 mg/kg), at which all subjects who responded selected the drug lever ($P < 0.05$, Binomial Test). Furthermore, the Percentage Drug Responding, scores were not significantly different from those generated by fenfluramine (Randomisation Test for Matched Pairs). The results consequently demonstrate that subjects generalized to norfenfluramine, in contrast to the discrimination noted with amphetamine.

A comment is appropriate on the fact that at the 2.0 mg/kg dose two subjects failed to respond at all in extinction. In fact, all subjects emitted very few responses in the extinction test at this dose. This effect may reflect the potent anoretic and behavioural effects of norfenfluramine, which is more active dose for dose than fenfluramine (Goudie and Taylor, 1974).

DISCUSSION

It is clear that relatively low doses of fenfluramine possess discriminative stimulus properties that can be used by rats as a cue for lever selection in an operant task. Overton (1973) has emphasised that drugs with high abuse potential are characterised by potent stimulus properties in state-dependent and discriminative learning tasks. However, the ability to act as a discriminative stimulus is not in itself an indication of the abuse potential of a particular drug. There have been extremely few reports of abuse of fenfluramine in man (Pinder et al., 1975). The data reported here suggest that the mere ability of a drug to induce a discriminative cue may be a necessary but not a sufficient characteristic to consider the drug liable to abuse. Colpaert et al. (1975b) have suggested that *one* further necessary condition for a drug to be a drug of abuse is that it should induce cue properties at doses lower than those that have marked aversive effects. This hypothesis seems to be in accord with the finding that fenfluramine (generally considered a non-abused drug) possesses discriminative stimulus properties as well as aversive properties in humans (Stunkard et al., 1973; Griffith et al., 1975) and in rats (Goudie and Thornton, 1975).

In a study of the discriminative properties of fenantyl, Colpaert et al. (1975a) have claimed that

for sessions in which reinforcement was available "the (high) percentage of responding on the reinforced lever evidences the extreme and virtually perfect accuracy with which lever selection is executed." This conclusion is potentially misleading since it is clear (Fig. 1) that the percentage of responding on the reinforced lever can reach a very high level despite the fact that an 'error' in lever selection occurs. In two-lever drug discrimination tasks in which only one lever is operative during acquisition and maintenance of the discrimination, the percentage responding on the operative lever in reinforced sessions is a poor measure of the discriminative stimulus properties of drugs since it may provide a spuriously high index of discriminative control. That this is the case was indicated by the results of the stimulus control tests in extinction with fenfluramine, from which it was clear that the stimulus control exerted by the drug was relatively weak (in some subjects lever selection degenerated to chance levels). This effect, in conjunction with the finding that in sessions in which the inoperative lever was selected the subjects switched rapidly to the correct lever, suggested that in this study subjects effectively learned a 'win-stay, lose-shift' discrimination (Weiskrantz, 1968) upon which the discriminative stimulus properties of drugs were superimposed in any specific session. Thus the information provided by the stimulus properties of the drug is in effect redundant once the subjects have emitted ten responses. This analysis of the behavioural strategies adopted in this study again suggests that the initial lever selection index used in this and related studies (Colpaert et al., 1975a; b; c; d) provides a more reliable and more readily interpretable index of the discriminative stimulus properties of drugs than the more conventional measure of percentage responding on the drug lever in extinction. A further advantage of this index is that it is not confounded by possible drug effects on motor output. It has been suggested that one of the major features of the behavioural effects of amphetamine is to cause perseveration of responding (Lyon and Robbins, 1975); such an effect will confound percentage drug responding indices of drug generalization. Although no quantitative data relevant to this point were collected in this study, examination of the cumulative records obtained in the amphetamine generalization tests indicated that at all doses some subjects showed perseverative responding on both levers with few alternations between levers. Any such effect of the test drug on motor output limits the extent to which a subject's behaviour reflects the discriminative properties of the test drug when such properties are assessed over long response sequences. However, such an effect becomes irrelevant when one considers very short response sequences, as in the lever selection (CRD 10) index. Thus there are a number of theoretical and statistical reasons for suggesting that a response selection index is at present the index of choice in studies of the discriminative properties of drugs. In this study the conclusions drawn from the Percentage Responding index are essentially the same as those derived from the lever selection index, although it is clear that the results obtained from the latter index are much less equivocal. However, it is perhaps relevant to note that although a selection index as used here provides statistical and methodological clarity, it suffers from a major limitation in that it does not allow for the possibility that drugs may vary along a variety of stimulus dimensions. Since one drug may be similar to another on some dimensions and not on others, it is to be expected that 'true' partial transfer may occur between drugs. It does not appear that contemporary techniques for the study of the stimulus properties of drugs can address themselves to this problem at the present.

The finding that subjects generalized in extinction to norfenfluramine supports the hypothesis that norfenfluramine is an important active metabolite of fenfluramine (Goudie et al., 1974; Broekkamp et al., 1975; Duhault et al., 1975) since the pharmacological effects of norfenfluramine presumably constitute a major part of the discriminative stimulus complex mediating the cue properties of the parent drug. This hypothesis is supported by the finding that subjects injected with norfenfluramine emitted fewer responses in the extinction test with norfenfluramine at the 2.0 mg/kg dose than in the extinction test with fenfluramine at a higher dose (3.0 mg/kg) due to the more potent anorectic and sedative effects of the metabolite.

The discrimination between amphetamine and fenfluramine noted in this study provides further evidence of a fundamental pharmacological difference between these two related compounds and clearly does not support suggestions that fenfluramine has amphetaminelike effects. At no dose studied was there *any* indication of generalization to amphetamine. These findings are in accord with studies of the subjective effects of the two drugs in humans (Gotestam and Gunne, 1972; Griffith et al., 1975), which indicate that addict volunteers can discriminate the two drugs. The results consequently illustrate the predictive value of cross-drug generalization in tests in animals for assessing the abuse potential in humans of novel derivatives of drugs of abuse and in the classification of psychoactive agents (Barry, 1974).

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Psychopharmacology

Anorectic effect of fenfluramine isomers and metabolites: Relationship between brain levels and in vitro potencies on serotonergic mechanisms

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Abstract. A study of the possible molecular mechanisms of action by which the isomers and metabolites of fenfluramine increase serotonin transmission, leading to anorectic activity, is presented. The actual brain levels of fenfluramine and norfenfluramine isomers after administration of equi-anorectic doses to rats are compared with their potencies in affecting serotonergic mechanisms in vitro. Isomers and metabolites of fenfluramine can have the same pharmacological action by influencing serotonin uptake, release and binding in a quantitatively different manner.

Key words: Fenfluramine – Anorectic effect – Serotonin uptake – Serotonin release – $5HT_1$ binding sites – $5HT_2$ binding sites

There is ample evidence that fenfluramine exerts its anorectic activity by selectively enhancing serotonergic mechanisms in the brain (Garattini et al. 1978, 1979), although its precise mechanism of action is at present unknown. Fenfluramine (F) is a racemic compound, and the *d*- and *l*-isomers are metabolized to form the respective norfenfluramine (NF) isomers (Caccia et al. 1979, 1981); all four different compounds display anorectic activity in rats (Garattini et al. 1979). In this study we compare the brain concentrations of fenfluramine and norfenfluramine isomers after administration of equi-active anorectic doses of the compounds, with their potencies in affecting serotonergic mechanisms in vitro. We selected three main sites at which drugs can increase serotonin (5HT) transmission: (a) inhibiting reuptake of the released 5HT, (b) increasing 5HT release from nerve endings, (c) mimicking 5HT action on post-synaptic receptors.

Materials and methods

CD-COBS (Charles River, Italy) male rats weighing 180–200 g were used. The animals were housed in plastic cages at constant room temperature (21 ± 1° C) and relative humidity (60%).

In vitro studies

^{3}H-5HT (specific radioactivity 28 Ci/mmol) and ^{3}H-spiroperiodol (specific radioactivity 29 Ci/mmol) were purchased from NEN. Uptake of ^{3}H-5HT (0.1 μM) was studied in 0.6-ml aliquots of purified synaptosomes in Krebs-Henseleit buffer, incubated for 5 min at 30° C or 0° C (to determine passive transport) as previously described (Mennini et al. 1978). Release experiments were performed as described by Mennini et al. (1981a), using synaptosomes purified from brains of normal male rats and of males treated 24 h before with 10 mg/kg reserpine IP. Briefly, 0.6-ml aliquots of synaptosome suspension, preloaded with 0.1 μM ^{3}H-5HT, were filtered and put on the bottom of superfusion chambers, at 37° C. Drugs, dissolved in Krebs-Henseleit buffer, were superfused for 20 min at 0.5 ml/min; the effluent was collected every 5 min and counted for radioactivity content. Crude membrane preparations from rat cortex were used for binding assays, using a semiautomatic filtration technique as reported in a previous paper (Mennini et al. 1981b). ^{3}H-5HT, for measuring $5HT_1$ binding sites, and ^{3}H-spiroperidol, for detecting $5HT_2$ binding sites, were used at concentrations of 2 nM and 0.7 nM, respectively. For both ^{3}H ligands, non-specific binding was determined in the presence of 1 μM dLSD.

In vivo studies

a) Food intake. Each ED_{50} (dose inducing 50% reduction of food intake) was calculated in separate experiments (Garattini et al. 1979) on at least five dose levels with six animals for each dose, measuring the 1-h food intake beginning 30 min after drug administration, as described before (Samanin et al. 1979).

b) Drug measurement. Rats, injected IP with drugs at doses corresponding to the determined ED_{50}, were killed by decapitation 30 or 90 min after dosing. Their brains were quickly removed, frozen on dry ice, and stored at −20° C until assay.

Fenfluramine isomers and metabolites were determined by gas-liquid chromatography, as described by Caccia and Jori (1977).

Drugs

Fenfluramine isomers and metabolites were a kind gift from Servier Labs, Neully/Seine, France; reserpine (Serpasil) from Ciba-Geigy, Origgio, Italy; LSD from Sandoz, Basel, Switzerland.

Results

Table 1 shows the concentrations of fenfluramine and norfenfluramine isomers in rat brain after intraperitoneal

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Table 1. Brain concentrations of fenfluramine (F) and norfenfluramine (NF) isomers after IP injection of anorectic ED_{50} doses to rats

Compound	Anorectic ED_{50} (μmoles/kg, IP) (95% confidence limits)	Time (min)	Brain concentrations (nmoles/g ± SE)			
			*d*F	*d*NF	*l*F	*l*NF
d-Fenfluramine	5.6 (3.7 – 8.4)	30	8.8 ± 0.5	3.6 ± 0.1	–	–
		90	4.6 ± 0.4	5.7 ± 0.4	–	–
d-Norfenfluramine	3.9 (2.5 – 5.7)	30	–	7.4 ± 0.9	–	–
		90	–	7.2 ± 0.5	–	–
l-Fenfluramine	12.8 (7.3 – 22.2)	30	–	–	15.1 ± 1.3	15.8 ± 1.0
		90	–	–	5.5 ± 0.3	22.3 ± 1.0
l-Norfenfluramine	9.5 (6.9 – 13.1)	30	–	–	–	23.5 ± 1.8
		90	–	–	–	23.5 ± 1.2

Brain concentration of F and NF isomers are the mean ± SE of six rats

Table 2. Effect of the optical isomers of fenfluramine and norfenfluramine on 5HT uptake, release and binding in vitro

Compound	^{3}H-5HT uptake IC_{50} (μM)	^{3}H-5HT release SC_{25} (μM)		5HT receptors IC_{50} (μM)	
		Normal	Reserpine	$5HT_1$	$5HT_2$
d-Fenfluramine	0.5 ± 0.1	5.0 ± 0.4	> 100	7.0 ± 0.7	> 30
d-Norfenfluramine	1.4 ± 0.1	1.0 ± 0.1	0.2 ± 0.01	4.2 ± 0.3	2.2 ± 0.1
l-Fenfluramine	8.9 ± 1.0	3.0 ± 0.1	1.0 ± 0.2	2.7 ± 0.2	4.5 ± 0.3
l-Norfenfluramine	14.0 ± 1.8	2.0 ± 0.3	2.0 ± 0.1	2.2 ± 0.2	3.0 ± 0.2
Chlorimipramine	0.3 ± 0.1	–	–	–	–
LM 5008	0.2 ± 0.1	> 100	> 100	–	–
5HT	–	–	–	0.002 ± 0.0001	1.3 ± 0.2
Metergoline	–	–	–	0.060 ± 0.005	0.004 ± 0.0005
Methiothepin	–	–	–	0.3 ± 0.04	0.003 ± 0.0003
Cyproheptadine	–	–	–	1.0 ± 0.1	0.012 ± 0.002

Data are means ± SE of four replications
IC_{50} are the drug concentrations producing 50% inhibition of ^{3}H-5HT uptake or binding, and are calculated from the log dose-effect plot of the data, using three-four drug concentrations. SC_{25} are the drug concentrations stimulating ^{3}H-5HT release by 25%, calculated from the log dose-effect plot of the data using three drug concentrations
% release stimulation = (% release with drugs/% release of controls × 100)−100

administration of the dosages found to induce 50% reduction in food intake. The *d*-forms of fenfluramine and norfenfluramine were both more active than the *l*-forms: the injected dosages and the brain concentrations necessary to elicit anorectic effects in the rat were lower than those of the *l*-forms. In fact, fenfluramine concentrations of about 9 nmoles/g (2 μg/g) were measured in rat brain 30 min after administration of *d*-fenfluramine, while after *l*-fenfluramine injection the brain concentrations were higher (about 15 nmole/g or 3.5 μg/g). At this interval *d*-norfenfluramine amounted to only 40% of the parent concentrations, while the *l*-metabolite reached brain concentrations slightly higher than *l*-fenfluramine.

Table 2 shows the in vitro activities of fenfluramine and norfenfluramine isomers on serotonergic mechanisms. Preliminary data were reported in a previous paper (Garattini et al. 1979). For uptake inhibition results were the same, but for $5HT_1$ binding assay and release studies slight modifications in the method used and calculations of results (Mennini et al. 1981a, b) resulted in disparities between data reported previously and data presented here. The present experimental data in Table 2 are more homogeneous and thus give a better indication of relative drug potencies than earlier findings. The *d*-isomers of fenfluramine and norfenfluramine were both more active than the *l*-forms in inhibiting 5HT accumulation, *d*F being the most active (similar to chlorimipramine and LM 5008). Further experiments in our laboratories using synaptosomes from reserpinized animals have shown that while *d*F is a true inhibitor of 5HT uptake, the reduced 5HT accumulation is due to the releasing ability of *d*NF (Borroni et al. 1983).

The *d* and *l* metabolites were slightly more active than the parent compounds in releasing ^{3}H-5HT from normal

Table 3. Ratios of brain concentrations to in vitro activities of the optical isomers of fenfluramine and norfenfluramine

Treatment	Time	Compounds in the brain	Uptake	Release		Binding	
				Normal	Reserpine	$5HT_1$	$5HT_2$
*d*F	30	*d*F	17.0	1.8	–	1.3	–
		*d*NF	2.6	3.6	18.0	0.9	1.6
	90	*d*F	8.9	0.9	–	0.7	–
		*d*NF	4.1	5.7	28.5	1.4	2.6
*d*NF	30	*d*NF	5.3	7.4	36.9	1.8	3.4
	90	*d*NF	5.2	7.2	36.2	1.7	3.3
*l*F	30	*l*F	1.7	5.0	15.1	5.6	3.3
		*l*NF	1.1	7.9	7.9	7.9	5.3
	90	*l*F	0.6	1.8	5.5	2.0	1.2
		*l*NF	1.6	11.2	11.2	10.1	7.4
*l*NF	30	*l*NF	1.7	11.7	11.7	10.7	7.8
	90	*l*NF	1.6	11.7	11.7	10.7	7.8

Ratios were calculated from the data in Table 1 and 2 as follows: Brain concentrations (nmoles/g)/in vitro activities (nmoles/ml)

synaptosomes in superfusion. However, in synaptosomes of reserpine-treated rats the effect of *d*-fenfluramine was virtually abolished, indicating that most of 5HT released by *d*F in normal synaptosomes originates from a reserpine-sensitive pool. In contrast, the effect of *d*NF was enhanced in synaptosomes of reserpine-treated animals, indicating that *d*NF is able to release 5HT from an extra-granular compartment. This is supported by pharmacological data showing that reserpine treatment potentiates the anorectic effect of *d*NF in rats (Borsini et al. 1982).

The pattern of effects of the *l*-isomers of fenfluramine and norfenfluramine was different from that of the *d*-isomers, *l*-fenfluramine's effect being increased by reserpine whereas that of *l*-norfenfluramine was not affected.

The *l*-forms were slightly more potent than the *d*-forms at $5HT_1$ binding sites; *d*NF was the most active compound at $5HT_2$ binding sites, although their IC_{50}-values were considerably higher than those obtained for known 5HT receptor agonists and antagonists (Table 2). *d*F was the least active compound both at $5HT_1$ and $5HT_2$ binding sites.

Table 3 reports the ratios between the brain levels of drugs and metabolites and their relative in vitro activities on serotonergic mechanisms (see Discussion).

Discussion

In the present investigation of the possible molecular mechanism of action by which the isomers and metabolites of fenfluramine increase serotonin transmission leading to anorectic activity, we compared the actual brain levels of fenfluramine and norfenfluramine isomers after administration of equi-active doses to rats, with their in vitro potencies on serotonergic synaptic mechanisms. Since fenfluramine distribution is the same in different brain regions (Garattini et al. 1979) and the compound has not been shown to accumulate selectively in serotonergic terminals (Mennini et al. 1980), we assumed that under these experimental conditions, its brain level distribution was uniform, representing the drug concentration available in vivo at target molecules to produce 50% of its maximal effect.

Then we took the in vitro activities (concentrations producing half-maximal effects or 25% in the cases of release) of fenfluramine isomers and metabolites as an index of their affinities for the three possible "targets" leading to increased serotonergic transmission. The ratios presented in Table 3 are therefore directly proportional to the expected activities of the four compounds on serotonergic mechanisms, taking into account the actual presence of the parent compound and metabolites in the rat brain.

It is important to underline that we do not know the exact extent to which uptake inhibition, release and receptor stimulation contribute to the final effect: no direct quantitative comparison of the different mechanisms is at present possible.

d-Norfenfluramine was the most active compound in terms of doses and brain concentrations necessary to elicit anorectic effect in the rat. Its action may be principally due to serotonin release from a reserpine-insensitive pool (Mennini et al. 1981a), followed by its ability to bind to postsynaptic serotonin binding sites. That the postsynaptic activity of *d*NF results in stimulation of receptors rather than blockade is supported by the fact that metergoline significantly reduced the depletion of brain serotonin caused by *d*NF in the rat (Invernizzi et al. 1982).

*d*F was the compound with pharmacological activity nearest to that of *d*NF (1.4 times in term of dosage), but its potency cannot be predicted simply from in vitro experiments because of its rapid metabolism to *d*NF in the rat. At the beginning (30 min) the parent compound induces a powerful inhibition of 5HT uptake, but this effect is probably not sufficient per se to reduce food intake in rats (Samanin et al. 1980). Its activity as a 5HT releaser from a reserpine-sensitive pool (Mennini et al. 1981a) and as a direct agonist on post-synaptic receptors, although not marked, could play a role in the anorectic effect. However the presence in the brain of *d*F-treated rats of *d*NF, which

represents only 40% of the parent compound levels at 30 min but which on account of its longer half life reaches 123% at 90 min, probably also contributes to the anorectic effect of fenfluramine, with the enhancement of 5HT release that can be obtained in such conditions. It is important to consider that *d*F and *d*NF release 5HT through two different mechanisms (Mennini et al. 1981a), the former being active on a reserpine-sensitive pool, the latter on a reserpine-insensitive pool. Thus the final effect of the administered *d*F on 5HT release may be the result of potentiation between the parent compound and its metabolite simultaneously present at the synapse (see Table 3).

The mechanism of action of *l*NF seems balanced between a direct stimulation of 5HT postsynaptic receptor sites and the increase of 5HT release from the reserpine-insensitive pool; uptake inhibition does not seem to be important for the activity of the *l*-isomers (Table 3). When rats were treated with *l*F, the levels of *l*F and *l*NF were roughly the same at 30 min, while *l*F present at the end of experiment amounted to only 25% of its metabolite.

This is in accordance with previous reports of a faster N-demethylation of the *l*- than the *d*-form after administration of the isomers to rats (Caccia et al. 1981; Jori et al. 1978), and suggests that, even if in vitro the mechanism of action of *l*F and *l*NF on serotonergic neurons seems to be similar, the anorectic effect obtained after *l*F treatment might well derive from the presence of high concentrations of *l*NF in the brain.

In conclusion, the present study demonstrates that the isomers and metabolites of fenfluramine can have the same pharmacological action (anorexic effect) by influencing basic mechanisms (uptake, release, and receptor binding) of stimulation of serotoninergic neurons in a quantitatively different manner.

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Comparative studies on the anorectic activity of *d*-fenfluramine in mice, rats, and guinea pigs

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Summary. The present study compares the anorectic activity of *d*-fenfluramine and its metabolite *d*-norfenfluramine in three animal species. *d*-Fenfluramine and *d*-norfenfluramine show anorectic activity at increasing doses (ED_{50}) in rats, guinea pigs, and mice, *d*-norfenfluramine being more active than *d*-fenfluramine in all three species. Equiactive anorectic activities are reached with different brain levels of *d*-fenfluramine and *d*-norfenfluramine, guinea pigs being the most sensitive species, followed by rats then mice. The metabolite most probably plays a major role in the anorectic effect of *d*-fenfluramine in guinea pigs, contributes to the anorectic activity in rats, but adds little to the action of the parent drug in mice. The different sensitivity to *d*-fenfluramine and *d*-norfenfluramine in these three species does not appear to be explained by a number of biochemical parameters, including serotonin uptake or release, receptor subtypes, or ^{3}H-*d*-fenfluramine binding and uptake.

Key words: *d*-Fenfluramine – Anorectics – Rats – Mice – Guinea pigs – Serotonin – Serotonin receptors – Serotonin uptake – Serotonin release

Introduction

Fenfluramine has long been considered an anorectic agent which acts through serotonergic system (Duhault and Verdavainne 1967; Garattini et al. 1975), although at higher doses fenfluramine also affects catecholamines in the brain (Invernizzi et al. 1986). The two isomers of fenfluramine have different biochemical and functional effects, with the *d*-isomer showing more potency and specificity in its effects on the serotoninergic system and food intake (Garattini et al. 1987).

d-Fenfluramine is an anorectic agent that differs from *d*-amphetamine in that it has no stimulating or stereotypic effects (Le Douarec and Neveu 1970). In some experimental conditions *d*-fenfluramine shows a clear anti-amphetamine activity (Berger et al. 1973; Garattini et al. 1975; Bendotti et al. 1980). Unlike *d*-amphetamine, *d*-fenfluramine does not significantly affect the catecholamine metabolism (Garattini et al. 1986; Invernizzi et al. 1986) but it enhances serotonin transmission (Garattini et al. 1987). The anorectic effect of fenfluramine is not reduced by antidopaminergic or antinoradrenergic drugs (Garattini and Samanin 1976) but is specifically blocked by antiserotoninergic drugs such as metergoline (Samanin and Garattini 1990).

The biochemical basis for the enhancement of the serotonergic system lies in the capacity of *d*-fenfluramine to block serotonin uptake (Borroni et al. 1983) and to release serotonin from nerve terminals (Mennini et al. 1981). In order to understand the mechanism of action of *d*-fenfluramine it is essential to know that this compound is rapidly transformed by the liver into an *N*-de-ethylated metabolite, *d*-norfenfluramine (Caccia et al. 1982). Also *d*-norfenfluramine is an anorectic agent (Garattini et al. 1979), inhibits serotonin uptake (Borroni et al. 1983) and enhances its release (Mennini et al. 1981). However, *d*-norfenfluramine differs from *d*-fenfluramine in that it also releases serotonin in reserpinized animals (Mennini et al. 1981).

The effect of *d*-fenfluramine on the serotoninergic system may be mediated by the high-affinity binding sites for ^{3}H-*d*-fenfluramine (Mennini et al. 1988; Gobbi et al. 1989) and by the fact that ^{3}H-*d*-fenfluramine is taken up by synaptosomes through a serotonin carrier mechanism (Garattini et al. 1989). Previous investigations have characterized the binding and uptake of ^{3}H-*d*-fenfluramine, showing that the two mechanisms can be differentiated using suitable inhibitors (Garattini et al. 1989). Most of the data concerning the described mechanism of action of *d*-fenfluramine have been obtained in the rat, and information on the effect of *d*-fenfluramine in other species is scanty and fragmentary. This investigation therefore compared the effect of *d*-fenfluramine and its metabolite *d*-norfenfluramine in three animal species:

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rats, mice, and guinea pigs. This paper summarizes the observations concerning (a) the anorectic activity, (b) the brain levels of *d*-fenfluramine and *d*-norfenfluramine at an equal anorectic effect, (c) the effect of *d*-fenfluramine on receptor binding, and uptake and release of serotonin, and (d) the presence of high-affinity binding sites and uptake for ^{3}H-*d*-fenfluramine in the three selected species.

Materials and methods

Animals. Male CD1 albino mice (20–25 g), male CD-COBS rats (175–200 g), and male albino guinea pigs (250–300 g) (Charles River, Italy) were used. The animals were housed at constant temperatures and relative humidity with fixed 12-h light/dark cycles. All the animals, with the exception of those used for evaluation of food intake, had free access to food and water.

In vivo studies. All experiments were performed between 9 a.m. and 12 a.m. *d*-fenfluramine hydrochloride and *d*-norfenfluramine hydrochloride (Servier, Neuilly-sur-Seine, France) were injected i.p. dissolved in saline. Animals concerning food intake evaluation were trained to eat their daily ration in 4 h (10 a.m.–2 p.m.). On the day of the experiment *d*-fenfluramine or *d*-norfenfluramine was administered i.p. and after 5 min (mice) or 30 min (rats and guinea pigs) food was made available. The amount of food eaten during the first hour was then measured and calculated as percentage of the amount eaten by controls.

The ED_{50} (reduction of 50% of food eaten by controls) was calculated at five dose levels with five rats and four guinea pigs per group or with three groups of four mice for each dose, according to the method of De Lean et al. (1978), adapted for use with a Macintosh computer (V. Guardabasso, personal communication). Statistical differences were assessed according to the F-test of the extra mean of squares (De Lean et al. 1978). Data concerning the ED_{50} in rats have already been published elsewhere (Mennini et al. 1985).

In a second experiment *d*-fenfluramine and *d*-norfenfluramine were given at doses corresponding to their anorectic ED_{50} and animals were killed by decapitation 5 and 60 min (mice) and 30 and 90 min (rats, guinea pigs) thereafter for determination of the parent drug and metabolite brain concentrations. *d*-Fenfluramine and *d*-norfenfluramine were extracted with benzene from aliquots (0.1–1 ml) of the brain homogenates (1 g/10 ml) after the addition of an internal standard and analyzed by electron capture gas liquid chromatography (Spinelli et al. 1988). Standard curves were prepared by spiking tissues daily with known concentrations of *d*-fenfluramine and *d*-norfenfluramine (calculated as free bases). Because of the wide range found for the drug and its metabolite in brain tissue in different animal species and in different experimental conditions, calibration graphs in the concentration range 0.05–1 µg/g were generally used. The slopes of these curves, determined by linear regression analysis, were used to calculate compound concentrations in unknown samples. The coefficient of variation for identical samples containing 0.1 µg was 10% or less and the recovery was approximately 90%.

In vitro studies. The brain regions were dissected as described by Glowinski and Iversen (1966).

^{3}H-d-fenfluramine binding. Frozen rat total brains were homogenized (Ultra-Turrax TP 1810, 2 × 20 s) in 50 vol Na^+/K^+ phosphate buffer, 50 mmol/l, pH 7.4. The homogenate was incubated at 37°C for 10 min and centrifuged at 50000 *g* for 10 min. The pellet was resuspended in 125 vol Na^+/K^+ phosphate buffer, 50 mmol/l, pH 7.4, and kept on ice until use. For the binding assay (Mennini et al. 1988) 0.50 ml of this preparation was incubated for 90 min at 37°C with 0.50 ml of the same buffer containing ^{3}H-*d*-fenfluramine [Commissariat a l'Energie Atomique (CEA, France), specific activity 15 Ci/mmol] at a final concentration of 10 nmol/l.

^{3}H-paroxetine, ^{3}H-ketanserin, ^{3}H-serotonin, ^{3}H-8OH-DPAT, ^{3}H-mesulergine binding. Crude membrane preparations were obtained from frozen brain areas [hippocampus for 2 (*N,N*-di[2,3 (*n*)-3H-propylamino)-8-hydroxy-1,2,3,4-tetrahydronephthalene (^{3}H-8OH-DPAT), cerebral cortex for ^{3}H-ketanserin, ^{3}H-paroxetine and ^{3}H-mesulergine, striatum for ^{3}H-5HT].

Binding assays, using the ligand ^{3}H-paroxetine, were performed according to Habert et al. (1985): ^{3}H-paroxetine (NEN, Du Pont, Germany, specific activity 23 Ci/mmol, final concentration 0.12 nmol/l) and crude membrane preparation from cerebral cortex (1000 vol) were incubated for 60 min at 22°C in 50 mmol/l Tris-HCl buffer, pH 7.4, containing 120 mmol/l NaCl and 5 mmol/l KCl in a final volume of 2 ml.

^{3}H-ketanserin ($5HT_2$) binding assay were performed according to the method of Leysen et al. (1982). In brief, ^{3}H-ketanserin (NEN, specific activity 62 Ci/mmol, final concentration 0.8 nmol/l) and tissue suspension (100 vol final dilution, cerebral cortex) were incubated at 37°C for 15 min in 50 mmol/l Tris-HCl buffer, pH 7.7, final volume 1 ml.

^{3}H-serotonin ($5HT_{1B}$ and $5HT_{1D}$) binding was assayed in a final incubation volume of 1 ml, consisting of membrane suspension 100 vol final dilution (mouse and rat striatum for $5HT_{1B}$ and guinea pig striatum for $5HT_{1D}$), ^{3}H-serotonin (NEN, specific activity 30 Ci/mmol, final concentration 2 nmol/l) and displacing agents or buffer. The samples were incubated at 25°C for 30 min (Peroutka 1986) in 50 mmol/l Tris-HCl buffer, pH 7.7, containing 10 µmol/l pargyline, 4 mmol/l $CaCl_2$, and 0.1% ascorbic acid.

^{3}H-8OH-DPAT ($5HT_{1A}$) binding was assayed in a final incubation volume of 0.5 ml, consisting of membrane suspension (100 vol final dilution, rat, mouse, or guinea pig hippocampus), ^{3}H-8OH-DPAT (NEN, specific activity 223 Ci/mmol, final concentration 1 nmol/l) and displacing agents or buffer (0.01 ml). The samples were incubated at 25°C for 30 min (Peroutka 1986) in 50 mmol/l Tris-HCl buffer, pH 7.7, containing 10 µmol pargyline, 4 mmol/l $CaCl_2$ and 0.1% ascorbic acid.

^{3}H-mesulergine binding to $5HT_{1C}$ receptors was studied in the presence of 0.1 µmol/l spiperone using cerebral cortex (Mengod et al. 1990) in a final incubation volume of 1.0 ml, with ^{3}H-mesulergine (NEN, specific activity 85 Ci/mmol, final concentration 1 nmol/l), membrane preparation (50 vol) and displacing agents or buffer (0.02 ml). The mixture was incubated for 30 min at 37°C in 50 mmol/l Tris-HCl buffer, pH 7.7, containing 10 µmol/l pargyline, 4 mmol/l $CaCl_2$ and 0.1% ascorbic acid.

After incubation, the samples for ^{3}H-paroxetine, ^{3}H-ketanserin, ^{3}H-*d*-fenfluramine, ^{3}H-serotonin, ^{3}H-8OH-DPAT, and ^{3}H-mesulergine binding were rapidly filtered (using a Brandel M-48RP model) under vacuum through Whatman GF/B glass fiber filters (GF/C for ^{3}H-paroxetine binding) and washed three times with 4 ml ice-cold buffer. The radioactivity trapped on the filters was counted in 8 ml Filter Count (Packard) in a Beckman LS 7500 liquid scintillation spectrometer with a counting efficiency of 45%. Inhibition curves were calculated using the "Allfit" program (De Lean et al. 1978) running on an IBM-AT personal computer.

^{3}H-serotonin and ^{3}H-d-fenfluramine uptake. Crude mitochondrial pellets (P2) were obtained from fresh brain regions (hypothalamus for ^{3}H-serotonin and total brain minus cerebellum for ^{3}H-*d*-fenfluramine) as previously described (Mennini et al. 1981). The final pellet was diluted (100 vol initial weight for ^{3}H-serotonin, 67 vol for ^{3}H-*d*-fenfluramine) with Krebs-Henseleit buffer having the following composition (mmol/l): NaCl (116); $NaHCO_3$ (25); NaH_2PO_4 (1); KCl (6); $MgSo_4$ (1); $CaCl_2$ (2); glucose (10); pargyline (10); EDTA (0.07); ascorbic acid (0.3); pH 7.2–7.4. Samples of 0.6 ml (for ^{3}H-serotonin) and 1.5 ml (for ^{3}H-*d*-fenfluramine) with final protein concentrations of 0.5–1.0 mg/ml (Peterson 1977) were incubated at 4°C or 30°C in a water bath. Drugs in a concentration range 10 pmol–100 µmol were added during 5-min preincubation at 30°C. Uptake was started by the

Table 1. Anorectic activity of *d*-fenfluramine (*d*-F) and *d*-norfenfluramine (*d*-NF) expressed as ED_{50} (mg/kg, i.p.) and brain concentrations after administration of these doses to mice, rats, and guinea pigs

Species	Compound	ED_{50} (95% confidence limits) mg/kg, i.p.	Time (min)	Brain concentrations (nmol/g)[a]	
				d-F	*d*-NF
Mouse	*d*-F	16.3 (14.3–18.8)	5	50.5 ± 7.8	<0.1
			30	138.5 ± 6.6	14.9 ± 0.5
			60	106.8 ± 21.3	16.9 ± 2.5
	d-NF	6.8 (5.5– 8.1)	5	–	38.6 ± 4.9
			30	–	124.8 ± 14.9
			60	–	60.0 ± 6.7
Rat[b]	*d*-F	1.3 (0.9– 2.0)	30	8.8 ± 1.2	3.6 ± 0.2
			90	4.6 ± 0.9	5.7 ± 0.9
	d-NF	0.8 (0.5– 1.2)	30	–	7.4 ± 2.2
			90	–	7.2 ± 1.2
Guinea pig	*d*-F	4.9 (2.2– 7.6)	30	1.9 ± 0.6	2.2 ± 0.4
			90	1.7 ± 0.6	12.6 ± 2.8
	d-NF	3.0 (1.8– 4.1)	30	–	2.0 ± 0.2
			90	–	5.0 ± 0.9

[a] Each value is the mean ± SD of 4–5 animals
[b] From Mennini et al. 1985

addition of 50 nmol/l ^{3}H-serotonin or ^{3}H-*d*-fenfluramine. The reaction was stopped 5 min later by adding 1 ml ice-chilled Krebs-Henseleit buffer and rapid filtration under vacuum on cellulose nitrate filters (0.65 µm pore size, Società Italiana Microfiltrazione), which were washed twice with 2 ml Krebs-Henseleit buffer. The radioactivity trapped on the filters was counted in 8 ml Filter Count (Packard) in a Beckman LS 7500 liquid scintillation spectrometer with a counting efficiency of 45%. Inhibition curves were calculated using the Allfit program (De Lean et al. 1978) running on an IBM-AT personal computer.

^{3}H-serotonin release. Crude synaptosomal pellets (P2; Mennini et al. 1981) were obtained from fresh rat and guinea pig hypothalamus or mouse whole brain. The synaptosomes were then resuspended in 5 ml (about 50 vol) Krebs-Henseleit buffer having the following composition (mmol/l): NaCl (125); KCl (3); $CaCl_2$ (1.2); $MgSO_4$ (1.2); Na_2PO_4 (1); $NaHCO_3$ (22); glucose (10) (aeration with 95% O_2 and 5% CO_2); pH 7.2–7.4. The suspension was then added to an equal volume of the same buffer containing ^{3}H-serotonin (Amersham, England, 27.8 Ci/mmol), final concentration 60 nmol/l. After incubation for 15 min at 37°C, the solution was diluted to 80 ml with fresh buffer and 5-ml aliquots were then distributed on 0.65 µm cellulose nitrate filters in a 16-chamber superfusion apparatus (Raiteri et al. 1974) thermostatically maintained at 37°C. The synaptosomes were stratified on the filters through aspiration from the bottom under moderate vacuum. Superfusion was started (t = 0) at a rate of 0.6 ml/min; after 42 min, to equilibrate the system, fractions were collected every 2 min. At t = 47 min the medium in the chambers was replaced with a new one containing the drugs (3–4 chambers each) which was left for 3 min. At t = 51 min the medium was replaced again with the standard one and the superfusion and fraction collection continued until t = 60 min. The filters were then put in the scintillation vials and counted for radioactivity, as the fractions, in 8 ml Atom-Light (Packard).

Percentage of serotonin release was calculated as the amount of radioactivity released into each 2-min fraction over the total radioactivity present on the filter at the start of the fraction considered; after 40-min superfusion the baseline was stabilized at about 2%. Serotonin overflow was the difference between the radioactivity released in the presence and absence (baseline) of the drugs. Concentration–effect curves were calculated using the Allfit program (De Lean et al. 1978) running on an IBM-AT personal computer.

Results

In vivo studies

Table 1 summarizes the anorectic properties of i.p. *d*-fenfluramine in the rat, mouse, and guinea pig. The ED_{50} calculated on giving different doses of *d*-fenfluramine or *d*-norfenfluramine to overnight-starved rats used to taking their daily food ration during a period of 4 h and by increasing food consumption within the first hour show that the efficacy of *d*-fenfluramine was as follows; rat > guinea pigs > mouse. The activity ranking was the same for *d*-norfenfluramine, although in all three species *d*-norfenfluramine was more active than *d*-fenfluramine in terms of dosage. However, the differences reached statistical significance only in mice.

In mice the interval between treatment and the first measurement of food intake was kept shorter (5 min) than in rats and guinea pigs, because pilot experiments had shown that the anorectic effect of *d*-fenfluramine in mice was particularly short-lasting. In an experiment comparing these treatments, the ED_{50} of *d*-fenfluramine given 5 min before food intake was 16.3 mg/kg while, when *d*-fenfluramine was given 30 min before, the ED_{50} was 26.5 mg/kg (P = 0.07).

To assess whether the difference in anorectic activity was due to different kinetics of *d*-fenfluramine or *d*-norfenfluramine in the three animal species, brain concentration of *d*-fenfluramine and *d*-norfenfluramine after administration of the respective ED_{50} were measured (Table 1) at two times, corresponding to the beginning and the end of the period considered for food intake measurements. The brain concentrations necessary to obtain an anorectic ED_{50} after either drug were quite different in the three species. Much higher brain concentrations of *d*-fenfluramine were needed in mice than in guinea pigs and rats to obtain the same anorectic effect. Thus the

Table 2. Kinetic parameters of 5HT receptor subtypes and ^{3}H-5HT uptake in mice, rats, and guinea pigs

Receptor type	Ligand	Area	Species					
			Mouse		Rat		Guinea pig	
			K_d	B_{max}	K_d	B_{max}	K_d	B_{max}
$5HT_{1A}$	^{3}H-8OH-DPAT	Hippo-campus	1.6 ± 0.6	0.08 ± 0.02	0.9 ± 0.07	0.27 ± 0.01	1.0 ± 0.1	0.27 ± 0.02
$5HT_{1B}$	^{3}H-5HT	Striatum	2.9 ± 0.9	0.06 ± 0.01	1.9 ± 0.6	0.19 ± 0.03	–	–
$5HT_{1C}$	^{3}H-mesulergine + spiperone	Cerebral cortex	2.7 ± 1.9	0.02 ± 0.01	3.2 ± 2.3	0.01 ± 0.00	0.7 ± 0.6	0.02 ± 0.00
$5HT_{1D}$	^{3}H-5HT	Striatum	–	–	–	–	3.6 ± 2	0.12 ± 0.05
$5HT_2$	^{3}H-ketanserin	Cerebral cortex	0.8 ± 0.1	0.06 ± 0.004	0.5 ± 0.0	0.15 ± 0.004	0.5 ± 0.1	0.11 ± 0.008
5HT uptake site	^{3}H-paroxetine	Cerebral cortex	0.6 ± 0.1	0.22 ± 0.06	0.2 ± 0.1	0.20 ± 0.08	0.3 ± 0.1	0.25 ± 0.08
			K_m	V_{max}	K_m	V_{max}	K_m	V_{max}
^{3}H-5HT uptake	^{3}H-5HT	Hypo-thalamus	61 ± 9	3.6 ± 0.2	102 ± 13	3.3 ± 0.3	71 ± 14	3.7 ± 0.4

K_m (nmol/l) and V_{max} (pmol/min/mg protein) and K_d (nmol/ml) and B_{max} (pmol/min/mg protein) were calculated using the "Ligand" program (Munson and Roadbard 1984)

relative potency of *d*-fenfluramine established on the basis of *d*-fenfluramine brain concentrations does not parallel that obtained on the basis of the doses. It was clear that the shorter lasting effect of *d*-fenfluramine in mice than in rats and guinea pigs was not due to kinetic reasons since brain concentrations of *d*-fenfluramine in mice increased during the first 30 min of food intake and then remained relatively constant until the end of the observation period.

The potency ranking in the three species was similar for *d*-norfenfluramine. However the presence of the metabolite *d*-norfenfluramine in relation to the parent compound after administration of *d*-fenfluramine was quite different; brain *d*-norfenfluramine concentrations were comparable to or exceeded those of *d*-fenfluramine in guinea pigs and rats but were markedly lower than the parent drug brain concentrations in mice.

In vitro serotoninergic effects

In order to clarify the differences in anorectic potency of *d*-fenfluramine and *d*-norfenfluramine in the three species several experiments were done in vitro to establish the sensitivity of serotoninergic parameters such as serotonin receptors, uptake, and release. In addition the binding and uptake of ^{3}H-*d*-fenfluramine were studied in the whole brain of mice, rats, and guinea pigs.

Effect on serotonin receptor subtypes

The kinetic parameters of serotonin receptor subtypes in the three animal species are summarized in Table 2. The affinities of the various ligands were not different in the three species, thus making it simple to compare the data obtained with inhibitors. The maximum number of bindings sites for $5HT_{1A}$, $5HT_{1B}$, and $5HT_2$ was lower in the mouse than in the rat and guinea pig.

The effects of *d*-fenfluramine and *d*-norfenfluramine on various serotonin subtypes are summarized in Table 3; affinity was always in the µmol range with the exception of $5HT_{1C}$ receptors, for which *d*-norfenfluramine shows a relatively high affinity, ranging from 0.17 and 0.28 µmol/l in mouse and rats to 0.55 µmol/l in guinea pigs. *d*-Fenfluramine was slightly more active than *d*-norfenfluramine on $5HT_{1A}$ receptors but there was no marked difference in the three species. $5HT_{1B}$ receptors were present only in mice and rats (Heuring et al. 1986) but their sensitivity to *d*-fenfluramine or *d*-norfenfluramine was slight. Guinea pigs had $5HT_{1D}$ receptors (Waeber et al. 1989) but in this case too *d*-fenfluramine and *d*-norfenfluramine had a relatively high IC_{50}, i.e. 13.5 and 5.13 µmol/l respectively. $5HT_{1D}$ receptor binding is not relevant for mice and rats.

$5HT_2$ receptors are more sensitive to *d*-fenfluramine in mouse cortex than in the same brain area in rats and guinea pigs; *d*-norfenfluramine is about five times more effective in mice and rats than in guinea pigs.

Effect on ^{3}H-5HT uptake and ^{3}H-paroxetine binding

The kinetic parameters for ^{3}H-5HT uptake and ^{3}H-paroxetine binding were similar in the three animal species (Table 2). *d*-Fenfluramine and *d*-norfenfluramine were quite effective in blocking the uptake of ^{3}H-5HT from hypothalamus in vitro (Table 3). *d*-Fenfluramine shows about the same potency in guinea pigs (IC_{50} = 0.08 µmol/l), rats (IC_{50} = 0.07 µmol/l), and mice (IC_{50} = 0.10 µmol/l). The same is true for *d*-norfenfluramine, although its effect on mouse hypothalamus tends to be two to three times higher than for the same brain area of guinea pigs or rats. In contrast to the high nanomolar inhibition exerted by *d*-fenfluramine and *d*-norfenfluramine on serotonin uptake, activity on ^{3}H-paroxetine binding, a putative site for serotonin carrier-mediated

Table 3. In vitro effects of *d*-fenfluramine and *d*-norfenfluramine on 5HT receptor subtypes and transport mechanisms

Receptor type	Ligand	Area	IC_{50} (μmol/l)		
			Mouse	Rat	Guinea pig
$5HT_{1A}$	^{3}H-8OH-DPAT	Hippocampus	3.73 (6.92)	3.56 (7.91)	2.33 (3.56)
$5HT_{1B}$	^{3}H-5-HT	Striatum	16.30 (3.55)	61.00 (13.00)	–
$5HT_{1C}$	^{3}H-mesulergine + spiperone	Cerebral cortex	4.43 (0.17)	6.80 (0.28)	12.60 (0.55)
$5HT_{1D}$	^{3}H-5HT	Striatum	–	–	13.50 (5.13)
$5HT_2$	^{3}H-ketanserin	Cerebral cortex	7.25 (2.09)	30 (2.20)	37.70 (10.6)
5HT uptake site	^{3}H-paroxetine	Cerebral cortex	26.30 (25.0)	10.25 (21.9)	28.40 (68.5)
d-F	^{3}H-*d*-F	Whole brain	0.25 (3.1)	0.04 (0.5)	0.27 (3.3)
3H-5HT uptake		Hypothalamus	0.10 (0.08)	0.07 (0.17)	0.08 (0.24)
3H-*d*-F uptake		Whole brain	0.37 (0.60)	0.26 (1.03)	0.25 (0.67)
3H-5HT release (EC_{50} μmol/l)		Hypothalamus	1.25 (1.98)[a]	1.78 (1.10)	1.30 (1.60)

IC_{50} or EC_{50} refers to *d*-fenfluramine (*d*-F) and (in parentheses) to *d*-norfenfluramine (*d*-NF). Statistical comparison between parameters was done by Student's *t*-test, and was as follows: ^{3}H-*d*-fenfluramine receptor binding: *d*-F and *d*-NF rat different from mouse and guinea pigs, $P < 0.01$; *d*-NF different from *d*-F in all species, $P < 0.01$; ^{3}H-*d*-F uptake: *d*-F mouse different from rat and guinea pigs, $P < 0.05$; *d*-NF rat different from mouse and guinea pigs, $P < 0.05$; *d*-NF different from *d*-F in all species, $P < 0.05$; ^{3}H-5HT release: *d*-NF rat different from mouse and guinea pigs, $P < 0.05$. [a] whole brain

transport, was much less marked (IC_{50} ranging from 10.2 to 68.5 μmol/l; Table 3).

Effect on ^{3}H-5HT release

Concentrations of *d*-fenfluramine that affect serotonin uptake do not influence the spontaneous release of ^{3}H-serotonin in superfused synaptosomes from rat and guinea pig hypothalamus or mouse whole brain. In fact the concentrations that raise serotonin release are at least one order of magnitude higher than those affecting serotonin uptake in the three animal species. *d*-Norfenfluramine shows a trend (not statistically significant) to be more active than *d*-fenfluramine in rats in stimulating ^{3}H-serotonin release, but *d*-fenfluramine and *d*-norfenfluramine were equipotent in mice and guinea pigs. *d*-Norfenfluramine was more active in stimulating serotonin release in the rat than in mice and guinea pigs. The ratio between enhancement of serotonin release and inhibition of serotonin uptake by *d*-fenfluramine was higher for rats (about 25) and guinea pigs (about 16) than for mice (about 12.5), while for *d*-norfenfluramine it was higher in mice (about 25) than in rats or guinea pigs (about 6).

The EC_{50} reported in Table 3 are somewhat different than the SC_{25} (concentration stimulating release by 25%) previously reported for *d*-fenfluramine and *d*-norfenfluramine in rats (Mennini et al. 1985). The reason is that in earlier studies drugs were added at the beginning of superfusion, and the effect was calculated on 10-min cumulative release as the difference between samples with or without drugs. In the present experiments (see Materials and methods) drugs were added after 47 min of superfusion when basal efflux was stabilized at about 2%, and the effect was calculated as net overflow induced during 3-min drug superfusion. EC_{50} are drug concentrations producing half-maximal effect, which was 20–25% for rats and mice and 15% for guinea pigs.

Table 4. In vitro ^{3}H-*d*-fenfluramine binding and ^{3}H-*d*-fenfluramine uptake by whole brain of mice, rats, and guinea pigs

Animal species	^{3}H-*d*-F binding		^{3}H-*d*-F uptake	
	K_d (nmol/l)	B_{max} (pmol/min/mg protein)	K_m (nmol/l)	V_{max} (pmol/min/mg protein)
Mouse	122 ± 15	1.34 ± 0.148[b]	359 ± 57[c]	2.02 ± 0.30[d]
Rat	32 ± 3[a]	0.90 ± 0.054[b]	242 ± 34	1.37 ± 0.18[d]
Guinea pig	325 ± 62	3.52 ± 0.672[b]	183 ± 55	0.66 ± 0.16[d]

The two parameters (K_d and B_{max} or K_m and V_{max}) ± coefficient of variation were obtained using the "Ligand" program (Munson and Roadbard 1984). Statistical comparison between parameters was done by Student's *t*-test and was as follows: ^{3}H-*d*-fenfluramine binding: [a] $P < 0.01$ different from mouse and guinea pigs, [b] $P < 0.01$ different in all animal species; ^{3}H-*d*-fenfluramine uptake: [c] $P < 0.05$ different from rat and guinea pigs; [d] $P < 0.05$ different in all animal species

^{3}H-d-fenfluramine uptake in brain synaptosomes

^{3}H-*d*-fenfluramine is actively taken up, presumably with a 5HT-like carrier, by rat brain synaptosomes (Garattini et al. 1989). It was therefore of interest to investigate whether a similar mechanism existed in the guinea pig and mouse synaptosomes. As shown in Table 4, the V_{max} for ^{3}H-*d*-fenfluramine uptake was higher for mouse brain synaptosomes than for rats and guinea pigs, while K_m followed the opposite order in terms of affinity. Table 3 reports the IC_{50} for *d*-norfenfluramine, which was less active than *d*-fenfluramine in all animal species. *d*-Norfenfluramine was also less active in rat than in mouse and guinea pig.

^{3}H-d-fenfluramine binding in brain

^{3}H-*d*-Fenfluramine is bound to brain structures of rats both in vitro and in vivo (Mennini et al. 1988; Gobbi et

al. 1989). It was therefore of interest to investigate whether there was a high-affinity binding site in brain of mice and guinea pigs. As shown in Table 4, the B_{max} was higher in guinea pigs than in mice and rats; the affinity (K_d) of *d*-fenfluramine was considerably higher in rats; in fact in this species it was respectively about four and ten times higher than in mice and guinea pigs. *d*-Norfenfluramine inhibited the binding of ^{3}H-*d*-fenfluramine with an IC_{50} about ten times higher than for *d*-fenfluramine in all three animal species (Table 3), and similarly to *d*-fenfluramine, was more active in rat than in mouse and guinea pig.

Discussion

The possible mechanisms of the anorectic activity of *d*-fenfluramine have been summarized by several authors (Blundell and Hill 1988; Samanin and Garattini 1990; Garattini et al. 1979, 1986, 1987, 1988, 1989; Garattini 1987). There is a general consensus that *d*-fenfluramine should be considered as belonging to a different class from the classic prototype of anorectic agents, *d*-amphetamine. *d*-Amphetamine requires an intact catecholaminergic system to inhibit food intake (Samanin and Garattini 1982), whereas an intact serotoninergic system is necessary for the effect of fenfluramine (Samanin and Garattini 1990). Whereas *d*-amphetamine releases brain dopamine and noradrenaline (Garattini et al. 1978), *d*-fenfluramine lowers brain serotonin and 5-hydroxyindolacetic acid (5HIAA; Garattini et al. 1986), an effect which persists over time (Garattini et al. 1986; Zaczek et al. 1990). The mechanism by which *d*-fenfluramine depletes the stores of brain serotonin is not fully understood. Brain concentrations of *d*-fenfluramine and its active metabolite *d*-norfenfluramine found after an anorectic ED_{50} in rats are compatible with concentrations of *d*-fenfluramine and *d*-norfenfluramine which in vitro block serotonin uptake and enhance its release (Mennini et al. 1985). This has led to the suggestion that *d*-fenfluramine increases the transmission of serotonin in the brain, as indirectly confirmed by the increase of brain extracellular serotonin (Carboni and Di Chiara 1989; Schwartz et al. 1989) and 5HIAA (De Simoni et al. 1988).

That an involvement of serotonin is important in the anorectic activity of *d*-fenfluramine (and *d*-norfenfluramine) is sustained by the fact that serotonin antagonists prevent the anorectic effects of *d*-fenfluramine and *d*-norfenfluramine (Samanin and Garattini 1990). Furthermore indirect serotonin agonists such as fluoxetine (Yen et al. 1987), sertraline (Lucki et al. 1988), paroxetine (Bizzi, personal communication), zimelidine (Angel et al. 1988) and direct serotonin agonists such as m-chlorophenyl-piperazine (Samanin et al. 1979), quipazine (Samanin et al. 1977), RU24969 (Bendotti and Samanin 1987), and DOI (Schechter and Simansky 1988) show anorectic activity.

However almost all the studies that have helped elucidate the mechanism of action of *d*-fenfluramine have been done in rats, and scant data are available in other animal species; hence the interest of comparative studies to find out whether there is any difference when mice, rats, and guinea pigs are utilized, as in the present report.

It was found that *d*-fenfluramine reduces food intake in the three animal species investigated at doses which do not have gross behavioral effects that might indirectly interfere with food intake. The ED_{50} expressed in mg/kg indicated that rats are more sensitive than guinea pigs or mice, in terms of dosage. For *d*-fenfluramine the ED_{50} for rats was 3.7 and 12.5 times lower than for guinea pigs and mice respectively; for *d*-norfenfluramine the ED_{50} for rats was 3.7 and 8.5 times lower than for guinea pigs and mice. In all three species *d*-norfenfluramine was slightly more active than *d*-fenfluramine, 2.4 times more active in mice, and 1.6 times in rats and guinea pigs.

It was logical to investigate whether kinetic reasons could explain these quantitative differenees in the anorectic activity of *d*-fenfluramine. After administration of equiactive anorectic doses (ED_{50}) the brain concentrations of *d*-fenfluramine and *d*-norfenfluramine varied widely and were not dose-related; mice appeared to be the species least sensitive to *d*-fenfluramine, followed by rats and guinea pigs. *d*-Norfenfluramine administered as such was present in the brain approximately in the same order as *d*-fenfluramine, i.e. higher in mice than in rats than in guinea pigs. However, brain *d*-norfenfluramine concentrations after *d*-fenfluramine were comparable to or exceed those of the parent drug in guinea pigs and rats but were less than 20% of *d*-fenfluramine in mice. Comparing the brain concentrations of *d*-norfenfluramine after equiactive doses of *d*-fenfluramine or *d*-norfenfluramine, it thus appears that the active metabolite (Borroni et al. 1983; Garattini et al. 1979) most probably plays a major role in the parent drug's anorectic activity in guinea pigs, contributes to the effect in rats, but adds only a minor component to the pharmacological action in mice. The findings concerning the metabolism of *d*-fenfluramine to *d*-norfenfluramine in mice and guinea pigs are consistent with previously reported data (Caccia et al. 1982; Steranka and Sanders-Bush 1979; Fuller et al. 1988).

In an effort to understand the reason for these differences in sensitivity to *d*-fenfluramine and *d*-norfenfluramine, in vitro studies were made of parameters indicative of serotonin function, i.e. uptake, release, and affinity for receptor subtypes. Uptake and release of serotonin should be considered together, because inhibition of uptake and enhancement of release contribute in a synergistic manner to increase serotoninergic transmission by making more serotonin available at receptor sites. Unfortunately it is difficult, at least quantitatively, to reconcile the different anorectic sensitivities of the three species with these serotonin biochemical parameters. Comparing the brain levels of *d*-fenfluramine or *d*-norfenfluramine at equal anorectic doses with the concentrations of *d*-fenfluramine or *d*-norfenfluramine affecting serotonin uptake and/or release, the most sensitive species should be the mouse, but this was clearly not the case. Measurement of serotonin uptake sites by determining ^{3}H-paroxetine binding was not very helpful because *d*-fenfluramine and *d*-norfenfluramine have low

affinity for these sites, as previously reported for ^{3}H-imipramine binding (Gobbi et al. 1988).

The study of the affinity of *d*-fenfluramine and *d*-norfenfluramine for various serotonin receptor subtypes also led to no firm conclusion; as in rats (Mennini et al. 1985), in mice and guinea pigs the affinity of *d*-fenfluramine and *d*-norfenfluramine for or $5HT_1$ $5HT_2$ receptors is relatively low. $5HT_{1B}$ receptors, suggested to be the sites responsible for the anorectic activity of *d*-fenfluramine and *d*-norfenfluramine (Garattini et al. 1986), are more sensitive to *d*-fenfluramine in mice than in rats. $5HT_{1D}$ receptors are probably the equivalent of $5HT_{1B}$ receptors for guinea pigs (Waeber et al. 1989) but they did not show specially high affinity for *d*-fenfluramine or *d*-norfenfluramine (the IC_{50} was more than twice the brain concentration of *d*-norfenfluramine after an ED_{50} of *d*-fenfluramine or *d*-norfenfluramine.) $5HT_{1C}$ receptors are also probably involved in food intake (Garattini et al. 1989). It is of interest that *d*-norfenfluramine shows a fairly good affinity for $5HT_{1C}$ receptors in the three animal species, with IC_{50} compatible with the brain concentrations.

Activation of $5HT_{1A}$ receptors is presumably related to an increase of food intake (Garattini et al. 1988; Bendotti and Samanin 1987; Mennini and Garattini 1988) and in this light it is difficult to interpret the results with *d*-fenfluramine and *d*-norfenfluramine in the three animal species.

The studies on serotonin uptake were carried out in the mouse, rat, and guinea pig hypothalamus, while the receptor binding assay was done in whole brain or in brain areas (hippocampus, striatum, cortex) particularly suitable for the measurement of serotonin receptor subtypes. It thus cannot be excluded that receptors located in certain nuclei of the hypothalamus in the three species may have different sensitivity to *d*-fenfluramine or *d*-norfenfluramine. Studies are in progress on this point.

Finally, binding and uptake of ^{3}H-*d*-fenfluramine in brain were determined in vitro. Previous studies in rats have shown that various brain areas in vitro and in vivo bind ^{3}H-*d*-fenfluramine with high affinity and stereospecificity (Mennini et al. 1988; Gobbi et al. 1989). ^{3}H-*d*-Fenfluramine binding could be reduced either by lesioning the serotoninergic terminals with 5,7-DHT (Garattini et al. 1988) or by inhibition with several agents showing affinity for presynaptic serotonin carriers (Mennini et al. 1988).

The density of ^{3}H-*d*-fenfluramine binding was highest in guinea pigs, followed by mice and rats. The affinity of *d*-fenfluramine and *d*-norfenfluramine was higher in rats than in mice or guinea pigs, and *d*-norfenfluramine had about ten times less potency in all these species.

^{3}H-*d*-fenfluramine not only binds to brain structures but it is also taken up with a temperature- and ouabaine-sensitive mechanism presumably connected with the carrier of serotonin transport (Garattini et al. 1988). The V_{max} of ^{3}H-*d*-fenfluramine uptake is not directly related to the anorectic activity of *d*-fenfluramine or *d*-norfenfluramine since it was highest in mice, followed by rats and guinea pigs. The affinity for *d*-fenfluramine and *d*-norfenfluramine was substantially the same in the three species. Again it is possible that these measurements in the whole brain may not be representative of brain areas responsible for the anorectic effect of *d*-fenfluramine and *d*-norfenfluramine.

It is difficult at the moment to relate any particular effect of *d*-fenfluramine or *d*-norfenfluramine on single serotonin biochemical parameters to the anorectic sensitivity of the three animal species; a weighed combination of various serotonin parameters in selected crucial brain sites might yield more satisfactory results.

In conclusion we have shown that: 1. The anorectic activity of *d*-fenfluramine and *d*-norfenfluramine requires progressively higher doses in rats, guinea pigs, and mice. 2. *d*-Norfenfluramine is slightly more active than *d*-fenfluramine in all three species. 3. Equiactive anorectic activities are reached with different brain levels of *d*-fenfluramine and *d*-norfenfluramine, guinea pigs being the most sensitive species, followed by rats then mice. 4. *d*-Norfenfluramine may have great importance for the anorectic effect of *d*-fenfluramine in guinea pigs, contributes in rats, but has no significance in mice. 5. A number of biochemical parameters, including serotonin uptake, release and affinity for receptor subtypes as well as ^{3}H-*d*-fenfluramine binding and uptake, apparently could not explain the different sensitivity to *d*-fenfluramine and *d*-norfenfluramine in the three species considered.

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ORIGINAL ARTICLE

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In vitro studies on the mechanism by which (+)-norfenfluramine induces serotonin and dopamine release from the vesicular storage pool

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Abstract (+)-Norfenfluramine is the main metabolite of the serotoninergic anorectic agent (+)-fenfluramine. Both compounds inhibit 5-HT reuptake and stimulate its release, although they induce release from different pools, with (+)-norfenfluramine acting primarily on the cytoplasmic pool. Moreover, (+)-norfenfluramine was more potent than the parent drug in inducing dopamine release.
In order to investigate whether (+)-norfenfluramine induces a Ca^{2+}-dependent vesicular release, like some amphetamine derivatives, in the present study we preloaded synaptosomes with the [^{3}H]neurotransmitter ([^{3}H]5-HT or [^{3}H]dopamine), superfused (washed) them for 47 min in the absence of pargyline and then exposed them to the releasing stimulus. With this protocol, the cytoplasmic pool should be absent and the [^{3}H]neurotransmitter should mainly be stored in synaptic vesicles, where (+)-norfenfluramine should act to induce release. This was confirmed by a significant *decrease* of (+)-norfenfluramine-induced [^{3}H]5-HT and [^{3}H]dopamine release after reserpine pretreatment. The dose-response curves of (+)-norfenfluramine-induced [^{3}H]5-HT release were superimposable in hippocampus and hypothalamus, and also superimposable on the curve for (+)-fenfluramine-induced [^{3}H]5-HT release; the dopamine releasing potency of (+)-norfenfluramine in the striatum was more than ten times lower. The [^{3}H]5-HT release induced by (+)-norfenfluramine was partly (about 50%) but significantly Ca^{2+}-dependent, and it was also markedly (68%) inhibited by Cd^{2+}, a non-specific blocker of voltage-dependent Ca^{2+} channels, suggesting that the Ca^{2+}-dependent release is mediated by entry of Ca^{2+} into the synaptosomes through these channels. The [^{3}H]dopamine release induced by 5 μM (+)-norfenfluramine was completely Ca^{2+}-independent whereas at higher concentrations (10 and 20 μM) it was only slightly (20%) Ca^{2+}-dependent. We have no clear explanation why (+)-norfenfluramine has these different effects on serotoninergic and dopaminergic synaptosomes.

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Key words (+)-Norfenfluramine · Serotonin release · Dopamine release · Synaptosomes

Introduction

(+)-Norfenfluramine [(+)-NF] is the main metabolite of the serotoninergic anorectic agent (+)-fenfluramine [(+)-Fen], and has even greater anorectic effect than the parent drug (Mennini et al. 1991). This metabolite contributes to, but does not explain, the anorectic effect of (+)-Fen in rats and other animal species, except for guinea pigs where (+)-Fen seems to be a prodrug of (+)-NF (Mennini et al. 1991; Caccia et al. 1993a). In vitro, both compounds inhibit 5-HT reuptake and stimulate its release from brain synaptosomes of different animal species (Mennini et al. 1991, 1996a). Moreover, (+)-NF is more potent than the parent drug in inducing dopamine (DA) release (Mennini et al. 1996b) and binds to 5-HT_{2C} receptors with appreciable affinity (Mennini et al. 1991, 1996a), suggesting it might also act as a direct 5-HT_{2C} agonist (Gibson et al. 1993; Oluyomi et al. 1994; Curzon et al. 1997).

The mechanism by which (+)-NF induces 5-HT release is different from the mechanism underlying (+)-Fen-induced release since, in a release superfusion model in which the cytoplasmic neurotransmitter pool was artificially enhanced (i.e., by using unwashed synaptosomes in the presence of pargyline), reserpine pretreatment abolished the effect of (+)-Fen but it did not affect – or even increased – the [^{3}H]5-HT releasing properties of (+)-NF (Mennini et al. 1981).

Recently we described a carrier-dependent and calcium-dependent [^{3}H]5-HT and/or [^{3}H]DA release from the vesicular pool shared by amphetamine derivatives [including (+)-Fen, *p*-chloroamphetamine (pCA), 3,4-methylenedioxymethamphetamine (MDMA), and (+)-amphetamine] (Crespi et al. 1997). The aim of the present study was to verify, in experimental conditions where the cytoplasmic pool is absent, whether (+)-NF also induced exocytotic-like [^{3}H]5-HT and/or [^{3}H]DA release from synaptic vesicles.

We used a completely different superfusion system: the synaptosomes were superfused in the absence of pargyline for 47 min before adding the releasing agent, in order to deplete the cytoplasmic compartment. Under these conditions the [^{3}H]neurotransmitter is only stored in the synaptic vesicles, so presumably we are measuring release only from this pool. The effect of (+)-NF on this release mechanism could cast useful light on the pharmacological and toxicological (Gobbi et al. 1996a) effects of this compound.

Materials and methods

Preparation of the synaptosomal fraction. Male CRL:CD(SD)BR rats (Charles River, Italy) weighing about 150 g were used. Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national (D.L. n. 116, G.U., suppl. 40, Feb. 18, 1992, Circolare No. 8, G.U., July 14, 1994) and international laws and policies (EEC Council Directive 86/609, OJ L 358, 1, Dec.12, 1987; Guide for the Care and Use of Laboratory Animals, U.S. National Research Council, 1996). When used, reserpine (Ciba-Geigy, Switzerland) was given at a dose of 10 mg/kg, i.p., 24 h before killing. The rats were killed by decapitation and their hippocampi, hypothalami and striata were rapidly dissected and homogenized in 40 volumes of ice-chilled 0.32 M sucrose, pH 7.4, in a glass homogenizer with a Teflon pestle. The homogenates were centrifuged at 1000 *g* for 5 min and the supernatants centrifuged again at 12000 *g* for 20 min to yield the crude synaptosomal pellet (P_2; Gray and Whittaker 1962).

Release studies. The P_2 pellets were resuspended in about 20 volumes of Krebs-Henseleit buffer with the following composition (mM): NaCl (125); KCl (3); $CaCl_2$ (1.2); $MgSO_4$ (1.2); NaH_2PO_4 (1); $NaHCO_3$ (22); glucose (10); gassed with 95% O_2 and 5% CO_2, pH 7.2–7.4. The suspension was then added to an equal volume of the same buffer containing [^{3}H]5-HT (NEN, Germany; specific activity 30 Ci/mmol) or [^{3}H]DA (Amersham, UK; specific activity 7 Ci/mmol), both at a final concentration of 0.06 μM. After 15-min incubation at 37°C, the suspension was diluted with fresh buffer, and 5-ml samples (about 5 mg initial tissue) were distributed onto cellulose mixed-esters filters (0.65 μM pore size; Millipore, Italy) in a 20-chamber superfusion apparatus held thermostatically at 37°C (Raiteri et al. 1974). The synaptosomes were layered onto the filters by aspiration from the bottom under moderate vacuum.

Superfusion was started (t=0 min) at a rate of 0.5 ml/min with standard medium; after 44-min equilibration, fractions were collected every 2 min until t=60 min. The filters were put into scintillation vials and counted for radioactivity, as were the fractions, in 4 ml of Ultima Gold MV (Packard, The Netherlands). (+)-NF (Servier, France) was present in the superfusion medium for 3 min from t=47 to t=50 min. When used, 1 μM indalpine (Rhone-Poulenc, France) or 3 μM nomifensine (RBI, USA) were added from t=40 to t=60 min for [^{3}H]5-HT release or [^{3}H]DA release, respectively. In some experiments, synaptosomes were superfused from t=40 to t=60 min with a Ca^{2+}-free medium containing 3 mM EGTA for [^{3}H]5-HT release or 0.03 mM EGTA for [^{3}H]DA release (under these conditions there was no effect on basal release, whereas the depolarization-induced release was completely blocked). When used, $CdCl_2$ (100 μM) was added to the superfusion medium from t=40 to t=60.

The fractional release rate (FRR) was calculated as 100 times the amount of radioactivity released into each 2-min fraction over the total radioactivity present on the filter at the start of that fraction. The FRR before the releasing stimulus (t=44–46), expressed as a percentage in 2 min, was reported as basal outflow. The overflow (%) was calculated as the difference between the stimulated (t=48–56) and the non-stimulated FRR (mean t=44–48 and t=56–60; see for example Fig. 2). The effect of the drugs added at t=47 was only detectable 1 min later, since the fluid takes about 1.5 min to flow from the filters to the collecting vials.

The content of unmetabolized [^{3}H]5-HT and [^{3}H]DA in the superfusate was determined as previously described (Goldstein et al. 1981; Gobbi et al. 1992).

Statistical analysis. Data are generally reported as means ±SD from n replications obtained in different experiments, as specified. The data were analyzed by one-way analysis of variance (ANOVA) followed by post hoc comparison (Tukey's test).

Results

[^{3}H]5-HT and [^{3}H]DA releasing effect of (+)-NF

Figure 1 shows the concentration-response curves for the tritium releasing effect of (+)-NF from superfused synaptosomes preloaded with [^{3}H]5-HT (hippocampal and hypothalamic synaptosomes) and from rat striatal synaptosomes preloaded with [^{3}H]DA. For comparison, Fig. 1 also shows the release induced by (+)-Fen (Crespi et al. 1997). The overflows were calculated as described in Materials and methods from data similar to that shown, as examples, in Figs. 2A and 3A. The tritium overflow induced by (+)-NF and (+)-Fen was mainly (>80%) unmetabolized [^{3}H]neurotransmitter (Mennini et al. 1996b; Crespi et al. 1997 and unpublished data), and is referred to hereafter as [^{3}H]5-HT or [^{3}H]DA release.

Both (+)-NF and its parent compound were more potent in inducing [^{3}H]5-HT than [^{3}H]DA release (more than ten times); (+)-NF was equipotent with the parent compound in inducing [^{3}H]5-HT release in both brain regions but more potent as a [^{3}H]DA releaser.

We have previously demonstrated that, under our preloading conditions, [^{3}H]5-HT is only taken up by serotoninergic synaptosomes (Gobbi et al. 1996b). Similarly, it is also very likely that [^{3}H]DA is only taken up by dopaminergic synaptosomes: in fact, confirming previous data (Andersen 1989), we measured that the uptake of 60

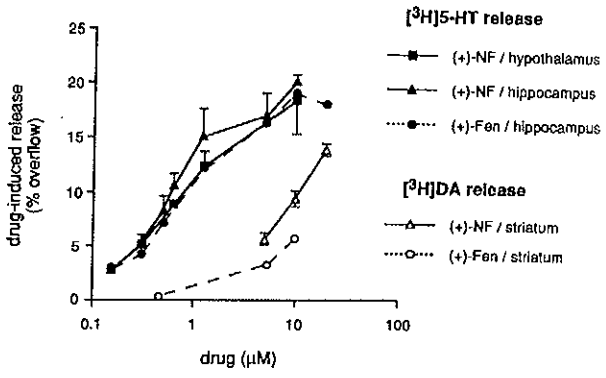

Fig. 1 Concentration-effect curves for (+)-norfenfluramine [(+)-NF]-induced [^{3}H]5-HT release from rat hippocampal synaptosomes (*filled symbols*) and [^{3}H]DA release from rat striatal synaptosomes (*empty symbols*). For the sake of comparison, the releasing effects of (+)-fenfluramine [(+)-Fen] are also shown (Crespi et al. 1997). Superfused synaptosomes were exposed to the drug for 3 min. Each overflow is the mean ±SD of 3–5 results from 1–5 experiments

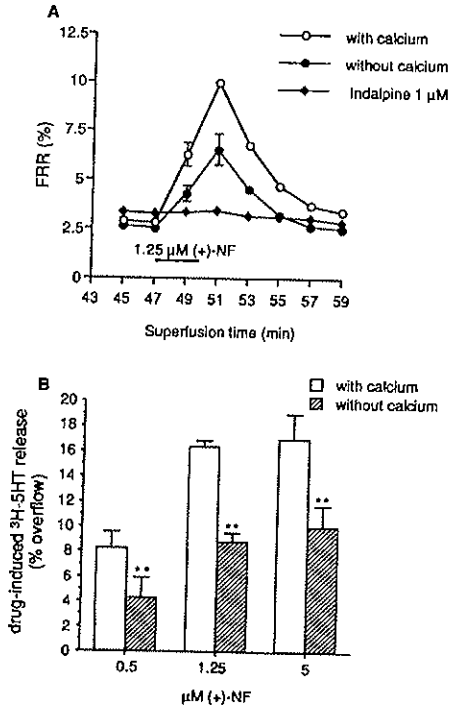

Fig. 2A,B Effect of extracellular Ca^{2+} ions on (+)-norfenfluramine [(+)-NF]-induced [^{3}H]5-HT release from superfused rat hippocampal synaptosomes. (+)-NF was applied for 3 min in the presence or absence of 1.2 mM $CaCl_2$, and in the presence of 3 mM EGTA. The effect of indalpine was evaluated in the presence of Ca^{2+} ions. **A** The fractional release rates (FRR), i.e., the tritium released in each 2-min fraction as a percentage of the total radioactivity in the synaptosomes at the same time (mean ±SD of three replications from a representative experiment; some of the SDs were too small to be graphically shown). **B** The effect of removal of Ca^{2+} ions on the (+)-NF-induced tritium overflow. Each value is the mean ±SD of 8–12 replications from 2–3 experiments; $^{**}P<0.01$, Student's *t*-test

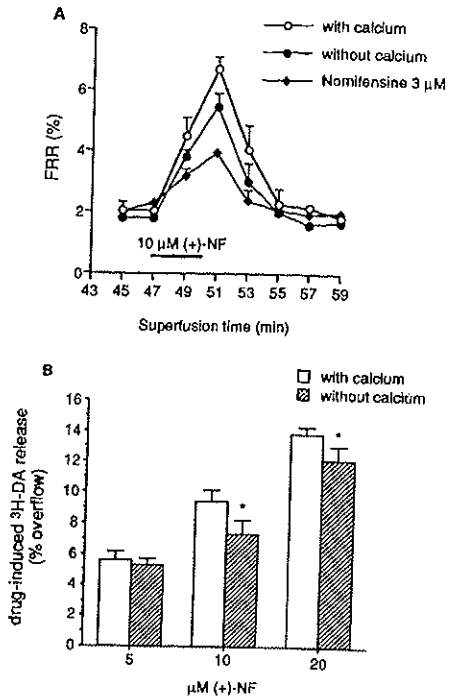

Fig. 3A,B Effect of extracellular Ca^{2+} ions on (+)-norfenfluramine [(+)-NF]-induced [^{3}H]DA release from superfused rat hippocampal synaptosomes. (+)-NF was applied for 3 min in the presence or absence of 1.2 mM $CaCl_2$, and in the presence of 0.03 mM EGTA. The effect of nomifensine was evaluated in the presence of Ca^{2+} ions. **A** The fractional release rates (FRR), i.e., the tritium released in each 2-min fraction as a percentage of the total radioactivity in the synaptosomes at the same time (mean ± SD of three replications from a representative experiment; some of the SDs were too small to be graphically shown). **B** The effect of removal of Ca^{2+} ions on the (+)-NF-induced tritium overflow. Each value is the mean ±SD of 4–6 replications from 2–3 experiments; $^{*}P<0.05$, Student's *t*-test

nM [^{3}H]DA in striatal synaptosomes is completely inhibited by GBR-12909 at a concentration (100 µM) which selectively blocks DA transporter without interacting with the noradrenaline transporter (Andersen 1989).

Effect of reserpine

Pretreatment of the rats 24 h before with 10 mg/kg of reserpine significantly reduced the accumulation of [^{3}H]5-HT in hippocampal and [^{3}H]DA in striatal synaptosomes (by about 80%), whereas FRR significantly increased (from 1.7±0.2 to 3.4±0.2 for [^{3}H]5-HT release, $P<0.01$, and from 1.18±0.17 to 1.62±0.14 for [^{3}H]DA release, $P<0.01$). The [^{3}H]5-HT overflow induced by maximal (10 µM) (+)-NF was decreased by reserpine from 22.3±0.4 to 9.8±0.2 ($P<0.01$ Student's *t*-test, means ± SD of three rats per group); the [^{3}H]DA overflow induced by maximal (20 µM) (+)-NF was reduced by reserpine from 17.88±2.53 to 0.45±0.36 ($P<0.01$, Student's *t*-test, mean ± SD of three rats per group).

Carrier dependency

[^{3}H]5-HT release induced by 1.25 µM (+)-NF was completely inhibited by 1 µM indalpine, a 5-HT transporter blocker, which has no releasing activity per se (Fig. 2A). The [^{3}H]DA release induced by 10 µM (+)-NF was largely, although not completely, inhibited by 3 µM nomifensine, a DA transporter blocker (64 and 75% in two different experiments; Fig. 3A); this concentration of nomifensine should be sufficient to completely inhibit the DA transporter, since we measured that its IC_{50} on synaptosomal [^{3}H]DA uptake is 234 nM (data not shown), similar to the value reported in the literature (134 nM; Andersen 1989). Moreover, we previously described that 3 µM nomifensine completely inhibited the [^{3}H]DA release induced by (+)-amphetamine, MDMA and pCA under identical experimental conditions (Crespi et al. 1997).

Ca^{2+} dependency

Removal of Ca^{2+} ions from the superfusion buffer partially but significantly reduced [^{3}H]5-HT release induced by (+)-NF (Fig. 2). [^{3}H]5-HT overflow induced by 0.5, 1.25 and 5 μM (+)-NF was reduced by 48%, 46% and 41%, respectively (Fig. 2B). The [^{3}H]5-HT release induced by 1.25 μM (+)-NF was also reduced by 68% in the presence of 100 μM $CdCl_2$, a non-specific blocker of voltage-dependent Ca^{2+} channels (from 11.56±0.56 to 3.64±0.38, mean ± SD, n=5, P<0.01, Student's t-test).

Removal of Ca^{2+} ions from the superfusion buffer slightly reduced the [^{3}H]DA release induced by 10 and 20 μM (+)-NF (by 22 and 12%, respectively, P<0.05), whereas it had no significant effect on the release induced by 5 μM (+)-NF (Fig. 3).

Discussion

This study set out to verify the effect of (+)-NF on 5-HT and DA release in experimental conditions where the cytoplasmic pool (for which (+)-NF has preferential activity) is abolished. Thus, with the experimental protocol used [preloaded synaptosomes superfused (washed) for 47 min in the absence of pargyline and then exposed to the releasing stimulus], [^{3}H]5-HT is presumably mainly stored in the synaptic vesicles and (+)-NF should act on this pool to induce its release. This was confirmed by the significant (56%) *decrease* of (+)-NF-induced [^{3}H]5-HT release after reserpine pretreatment, resembling the data obtained with (+)-Fen (60% decrease by reserpine; Gobbi et al. 1992). The (+)-NF-induced [^{3}H]DA release was also strongly (98%) reduced by reserpine.

With the superfusion apparatus employed, the neurotransmitter released by the drug is immediately removed and cannot interact with presynaptic receptors or be taken up again. This is particularly important when comparing the effects of compounds that act both as releasers and reuptake inhibitors.

[^{3}H]5-HT release

Under these experimental conditions, (+)-NF induced [^{3}H]5-HT release in a concentration-dependent manner, with similar potency in the hypothalamus and hippocampus. We thus confirmed that in vitro (+)-NF has the same potency as, or is even slightly more potent than, the parent compound (+)-Fen, as previously shown in different animal species (Mennini et al. 1991; Caccia et al. 1993b; Mennini et al. 1996a). The IC_{50}s of (+)-NF and (+)-Fen as [^{3}H]5-HT uptake inhibitors are 0.6 and 0.4 μM, respectively (Garattini et al. 1992). Recent in vivo studies showed that (+)-Fen (2.5 mg/kg, i.p.) but not (+)-NF (1.5 mg/kg, i.p.) increased medial hypothalamic dialysate 5-HT, thus suggesting a significant difference in the releasing properties of the two compounds in vivo (Oluyomi et al. 1994). These findings are hard to explain, since the brain concentrations of the two compounds after these acute treatments should not differ significantly (Mennini et al. 1991), and in view of our in vitro results. However, there are other in vivo data obtained either by microdialysis (Puig de Parada et al. 1995; Paez and Hernandez 1996) and by voltammetry (De Simoni et al. 1988) suggesting that (+)-NF is equally potent, or even more so than the parent compound in releasing 5-HT.

The [^{3}H]5-HT release induced by (+)-NF was partly but significantly Ca^{2+}-dependent, thus confirming with (+)-NF a finding previously shown with (+)-Fen (Gobbi et al. 1992, 1993), pCA and MDMA (Crespi et al. 1997). The Ca^{2+}-dependent release was about 50% of the total (+)-NF-induced release at all concentrations used (0.5, 1.25 and 5 μM); these values are similar to those for MDMA and pCA (Crespi et al. 1997), whereas (+)-Fen-induced 5-HT release was 82% Ca^{2+}-dependent with 0.5 μM (+)-Fen, and 30% Ca^{2+}-dependent with 10 μM (+)-Fen (Gobbi et al. 1992). It is unlikely that the Ca^{2+} dependency of the releasing effect is due to an effect on the transporter protein since in our experimental conditions [^{3}H]5-HT uptake was not modified by removing Ca^{2+} ions from the buffer (Gobbi et al. 1993; Crespi et al. 1997).

The 5-HT release induced by (+)-NF was also markedly (68%) inhibited by Cd^{2+}, a non-specific blocker of voltage-dependent Ca^{2+} channels, thus suggesting that the Ca^{2+}-dependent release is mediated by Ca^{2+} entering the synaptosomes through these channels. This agrees with previous findings that release induced by 0.5 μM (+)-Fen, MDMA and pCA was significantly inhibited by ω-agatoxin-IVA (Frittoli et al. 1994; Crespi et al. 1997), a specific blocker of P/Q type voltage-operated Ca^{2+} channels (Mintz et al. 1992). The mechanism by which amphetamine derivatives induce Ca^{2+} influx, and the subsequent exocytotic release, is not yet understood. However, we previously reported that this mechanism can be antagonized by nanomolar concentrations of methiotepine not acting on 5-HT extracellular receptors or Ca^{2+} channels (Crespi et al. 1997). It is thus very interesting that methiotepine also inhibited the (+)-NF-induced [^{3}H]5-HT release (Mennini et al. 1996b), suggesting a common mechanism for the Ca^{2+}-dependent [^{3}H]5-HT release induced by (+)-Fen and (+)-NF.

In conclusion, (+)-NF, like the other amphetamine derivatives tested so far [(+)-Fen, pCA and MDMA], induces Ca^{2+}-dependent 5-HT release, which may be due to drug-induced Ca^{2+} influx into the nerve endings. Ad hoc studies are required to clarify whether these mechanisms apply in vivo, and whether they are relevant to the pharmacological and/or toxicological effects of these drugs.

[^{3}H]DA release

In the present study we confirmed that (+)-NF was a more potent DA releaser than (+)-Fen, possibly because of higher affinity for the DA transporter (the IC_{50}s of (+)-NF and (+)-Fen as [^{3}H]DA uptake inhibitors in rat striatal synaptosomes are 4.2 and 16.3 μM, respectively; Garattini et al. 1992). The concentrations of (+)-NF required to induce

[^{3}H]DA release from rat striatal synaptosomes are, however, ten times those required to induce [^{3}H]5-HT release, and this is also likely due to higher affinity of (+)-NF for the 5-HT transporter (see above). Similarly, we previously described that MDMA and pCA induce [^{3}H]DA release at concentrations higher than those required to induce [^{3}H]5-HT release, and this was associated to their higher affinity for the 5-HT- than the DA-transporter (Crespi et al. 1997); however, the [^{3}H]DA release induced by 5 μM MDMA and pCA was similar to the [^{3}H]5-HT release induced by 0.5 μM MDMA and pCA in that both of them were decreased by about 50% using a Ca^{2+}-free buffer (Crespi et al. 1997). On the contrary, the [^{3}H]DA release induced by 5 μM (+)-NF was completely Ca^{2+}-independent, whereas at higher concentrations (10 and 20 μM) it was only slightly (20%) Ca^{2+}-dependent. This would agree with previous data showing that methiotepine (which antagonized only the Ca^{2+}-dependent component of amphetamine-induced [^{3}H]DA release; Crespi et al. 1997) had no effect on (+)-NF-induced [^{3}H]DA release (Mennini et al. 1996b).

Conclusions

The present study, using an experimental protocol in which the releasing effect of (+)-NF from the vesicular neurotransmitter pool can be studied, indicated that (+)-NF shares with other amphetamine derivatives [(+)-Fen, pCA and MDMA] the ability to induce a Ca^{2+}-dependent [^{3}H]5-HT release. However, the same amphetamine derivatives also induced a relevant Ca^{2+}-dependent [^{3}H]DA release, but this was not found with (+)-NF.

We have no clear explanation why (+)-NF has these different effects on serotoninergic and dopaminergic synaptosomes.

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THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

FOURTEENTH EDITION

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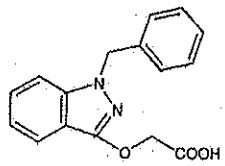
2006

mol wt 282.29. C 68.08%, H 5.00%, N 9.92%, O 17.00%. Principle action is inhibition of protein denaturation. Prepn: **BE 699226**; G. Palazzo, **US 3470194** (1967, 1969 both to Francesco Angelini). Pharmacology: B. Silvestrini *et al.*, *Inflammation Biochem. Drug Interaction, Proc. Int. Symp.* **1968**, A. Bertelli, Ed. (Excerpta Med., Amsterdam, 1970) p 283. Mechanism of action: *eidem, Arzneim.-Forsch.* **20**, 250 (1970). Photoprotective capacity: Fuga *et al.*, *Ann. Ital. Dermatol. Clin. Sper.* **24**, 205 (1970). NMR study of albumin, *q.v.*, binding: M. Delfini *et al.*, *Bioorg. Chem.* **31**, 378 (2003). Toxicity: *Rx Bulletin* **3**, 147 (1972).



Odorless, crystalline powder, mp 158-159°. Insol in water. Sol in chloroform, ethanol, acetone. uv max: 306 nm ($E^{1\%}_{1cm}$ 191). LD_{50} in mice, rats (mg/kg): 380, 304 i.v.; 355, 388 i.p.; 440, 910 s.c.; 1105, ~1200 orally (*Rx Bulletin*).

Lysine salt. [81919-14-4] bendaline; bendazac lysine; Bendalina; Dogalina. $C_{16}H_{13}N_2O_3.C_6H_{14}N_2O_2$; mol wt 427.47. HPLC determn: S. Scalia, M. Massaccesi, *Int. J. Pharm.* **82**, 179 (1992). Clinical evaluation in senile cataract: P. Baraldi *et al.*, *Graefe's Arch. Clin. Exp. Opthalmol.* **228**, 105 (1990); in *in vivo* contact lens cleaning: T. C. Evans *et al.*, *Optom. Vis. Sci.* **70**, 210 (1993). Review of pharmacology and therapeutic potential: J. A. Balfour, S. P. Clissold, *Drugs* **39**, 575-596 (1990).

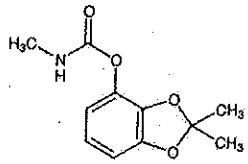
Sodium salt. [23255-99-4] Versus. $C_{16}H_{13}N_2NaO_3$; mol wt 304.28.

USE: Contact lens cleaning and wetting solution.

THERAP CAT: Anti-inflammatory; in treatment of cataracts.

THERAP CAT (VET): In treatment of cataracts.

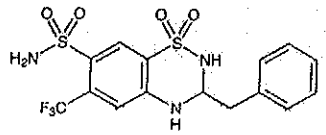
1036. Bendiocarb. [22781-23-3] 2,2-Dimethyl-1,3-benzodioxol-4-ol methylcarbamate; methylcarbamic acid 2,3-(isopropylidenedioxy)phenyl ester; NC-6897; Ficam. $C_{11}H_{13}NO_4$; mol wt 223.23. C 59.18%, H 5.87%, N 6.27%, O 28.67%. Acetylcholinesterase inhibitor. Prepn: Gates, Gillon, **ZA 6800736** *C.A.* **71**, 38941m (1969), corresp to **US 3736338** (1968, 1973 both to Fisons). Insecticidal activity: Story, *Int. Pest Control* **14**, 6 (1972).



White solid, mp 129-130°. Soly in water: 40 ppm; in hexane: 350 ppm.

USE: Contact insecticide.

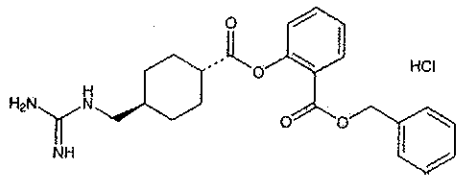
1037. Bendroflumethiazide. [73-48-3] 3,4-Dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide; 3-benzyl-6-trifluoromethyl-3,4-dihydro-7-sulfamoyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide; 3-benzyl-3,4-dihydro-7-sulfamyl-6-trifluoromethyl-1,2,4-benzothiadiazine 1,1-dioxide; bendrofluazide; benzydroflumethiazide; benzylhydroflumethiazide; Aprinox; Berkozide; Centyl; Naturetin; Neo-Naclex; Salures; Sinesalin. $C_{15}H_{14}F_3N_3O_4S_2$; mol wt 421.41. C 42.75%, H 3.35%, F 13.52%, N 9.97%, O 15.19%, S 15.22%. Prepn: C. T. Holdrege *et al.*, *J. Am. Chem. Soc.* **81**, 4807 (1959); F. Lund, W. O. Godtfredsen, **GB 863474**; *eidem*, **US 3392168** (1961, 1968 both to Lövens Kemiske Fabrik). Comprehensive description: K. Florey, F. M. Russo-Alesi, *Anal. Profiles Drug Subs.* **5**, 1-19 (1976).



Crystals from dioxane, mp 224.5-225.5° (U.S. patent). Also reported as mp 221-223° (Holdrege). uv max (methanol): 208, 273, 326 nm ($E^{1\%}_{1cm}$ 745, 565, 96). Insol in water, chloroform, benzene, ether. Sol in acetone, alcohol.

THERAP CAT: Diuretic, antihypertensive.

1038. Benexate Hydrochloride. [78718-25-9] 2-[[[*trans*-4-[[(Aminoiminomethyl)amino]methyl]cyclohexyl]carbonyl]oxy]benzoic acid phenylmethyl ester monohydrochloride; benzyl salicylate *trans*-4-(guanidinomethyl)cyclohexanecarboxylate hydrochloride; (2'-benzyloxycarbonyl)phenyl *trans*-4-(guanidinomethyl)cyclohexanecarboxylate hydrochloride. $C_{23}H_{28}ClN_3O_4$; mol wt 445.94. C 61.95%, H 6.33%, Cl 7.95%, N 9.42%, O 14.35%. Synthetic protease inhibitor with antiulcer activity. Prepn: **BE 885263**; M. Muramatsu *et al.*, **US 4348410** (1981, 1982 to Nippon Chemiphar; Teikoku Chem. Ind.). Prepn and protease inhibition: T. Satoh *et al.*, *Chem. Pharm. Bull.* **33**, 647 (1985). Prepn of the clathrate compound with β-cyclodextrin: **JP Kokai 83 38250**; M. Shinoda *et al.*, **US 4478995** (1983, 1984 both to Teikoku Chem. Ind.). Effect on gastric secretion and exptl ulcers in rats: S. Okabe *et al.*, *Oyo Yakuri* **27**, 829 (1984), *C.A.* **101**, 143881c (1984); I. Tanaka, H. Tagami, *Nippon Yakurigaku Zasshi* **85**, 167 (1985), *C.A.* **103**, 64660t (1985); F. Hirose *et al.*, *Yakuri to Chiryo* **15**, 4749 (1987), *C.A.* **108**, 137769a (1988).

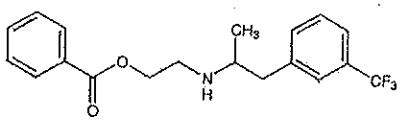


Crystals from methanol + ether, mp 83°.

Compd with β-cyclodextrin (1:1). [91574-91-3] Benexate-CD; TA-903; Lonmiel; Ulgut. $C_{65}H_{98}ClN_3O_{39}$; mol wt 1580.92.

THERAP CAT: Antiulcerative.

1039. Benfluorex. [23602-78-0] 2-[[1-Methyl-2-[3-(trifluoromethyl)phenyl]ethyl]amino]ethanol benzoate (ester); 2-[[α-methyl-*m*-(trifluoromethyl)phenethyl]amino]ethanol benzoate (ester); 1-(*m*-trifluoromethylphenyl)-2-(β-benzoyloxyethyl)aminopropane; *N*-(2-benzoyloxyethyl)norfenfluramine; benfluramate; S-780; SE-780. $C_{19}H_{20}F_3NO_2$; mol wt 351.36. C 64.95%, H 5.74%, F 16.22%, N 3.99%, O 9.11%. Prepn from 1-(*m*-trifluoromethyl)-2-(β-hydroxyethyl)aminopropane and benzoyl chloride: L. Beregi *et al.*, **FR 1517587**; *eidem*, **US 3607909** (1968, 1971 both to Sci. Union et Cie, Soc. Franc. Rech. Med.). Metabolism studies: A. H. Beckett *et al.*, *J. Pharm. Pharmacol.* **23**, 950 (1971); **24**, 281 (1972). Pharmacology: D. N. Brindley *et al.*, *ibid.* **28**, 670 (1976); P. Pritchard *et al.*, *ibid.* **29**, 343 (1977); *eidem*, *Biochem. J.* **166**, 639 (1977).



Colorless oil.

Hydrochloride. [23642-66-2] S-992; JP-992; Minolip; Mediator; Mediaxal. $C_{19}H_{20}F_3NO_2.HCl$; mol wt 387.82. Crystals from ethyl acetate, mp 161-162°.

THERAP CAT: Antilipemic.

1040. Benfluralin. [1861-40-1] *N*-Butyl-*N*-ethyl-2,6-dinitro-4-(trifluoromethyl)benzenamine; *N*-butyl-*N*-ethyl-α,α,α-trifluoro-2,6-dinitro-*p*-toluidine; *N*-butyl-*N*-ethyl-2,6-dinitro-4-trifluoromethylaniline; benefin; bethrodine; EL-110; Balan; Balfin; Benefex; Quilan. $C_{13}H_{16}F_3N_3O_4$; mol wt 335.28. C 46.57%, H 4.81%, F 17.00%, N 12.53%, O 19.09%. Selective pre-emergence herbicide. Prepn: Q. F. Soper, **US 3257190** (1966 to Lilly). Activity: E. F. Alder *et al.*, *Proc. Northeast. Weed Control Conf.* **15**, 298 (1961). Environmental fate: T. Golab *et al.*, *J. Agric. Food Chem.* **18**, 838 (1970). Soil degradn: J. H. Miller *et al.*, *Weed Sci.* **23**, 211 (1975); R. L. Zimdahl, S. M. Gwynn, *ibid.* **25**, 247 (1977). Toxicity study: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* **18**, 185 (1971).

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The use of common stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances

2002

Programme on International Nonproprietary Names (INN)
Quality Assurance and Safety: Medicines
Essential Drugs and Medicines Policy
World Health Organization
Geneva

Preface

WHO'S INN PROGRAMME

WHO has a constitutional responsibility to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products". This is the basis for many activities within WHO, such as International Nonproprietary Names (INN), WHO Good Manufacturing Practices, the International Pharmacopoeia, the WHO Certification Scheme and many others. The section of the WHO specifically dealing with selection of International Nonproprietary Names for pharmaceutical substances falls under the Department of Essential Drugs and other Medicines.

INN SELECTION PROCEDURE AND CRITERIA

A request for an INN is usually submitted on a form to the World Health Organization. In certain countries, where national nomenclature commissions exist, this is done through the corresponding national nomenclature authority.

Precise information on the chemistry, pharmacological action and use, as well as suggested nonproprietary names, name and address of the manufacturer are to be provided on the form. Each name proposed by the originator of such a request is then examined and a name selected.

All members of the WHO Expert Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated to select nonproprietary names have to agree to the name which is then first published as a proposed INN. During a four-month period, any person can forward comments, or lodge a formal objection to a name, e.g. on grounds of similarity with a trade-name. If no objection is raised the name will be published a second time as recommended INN.

The primary principles for selection are that an INN should be

- distinctive in sound and spelling,

- not too long,

- not liable to confusion with other names in common use.

INNs for substances belonging to a particular group of pharmacologically related substances show their relationship by the use of common stems, which are listed and defined in this document.

In addition to the above rules, certain rules have been established to allow the use of INNs internationally, i.e. in various languages. For example, the letters "h" and "k" should be avoided; "c" should be used instead of "ae" and "oe", "i" instead of "y" and "t", "f" instead ot "th" and "ph".

Further information on the selection procedure and general principles in devising INNs may be found in Annex 2 and 3.

THIS DOCUMENT

This document lists common stems for which chemical and/or pharmacological categories have been established. These stems and their definitions have been selected by the INN experts and are for use when selecting new international nonproprietary names for pharmaceutical substances that belong to an established series of related compounds.

The list is not exhaustive in that it might not include all stems used by the INN Committee. It is the nature of the nomenclature process that new, potential stems are constantly being created and that definitions of older stems may need to be modified as new information becomes available.

Examples of nonproprietary names have been selected from Lists 1 - 84 of Proposed International Nonproprietary Names. They were compared with:

Stems listed in article 9 of the "General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances", Annex to List 81 of proposed INN and some well-established old or new stems not included in article 9 of the general principles. Details on stems are indicated as follows:

(x) stems that are included in article 9 of the general principles

(d) stems deleted from article 9 of the general principles

The reference to TRS 581* indicates that the stem is listed in Annex 3 of the 20th Report of the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances.

References to syllables in the British Approved Names (BAN) dictionary and the USP Dictionary of USAN and International Drug Names have also been made wherever applicable. Whenever the BAN or USAN definitions are not identical to the INN definition they are given in brackets under the INN definition.

For each stem, the names have been classified as:

(a) names in which the preferred stem has been used in accordance with its definition;

(b) names in which the preferred stem has been used but not in accordance with its definition;

(c) names which belong to the same group of pharmaceutical substances and in which no preferred stem has been used. (This part of the list is not always complete).

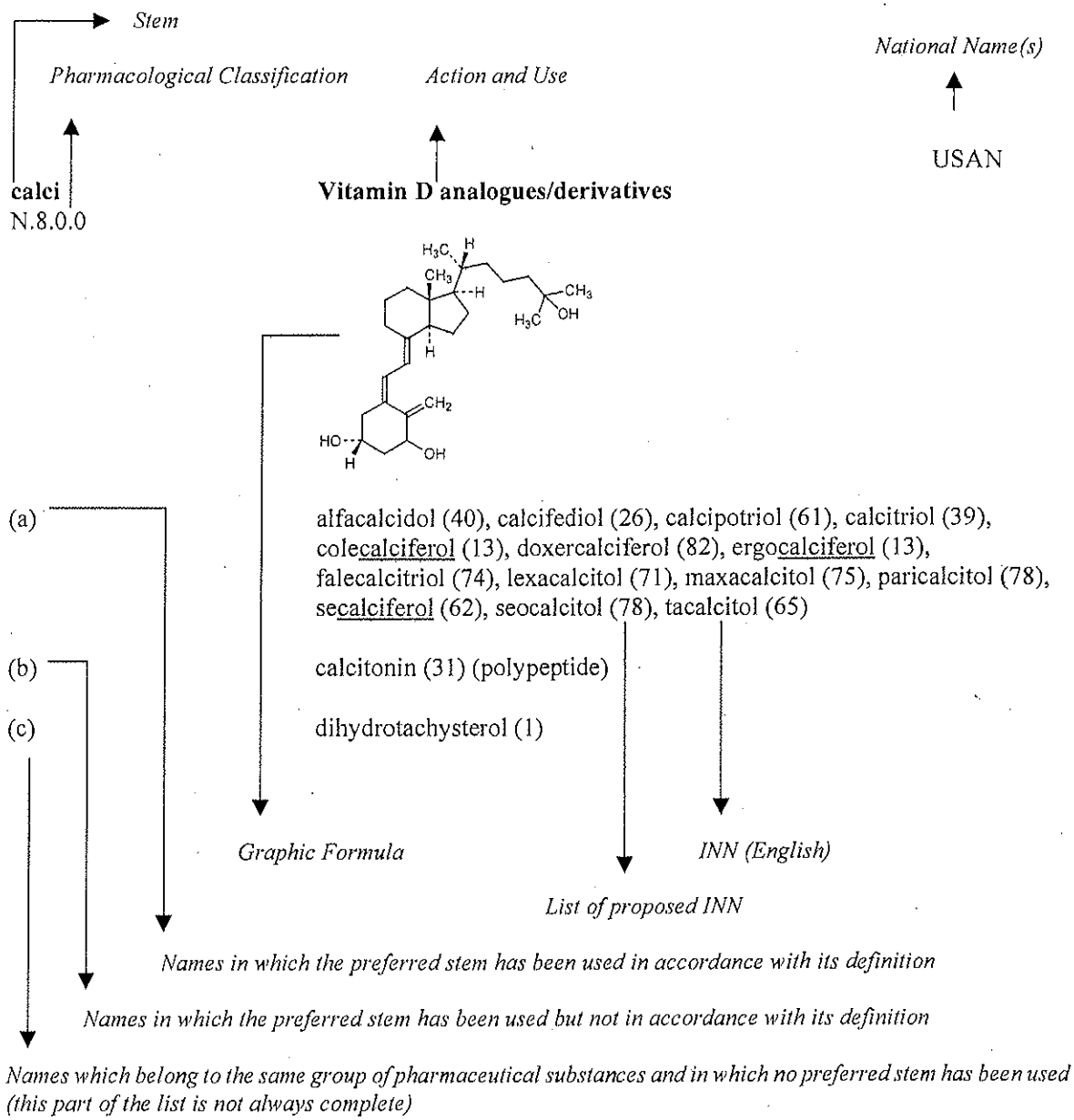
The codes given on the left-hand side under each stem refer to the WHO pharmacological classification used in the WHO Drug Evaluation and Monitoring Programme.

Note for trade-mark officers:

In line with the WHO World Health Assembly resolution (*WHA46.19***) it would be appreciated if trade-marks were not derived from INNs and if INN stems were not used in trade-marks. This practice endangers the principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature.

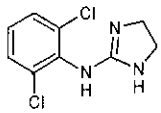
*Nonproprietary names for pharmaceutical substances, Twentieth Report of the WHO Expert Committee (1975)
** WHA resolution on nonproprietary names for pharmaceutical substances (1993)

Layout of information



-onidine **antihypertensives, clonidine derivatives**

H.3.0.0



(a) apraclonidine (59) (control of intraocular pressure), benclonidine (42), brimonidine (66), clonidine (40), flutonidine (31), moxonidine (48), piclonidine (44), tolonidine (28)

related: alinidine (40) (analgesic)

-nidine

H.3.0.0

(a) related antihypertensives: betanidine (13), indanidine (50), rilmenidine (57), tiamenidine (28)

(b) muscle relaxant: tizanidine (43)
topical antiinfective: octenidine (43), pirtenidine (57)
antibacterial: sulfaguanidine (4)
vet. coccidiostat: robenidine (25)

(c) dexlofexidine (48), levlofexidine (48), lofexidine (33)

-onium **see -ium**

-opamine **see -dopa**

BAN, USAN

-orex **anorexics**

M.1.0.0 (BAN: anorexic agents, phenethylamine derivatives)
(USAN: anorexants)

(a) acridorex (21), amfepentorex (16), aminorex (14), benfluorex (25), clobenzorex (18), cloforex (16), clominorex (14), difemetorex (41), etolorex (20), fenisorex (29), fenproporex (17), flucetorex (30), fludorex (19), fluminorex (14), formetorex (14), furfenorex (16), indanorex (30), mefenorex (19), morforex (26), oxifentorex (20), pentorex (16), picilorex (40), tiflorex (34)

(c) amfebutamone (31), amfecloral (12), amfepramone (13), amfetamine (55), amfetaminil (40), benzfetamine (55), brolamfetamine (55), chlorphentermine (11), clortermine (22), dexamfetamine (55), dimetamfetamine (38), etilamfetamine (40), fenbutrazate (12),

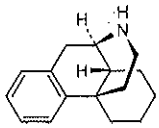
fenfluramine (14), hexapradol (12), levamfetamine (12), mephentermine (6), ortetamine (13), phendimetrazine (11), phenmetrazine (6), phentermine (11)

TRS 581

---

orphan **narcotic antagonists/agonists, morphinan derivates**

A.4.1.0
B.2.0.0 (USAN: -orphan: morphinan derivatives that are narcotic antagonists or agonists)



(a) A.4.1.0: butorphanol (31), dextromethorphan (1), dextrorphan (1), dimemorfan (30), ketorfanol (49), levomethorphan (1), levophenacylmorphan (9), levorphanol (4), norlevorphanol (9), oxilorphan (31), phenomorphan (5), proxorphan (43), racemethorphan (1), racemorphan (1), xorphanol (48)

TRS 581 B.2.0.0: levallorphan (2)

-orph- **-orphine**: acetorphine (17), alletorphine (25), buprenorphine (29), cyprenorphine (17), desomorphine (5), diprenorphine (21), etorphine (17), homprenorphine (25), methyldesorphine (5), methyldihydro-morphine (5), nalorphine (1), nicomorphine (7), normorphine (7)

-orphinol: hydromorphinol (11)

-orphone: conorfone (46), hydromorphone (1), oxymorphone (5), pentamorphone (60), semorphone (67)

(b) emorfazone (44), morforex (26), morpheridine (6), orphenadrine (8)

Annexe 1-28

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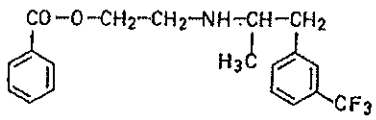
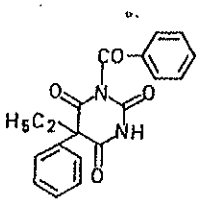
ORGANISATION MONDIALE DE LA SANTÉ
GENÈVE

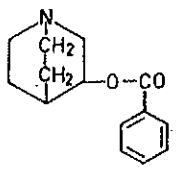
Dénomination commune internationale proposée (latin, français)	*Nom chimique ou description, formule brute et formule développée*
benfluorexum benfluorex	benzoate de (α-méthyl trifluorométhyl-4 phénéthylamino)-2 éthyle $C_{19}H_{20}F_3NO_2$



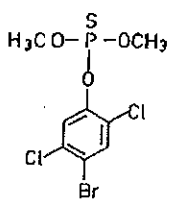
benzobarbitalum benzobarbital	acide benzoyl-1 éthyl-5 phényl-5 barbiturique $C_{19}H_{16}N_2O_4$



benzoclidinum benzoclidine	benzoate de quinuclidyle-3 $C_{14}H_{17}NO_2$



bromofosum bromofos	thiophosphate de *O*-(bromo-4 dichloro-2,5 phényle) et de *O,O*-diméthyle $C_8H_8BrCl_2O_3PS$



Annexe 1-29

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Neuilly, le 30 Août 1973

Monsieur le Directeur
du Service Central de la Pharmacie
et des Médicaments
Ministère de la Santé Publique
et de la Sécurité Sociale
9, avenue de Lowendal
75 007 PARIS

A l'attention de M. LALANNE

Bureau PH 4

Demande de changement de dénomination commune

Monsieur le Directeur,

Nous avons l'honneur de solliciter le changement de dénomination commune de l'un de nos principes actifs, le

benzoate de {[méthyl-I (trifluorométhyl-3 phényl)-2 éthyl] amino}-2 éthyle.

En effet, lorsqu'en Juin I970 nous avons demandé une dénomination commune internationale pour ce composé chimique, nous pensions que la principale indication thérapeutique serait l'obésité.

C'est ainsi que la dénomination commune BENFLUOREX a été retenue et publiée par la Commission de la Pharmacopée Française (Additif n° I3 à la Pharmacopée I965 et à son premier supplément paru au J.O. du 28 Juillet I97I) et par l'O.M.S. (liste des D.C.I. proposées n° 25[2] parue dans la chronique O.M.S., volume 25, n° 3 de Mars I97I).

Or, à la lumière des nombreux travaux d'expertises cliniques, l'activité anorexiante alors revendiquée s'est avérée en réalité très faible et tout à fait accessoire par rapport aux propriétés métaboliques de ce produit.

.../...

22, rue Garnier Tél. 758 I2-60
[redacted] - 92 201 - Neuilly-sur-Seine • B.P. 110 • Tél. 637-64-60 + • Télex 62542 NLLSN
Siège Social : 45 - Gidy - France • Société anonyme au capital de 2.220.000 F • R.C. Orléans 54 B 79 • I.N.S.E.E. 359.45.154.0001

Annexe 1-29 2

LES LABORATOIRES SERVIER

Les indications désormais retenues sont les suivantes :

- troubles métaboliques athérogènes
- troubles du métabolisme des lipides
- troubles du métabolisme des glucides
- troubles nutritionnels.

Le suffixe -OREX étant, selon les directives générales pour la formation des D.C.I., réservé aux agents anorexigènes, nous pensons donc nécessaire que la dénomination commune soit changée afin qu'elle ne soit pas en opposition avec les activités cliniques de notre produit.

Par ailleurs, nous vous signalons que la dénomination commune BENFLUOREX a été frappée d'antériorité par une marque autrichienne et, de ce fait, ne pourra jamais être recommandée par l'O.M.S.

Nous nous permettons de vous suggérer de nouvelles dénominations :

. BENZAFLUMINE

. BENFLURATE

Nous vous prions de croire, Monsieur le Directeur, à l'assurance de notre considération distinguée.

R.J.C. DENIS
Vice-Président Expansion

SERVICE CENTRAL DE LA PHARMACIE
ET DES MEDICAMENTS

Bureau PH.4

29 NOV. 1973

PH.4-73-D/ 29.11/1145

OBJET : Demande de changement de dénomination commune.

NOTE pour M. SAUNIE

J'ai l'honneur de vous communiquer la lettre, dont vous trouverez ci-joint photocopie, que les laboratoires SERVIER nous ont adressée pour solliciter un changement de dénomination pour le produit : BENFLUOREX (dénomination commune française et internationale).

La Commission de Nomenclature, saisie de ce problème, s'est étonnée de l'expression : "les indications désormais retenues..." employée dans la lettre précitée ; la Commission considère que les nouvelles propriétés thérapeutiques et indications cliniques n'ont pas annulé le risque d'utilisation de ce médicament par les toxicomanes.

Cependant, l'Organisation Mondiale de la Santé ayant attribué à un produit voisin la dénomination FENFLURAMINE, la Commission souhaite avoir l'avis des Experts de cet organisme et propose FENFLURAMATE par analogie.

Avant d'exposer ce problème à GENEVE, je souhaiterai connaître, dans les meilleurs délais possibles, votre avis sur la position de la Commission, afin que notre transmission à l'Organisation Mondiale de la Santé comporte, aussi, l'avis du Service.

Pièce jointe : 1.

P. LALANNE
Chargé de Mission
au Service Central de la Pharmacie
et des Médicaments

SERVICE CENTRAL DE LA PHARMACIE
ET DES MEDICAMENTS

Bureau PH.4

PHARMACOPEE, FORMULAIRE
RECHERCHE APPLIQUEE
---

25 JUIL. 1974

PH.4-74-D/ 25.07/640

V./Réf. : PH.5-12-14/2-F du 18 décembre 1973.

N./Réf. : PH.4-73-D/29-11/745 du 29 novembre 1973.

OBJET : Dénomination commune : BENFLUOREX.

NOTE pour M. NARGEOLET

- Directeur de la Pharmacie -

A l'attention de M. SAUNIÉ

Comme suite à ma note citée en référence et à votre réponse du 18 décembre 1973 à propos de la demande de changement de dénomination commune pour BENFLUOREX, sollicitée par le laboratoire SERVIER, j'ai l'honneur de vous faire connaître l'avis de l'Organisation Mondiale de la Santé interrogée, à ce sujet, par le secrétariat de la Commission Nationale de Pharmacopée.

Il a été décidé de retenir la dénomination commune internationale BENFLUOREX, car selon les Experts de cette Organisation, "le suffixe OREX utilisé pour les agents anorexigènes "évoque aussi les substances amphétaminiques puisque la presque "totalité des substances anorexigènes sont des dérivés de la "phénéthylamine".

La Commission de Nomenclature a adopté cette recommandation conformément aux accords internationaux ; la dénomination commune française reste donc identique à la dénomination commune internationale BENFLUOREX, et les propositions du laboratoire SERVIER ont été écartées.

Nous avons notifié cette décision au Laboratoire interessé.

P. LALANNE
Chargé de Mission
au Service Central de la Pharmacie
et des Médicaments

Dossier n° : 10008

Laboratoires : SERVIER

MEDIATOR

Le principe actif :

Benzoate de {(méthyl-1(trifluorométhyl-3 phényl)-2 éthyl) amino}-2 éthyle

est pourvu d'une dénomination commune française et internationale (liste proposée 25*) :

BENFLUOREX.

La volonté du laboratoire d'écarter cette dénomination officielle a déjà fait l'objet d'un échange de notes entre le Bureau PH.4 et le Service Central de la Pharmacie. (Voir documents joints). Cette dénomination devrait être imposée par le Bureau PH.11.

Pièces jointes : 3.

P. LALANNE
Chargé de Mission
au Service Central de la Pharmacie
et des Médicaments

FL/YK

REPUBLIQUE FRANCAISE

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Annexe 1-33

3.8

MINISTÈRE DE LA SANTÉ PUBLIQUE ET DE LA SÉCURITÉ SOCIALE

SERVICE CENTRAL DE LA PHARMACIE ET DES MÉDICAMENTS

4e BUREAU
PHARMACOPÉE, FORMULAIRE
ET RECHERCHE APPLIQUÉE

PARIS, LE 14 NOV. 1975
9, AVENUE LOWENDAL VIIe
TÉL. 544.16.35

H.4-75/YK/14-11/539

NOTE pour Monsieur NARGEOLET
Directeur de la Pharmacie

OBJET : Nomenclature des médicaments
- BENFLUOREX -

A l'attention de Madame BARRAU

J'ai l'honneur de vous informer, *pour suite à donner*, que le produit correspondant à la dénomination scientifique :

Benzoate de {(méthyl-1(trifluorométhyl-3 phényl)-2 éthyl) amino}-2 éthyle chlorhydrate

spécialisé sous le nom de

MEDIATOR (Laboratoires SERVIER)

dont il est fait mention dans l'arrêté *Inscriptions et modifications aux tableaux des substances vénéneuses (section II)* du 11 Juin 1975 (J. O. du 4 Juillet 1975), est pourvu d'une dénomination commune française (Pharmacopée française - 9ème édition - page II - 29) et internationale (liste proposée 25) :

BENFLUOREX

La volonté du laboratoire d'écarter cette dénomination officielle a déjà fait l'objet d'un échange de notes entre le Bureau PH.4 et le Service Central de la Pharmacie (PH.4-73/D/29-11/745 ; PH.5-12/14/2-F - 18 Décembre 1973 et PH.4-74/D/25-07/640.

P. LALANNE
Chargé de Mission
au Service Central de la Pharmacie
et des Médicaments

Classifications

The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD)

Purpose/Definition

The ATC/DDD system classifies therapeutic drugs. The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use.

Classification structure

In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified into five different levels. Drug consumption statistics (international and other levels) can be presented for each of these five levels.

Administrative status

Creation date:

The Guidelines were published for the first time in the current format in 1990.

The Index was published as a paper copy in the current format in 1990 for the first time.

The system has been in use for statistics since 1975.

Last date change: 2003

Annual updates, now in Version 6 for the Guidelines in the current format and Version 13 for the Index in the current format . Available indexes:

Reference documents

ATC Index with DDDs 2003. Guidelines for ATC classification and DDD assignment 2003.

Available formats:

The Guidelines are published in all 3 languages in paper format only.

Online searchable database.

Training and training materials:

2 days international course in Oslo, once a year. The course offers lectures and working groups.

Courses elsewhere on request. Approx. 2 additional courses annually.

Languages

The participants receive the Index and the Guidelines, copies of all the presentations, and the working group problems.

The Index is published in the following languages and formats:

English (all available indexes),

German (paper version only),

Relationships with other classifications

Spanish (paper version only)

Correspondence between revisions

The Anatomical Therapeutic Classification (AT) developed by the European Pharmaceutical Market Research Assiciation (EPhMRA). The ATC/DDD system and the AT classification have the same origin, but are developed for different purposes. Comparative tables are available.

Correspondence with international, multinational, national classifications

Relationships with other terminologies

Currently, the ICD contains no reference to any external classification of medical substances. However, guidelines for the ICD-10 section "Poisoning by drugs, medicaments and biological substances" (T36-T50) could contain suggestions on how to combine, or replace, ICD codes with specific substance codes, preferably using an internationally widespread and recommended standard system such as the ATC.

Contact information:

WHO Collaborating Centre for Drug Statistics Methodology

Name a person.

Norwegian Institute of Public Health

P.O.BOX 4404 Nydalen

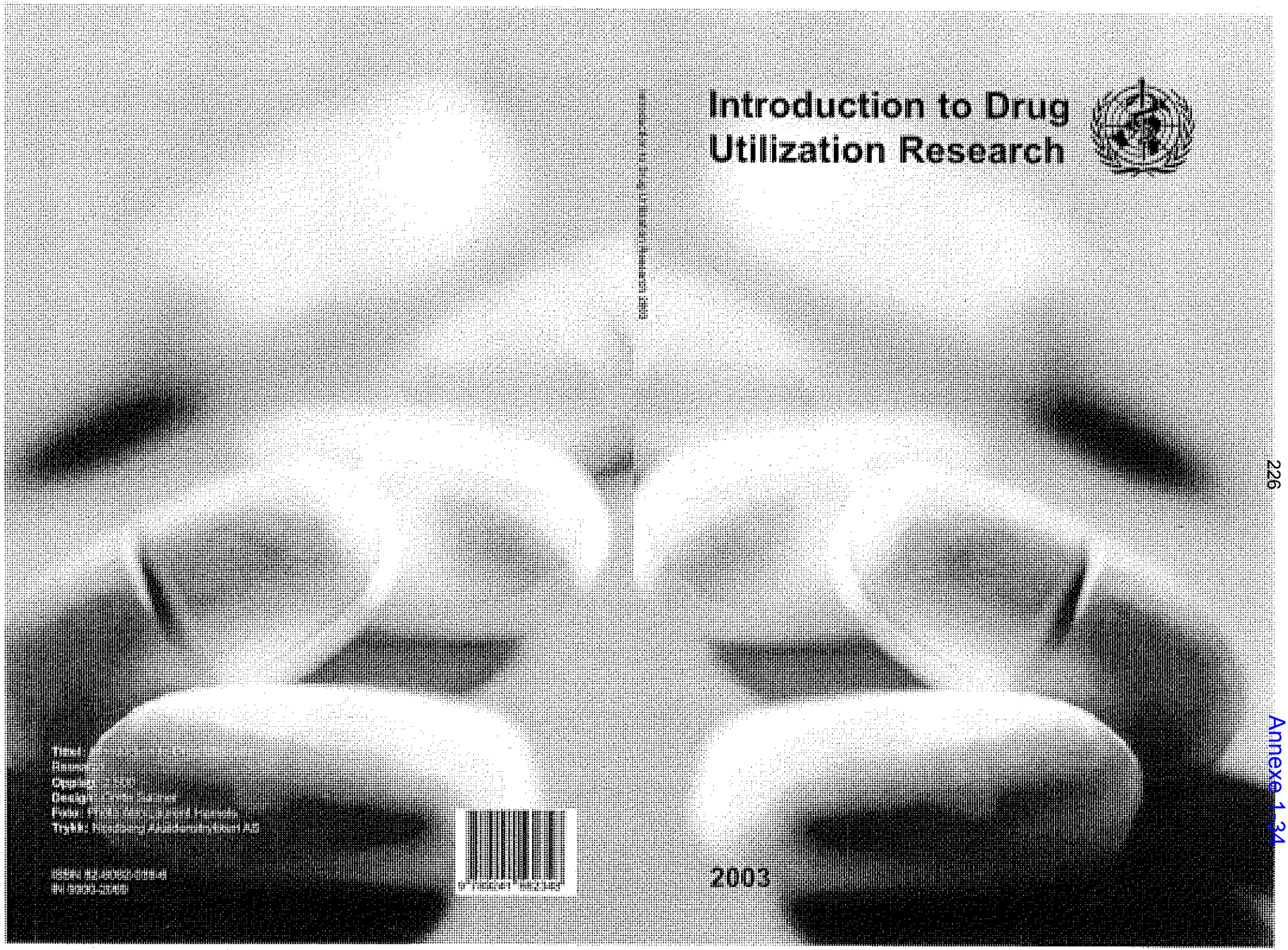
NO-0304 Oslo

NORWAY

whocc@fhi.no

www.whocc.no

Introduction to Drug Utilization Research



2003

Introduction to Drug Utilization Research

World Health Organization

WHO International Working Group for Drug Statistics Methodology

WHO Collaborating Centre for Drug Statistics Methodology

WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services

CHAPTER 5: DRUG CLASSIFICATION SYSTEMS

A drug classification system represents a common language for describing the drug assortment in a country or region and is a prerequisite for national and international comparisons of drug utilization data, which have to be collected and aggregated in a uniform way. Access to standardized and validated information on drug use is essential to allow audits of patterns of drug utilization, to identify problems in drug use, to initiate educational or other interventions and to monitor the outcomes of these interventions. The main purpose of having an international standard is to be able to compare data between countries. A recent example is the international focus on creating comparable systems for monitoring cross-national patterns of antibacterial utilization to aid work against bacterial resistance.

5.1 DIFFERENT CLASSIFICATION SYSTEMS

[*ATC classification; AT classification; EPhMRA; IMS; WHO Collaborating Centre for Drug Statistics Methodology*]

Drugs can be classified in different ways according to:
- their mode of action;
- their indications; or
- their chemical structure.

Each classification system will have its advantages and limitations and its usefulness will depend on the purpose, the setting used and the user's knowledge of the methodology. Comparisons between countries may require a classification system different from that needed for a local comparison (e.g. between different wards in a hospital). Of the various systems proposed over the years, only two have survived to attain a dominant position in drug utilization research worldwide. These are the «Anatomical Therapeutic» (AT) classification developed by the European Pharmaceutical Market Research Association (EPhMRA) and the «Anatomical Therapeutic Chemical» (ATC) classification developed by Norwegian researchers. These systems were originally based on the same main principles. In the EPhMRA system, drugs are classified in groups at three or four different levels. The ATC classification system modifies and extends the EPhMRA system to include a therapeutic/pharmacological/chemical subgroup as the fourth level and the chemical substance as the fifth level (see, for example, the classification of glibenclamide in the box below).

The ATC classification is also the basis for the classification of adverse drug reactions used by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden (www.who-umc.org).

The main purpose of the ATC classification is as a tool for presenting drug utilization statistics and it is recommended by WHO for use in international comparisons. The EPhMRA classification system is used worldwide by IMS for providing market research statistics to the pharmaceutical industry. It should be emphasized that the many technical differences between the EPhMRA classification and the ATC classification mean that data prepared using the two classification systems are not directly comparable.

In 1996, WHO recognized the need to develop the ATC/DDD system from a European to an international standard in drug utilization studies. The European WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway, which is responsible for coordinating the use of the methodology, was then linked to WHO Headquarters in Geneva. This was intended to assist WHO in its efforts to ensure universal access to essential drugs and to stimulate rational use of drugs particularly in developing countries.

5.2 THE ATC CLASSIFICATION SYSTEM

[*Structure; coding principles; therapeutic use; pharmaceutical formulations; strengths*]

The ATC classification system divides the drugs into different groups according to the organ or

system on which they act and according to their chemical, pharmacological and therapeutic properties.

Drugs are classified in groups at five different levels. The drugs are divided into 14 main groups (first level), with two therapeutic/pharmacological subgroups (second and third levels). The fourth level is a therapeutic/pharmacological/chemical subgroup and the fifth level is the chemical substance. The second, third and fourth levels are often used to identify pharmacological subgroups when these are considered to be more appropriate than therapeutic or chemical subgroups.

The complete classification of glibenclamide (see box below) illustrates the structure of the code.

A	Alimentary tract and metabolism (first level, main anatomical group)
A10	Drugs used in diabetes (second level, main therapeutic group)
A10B	Oral blood-glucose-lowering drugs (third level, therapeutic /pharmacological subgroup)
A10B B	Sulfonamides, urea derivatives (fourth level, chemical/therapeutic /pharmacological subgroup)
A10B B01	Glibenclamide (fifth level, subgroup for chemical substance)

Thus, in the ATC system all plain glibenclamide preparations are given the code A10B B01.

Medicinal products are classified according to the main therapeutic use of their main active ingredient, on the basic principle of assigning only one ATC code for each pharmaceutical formulation (i.e. similar ingredients, strength and pharmaceutical form).

A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses. Two examples of this are given below:

- Sex hormones in certain dosage forms or strengths are used only in the treatment of cancer and are thus classified under L02 - Endocrine therapy. The other dosage forms and strengths are classified under G03 - Sex hormones and modulators of the genital system.
- Bromocriptine is available in different strengths. The low-dose tablets are used as prolactin inhibitors and are classified in G02 - Other gynaecologicals. Bromocriptine tablets in higher strengths are used to treat Parkinson disease and are classified in N04 - Anti-Parkinson drugs.

Different formulations with different indications may also be given separate ATC codes, for example prednisolone is given several ATC codes because of the different uses of the different formulations (see box below).

A07E A01	Intestinal anti-inflammatory agents (*enemas and rectal foams*)
C05A A04	Antihaemorrhoidals for topical use *rectal suppositories*)
D07A A03	Dermatological preparations (*creams, ointments, lotions*)
H02A B06	Corticosteroids for systemic use (*tablets, injections*)
R01A D02	Nasal decongestants (*nasal spray, drops*) S01B A04 Ophthalmologicals (*eye drops*)
S02B A03	Otologicals (*ear drops*)

The ATC system is not strictly a therapeutic classification system. At all ATC levels, ATC codes can be assigned according to the pharmacological properties of the product. Subdivision on the basis of mechanism of action will understandably be rather broad, since a very detailed classifi-

cation of this kind would result in having only one substance per subgroup, which is better avoided (e.g. in the case of antidepressants). Some ATC groups are subdivided into both chemical and pharmacological groups (e.g. ATC group J05A - Agents affecting the virus directly). If a new substance fits in both a chemical and pharmacological fourth level, the pharmacological group is normally chosen.

Substances classified as having the same ATC fourth level should not be considered as pharmacotherapeutically equivalent since the profiles for their mode of action, therapeutic effects, drug interactions and adverse drug reactions may differ.

As the drugs available and their uses are continuously changing and expanding, regular revisions of the ATC system are necessary. An important principle is to keep the number of alterations to a minimum. Before alterations are made, any potential difficulties arising for the users of the ATC system are considered and related to the benefits that would be achieved by the alteration. Changes to the ATC classification would be made when the main use of a drug had clearly changed, and when new groups are required to accommodate new substances or to improve the specificity of the groupings.

Because the ATC system separates drugs into groups at five levels (described above), statistics on drug utilization grouped at the five different levels can be provided. The information available ranges from figures showing total use of all drug products classified e.g. in main group C - Cardiovascular system (first level), to figures for the different subgroups (i.e. second, third and fourth level) to figures for the use of the separate substances.

More detailed information can be obtained at the lower (i.e. the fourth and fifth) levels. The higher levels are used if comparison of drug groups is the aim of a study (see Fig. 5). This gives a better overview and trends in drug use related to different therapeutic areas can easily be identified.

5.3 Ambivalence towards an international classification system

All international standards demand compromises and a drug classification system is no exception to this rule. Drugs may be used for two or more equally important indications, and the main therapeutic use of a drug may differ from one country to another. This will often result in several

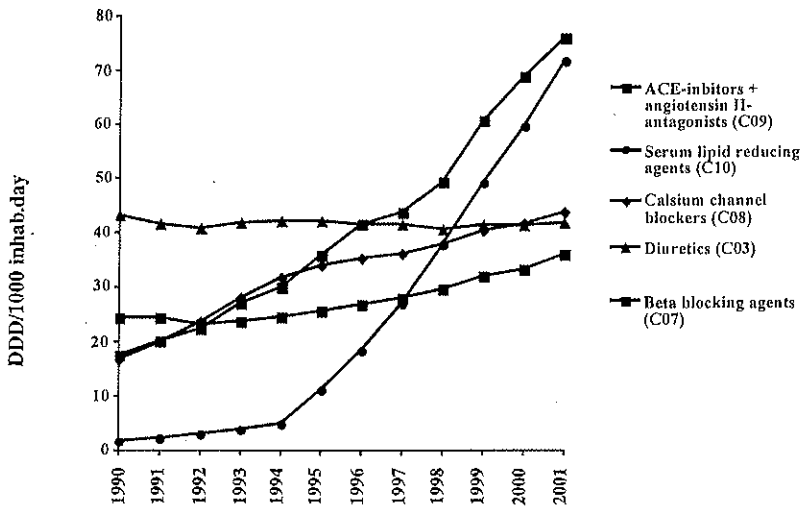


Figure 5 Total sales of drugs used in cardiovascular disorders in Norway 1990-2001. ATC/DDD version 2002

possible alternatives for classification, and a decision has to be made regarding the main use. Countries using a drug in a different way from that indicated by the ATC classification may not wish to adopt the ATC classification but prefer to develop national classification systems. However, national traditions have to be weighed against the opportunity to introduce a methodology that permits valid international comparisons of drug utilization. Indeed, there are now many examples where an enthusiastic application of the ATC/DDD methodology has been instrumental in stimulating national research in drug utilization and in developing an efficient drug control system.

5.4 Implementation of the ATC/DDD methodology

[*National drug register; dynamic system; different versions*]

As soon as the decision to introduce the ATC/DDD methodology is taken, it is essential to realize that its proper use inevitably includes an important and time-consuming first step. Each product has to be connected to the appropriate ATC code and DDD (see chapter 6). The linkage between the national drug register and ATC/DDDs has to be ascertained by persons with proper knowledge of the methodology. Experience has shown that in many countries, health authorities, health policy-makers and researchers have not always allocated adequate resources to this important initial step. Another problem is that some users seem to be unaware that the ATC/DDD methodology is a dynamic system to which changes are made continually. This has resulted in several different versions of the ATC/DDD system being used at the same time, sometimes even within the same country.

It is important to realize that adopting the ATC/DDD classification of drugs requires resources and the necessary competence to carry out the work of allocating ATC codes to the products. If possible, this work should be done on a national basis to secure consistent use of the methodology within a country. As described in the general introduction, the same substance may have several different ATC codes depending on the application form and, to some extent, even the strength. For combination products, specific guidelines have been established for allocating ATC codes. Allocating DDDs to the products necessitates many of the same considerations as the allocation of the ATC code. However, in order to link the drug list with sales figures or prescription figures to obtain drug utilization statistics, it is necessary to make appropriate calculations such as the number of DDDs per drug package.

Finally, a given country will nearly always have medicines and combination products for which no ATC codes or DDDs exist. In these cases, it is important to consult the WHO Collaborating Centre for Drug Statistics Methodology in Oslo and request new ATC codes and DDDs. Once ATC codes and DDDs have been linked to the national drug lists, it is necessary to update the drug list regularly in accordance with the annual updates of the ATC/DDD system.

The publication *Guidelines for ATC Classification and DDD Assignment* (see General reading) gives the information necessary for allocating ATC codes and DDDs at a national or local level. All officially assigned ATC codes and DDDs are listed in the *ATC Index with DDDs* (see General reading), a publication that is also available in electronic format and is updated every year. Training courses in the ATC/DDD methodology are arranged annually in Norway and from time to time in other countries. Further information is available on the web site of the WHO Collaborating Centre for Drug Statistics Methodology at http://www.whocc.no.

5.5 General reading

Guidelines for ATC classification and DDD Assignment. Oslo, Norway, WHO Collaborating Centre for Drug Statistics Methodology, 2003.

Annexe 1-35

XX qd code non attribué

De : Sabel DIALLO
Destinataire : Catherine REY-QUINIO
Date : 06/28/07 9:33
Objet : Rép. : Code ATC Mediator

CC : Anne PHAM-BA; Carole FOSSET; France ROUSSELLE

Bonjour,

Le nouveau code ATC de Médiator proposé d'après vous ne correspond pas au contexte. Par conséquent, il faut peut être vous référer à la lettre des Affaires Réglementaires du 03/07/2001, envoyée au SNIP et signée par Mr TROUVIN qui stipule que : **" Le titulaire de l'AMM d'un médicament contenant une substance active n'ayant pas de code ATC doit effectuer une demande de création de code auprès de l'OMS et transmettre ensuite pour information à l'Afssaps le code ATC complet de niveau 5 attribué par l'OMS. Une lettre sera envoyé dans ce sens par l'Afssaps au titulaire lors de l'octroi d'une AMM ou du rectificatif . L'actualisation de la rubrique 5.1 du RCP ne pourra être effectuée qu'à l'occasion d'une demande de rectificatif concernant les données cliniques de l'AMM du médicament. La demande faite par le titulaire ne donnera pas lieu à une redevance spécifique. Ainsi, le code ATC attribué par l'OMS sera intégré dans l'AMM lors de la notification du rectificatif concernant les données cliniques".**

Cordialement

Sabel Diallo

==========
Sabel DIALLO
AFSSAPS : DEMEB/Unité Outils de l'information
Tel : 01 55 87 34 90

e-Mail : sabel.diallo@afssaps.sante.fr
==========

>>> Catherine REY-QUINIO 28/06/07 09:02 >>>
Bonjour,

Merci pour vos réponses à toutes.

Le Code **ATC A10X** (voir mail ci dessous) tel que proposé ne correspond pas au contexte passé, présent et futur de ce dossier. De ce fait, d'un commun accord entre l'évaluation et la Pharmacovigilance nous ne pouvons à ce stade avaliser ce que souhaite la firme.

A ce stade du dossier et de cette procédure (pour rappel, envoi du projet de RCP modifié avec retrait d'une des indications et modification du code ATC), la question est de savoir si - indépendamment de notre avis "scientifique - QUELLE MARGE DE MANOEUVRE NOUS DISPOSONS ? Ou en quelques mots, l'Afssaps peut elle s'opposer à la contre- proposition de la Firme ?
Quelle est la procédure réglementaire sur ce point ? Devons nous adresser un courrier de refus à la firme après passage en Groupe de leur réponse voire en COM d'AMM?
La firme souhaite déposer une demande auprès de l'OMS et proposer son nouveau code ATC ? Est ce la procédure normale ?
Pouvons nous nous y opposer auparavant (si la firme n'a pas déjà effectué cette démarche?)

Merci d'avance de votre réponse qui va conditionner notre démarche future sur ce dossier que je souhaiterais clore avant juillet.

Une réponse rapide serait la bienvenue.

Cordialement

Catherine

****
Docteur Catherine REY-QUINIO
Responsable de l'Unité PTC2
DEMEB/Afssaps
Tel : 01.55.87.34.45/Fax : 01.55.87.34.42.
catherine.rey-quinio@afssaps.sante.fr
****

>>> Sabel DIALLO 06/26/07 10:22 >>>

Bonjour Carole,
Au vue des documents reçus, je suis d'accord avec le laboratoire pour mettre le code ATC A10X- AUTRES MEDICAMENTS DU DIABETEparce que l'indication et les propriétés pharmacodynamiques le justifient. Il ne me semble pas prématuré d'accorder ce code ATC dans la mesure où il n'a été précisé nulle part que c'est un hypoglycémiant oral qui est attribué à des substances actives bien identifiées.
Le jour où ces résultats complémentaires seront concluants (inspection de l'essai clinique MOULIN, positionnement plus précis du benfluorex dans l'arsenal thérapeutique du diabète de type 2...), le benfluorex pourra être considéré comme hypoglycémiant oral et donc être positionné sous MEDICAMENTS HYPOGLYCEMIANTS, INSULINES EXCLUSES (A10B).
J'espère avoir répondu à ta question. Je suis à ta disposition si tu veux d'autres précisions.
Bonne journée

==========
Sabel DIALLO
AFSSAPS : DEMEB/Unité Outils de l'information
Tel : 01 55 87 34 90

e-Mail : sabel.diallo@afssaps.sante.fr
==========

>>> Carole FOSSET 25/06/07 16:46 >>>
Bonjour Sabel,

Comme convenu par téléphone, tu trouveras ci-joint la lettre de procédure contradictoire que nous avons adressée au labo Servier le 29 mai dernier. Compte-tenu du changement d'indication, nous leur avons proposé le code A16AX divers médicaments des voies digestives et du métabolisme.
Le labo nous propose en retour le code A10X Autres médicaments utilisés dans le diabète.

D'un point de vue scientifique, Catherine Rey-Quinio considère que le code proposé par la firme semble "mettre la charrue avant les boeufs" puisqu'en aucun cas à ce stade nous ne pouvons dire s'il s'agit d'un médicament à utiliser dans le diabète (les dernières Recos Diabète d' ailleurs ne citent même pas MEDIATOR). Aussi, cela semble prématuré d'accorder ce code à MEDIATOR ; l'acceptation de ce code ancrerait chez les prescripteurs un effet thérapeutique pour lequel nous n'avons pas de certitude formelle à ce jour.

Nous sollicitons ton avis sur la possibilité de maintenir notre proposition, à savoir A16AX divers médicaments des voies digestives et du métabolisme.

Carole FOSSET MARTINETTI
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Annexe 1-35

Carole FOSSET - Code ATC Mediator

De : Carole FOSSET
Destinataire : ALLIEZ, Emilie; CHAMPART, Anne-Marie; REY-QUINIO, Catherine
Date : Ven, Juin 29, 2007 12:35
Objet : Code ATC Mediator
CC : DIALLO, Sabel; FORNAIRON, Sophie; France ROUSSELLE; PHAM-BA, Anne
Pièces jointes : DIALLO, Sabel; FORNAIRON, Sophie; France ROUSSELLE; PHAM-BA, Anne

Bonjour,

Je vous confirme que dans la mesure où Servier a l'attention de proposer à l'OMS un reclassement en A10X pour le code ATC de MEDIATOR, la seule marge de manoeuvre dont nous disposons est d'adresser nos commentaires à l'OMS, lors de la phase de consultation (cf. procédure ci-jointe).
En conséquence, serait-il possible que l'unité Outils de l'information nous informe en temps utile du démarrage de cette procédure de consultation ?

En parallèle, dès que nous recevrons (ces jours-ci) les commentaires de Servier sur le RCP, nous pourrons notifier le rectificatif d'AMM en attribuant comme code ATC provisoire AXX (ou XX ?).

Bien à vous,

Carole

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XXIII- MEDIATOR [Pages : 15 à 17]

Avant de débuter le débat sur cette spécialité, le Président demande aux éventuels membres de la commission ayant un conflit d'intérêt avec le laboratoire de s'abstenir de participer au débat.

Après présentation et discussion des conclusions du Groupe de Travail DEUG sur les données d'efficacité et des conclusions de la CNPV sur les données de sécurité d'emploi, les conclusions suivantes ont été émises :

1. La COM d'AMM souhaite que les modifications d'ajout d'effets indésirables suivants tels que décidés par la CNVP soient mentionnés au sein de la rubrique 4.8. du RCP : « *troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations)* ».

2. La COM d'AMM suit l'avis DEFAVORABLE émis par le Groupe DEUG au maintien de l'indication : « *Adjuvant au régime adapté dans les hypertriglycéridémies. L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée* », les données soumises ne montrant en effet qu'une efficacité très modeste et inconstante dans les études soumises sur les triglycérides et une absence d'efficacité sur les autres paramètres lipidiques tels que le LDL-cholestérol.

3. La COM d'AMM suit également l'avis du Groupe DEUG pour le maintien de l'indication : « *Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* » dans son libellé actuel. En l'attente de données plus complètes sur l'efficacité du benfluorex en association aux autres antidiabétiques oraux, la COM d'AMM n'a pas souhaité modifier le libellé actuel. A ce jour, seule l'étude MOULIN a permis de montrer une efficacité du benfluorex sur l'HbA1c en association à un sulfamide hypoglycémiant. D'autres études sont en cours dont une étude multicentrique, randomisée visant à comparer l'efficacité du benflurex (150 mg bid ou 150 mg tid) à la pioglitazone (30 mg une fois par jour ou 45 mg deux fois par jour) en association à un sulfamide hypoglycémiant.

4. Après un débat sur la robustesse des résultats de l'étude MOULIN et ses conséquences, la commission propose une inspection de l'étude MOULIN, , seule étude à ce jour ayant montré une efficacité sur les paramètres glucidiques devra être effectuée. Une saisine sera adressée en ce sens à la DIE (Direction de l'Inspection des Etablissements).

5. Les membres de la commission d'AMM souhaite qu'une communication soit fait sur l'usage hors AMM.

Au total, le libellé de l'indication retenu est le suivant : «*Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* ».

XXIV- AVIS SUR LE SEUIL D'ETHANOL DANS LES SOLUTIONS BUVABLES ADMINISTREES A L'ENFANT

Le dossier a été approuvé à l'unanimité.

XXVI- FICHE PATIENTS (le rhume de l'adulte)

Le dossier a été approuvé à l'unanimité.

XXVII- MISE AU POINT SUR L'UTILISATION DE LA SPECIALITE TYSABRI® 300 MG (NATALIZUMAB) DANS LE TRAITEMENT DE LA SCLEROSE EN PLAQUES [Pages : 18 à 29]

Le plan de gestion des risques a été présenté aux membres de la commission ainsi que la constitution du groupe référent qui aura pour mission d'établir de façon prospective des recommandations en cas de besoin afin de mieux encadrer les risques liés à ce médicament.

Dans le but d'établir un consensus, le Président demande aux membres de relire ce document et d'envoyer dans les meilleurs délais leurs commentaires, afin qu'il en soit tenu compte le plus rapidement possible. La version finale sera jointe en annexe du procès verbal de la Commission d'AMM.

RAPPORTS PUBLICS D'EVALUATION & FICHES DE SYNTHESE

- **SEROPLEX, toutes formes**
- **SIPRALEX, toutes formes**

Annexe 1-36

WHO Drug Information Vol 22, No. 1, 2008 World Health Organization

WHO Drug Information

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ATC level	INN/Common name	ATC code
	Sugammadex	V03AB35
	Temsirolimus	L01XE09
	Terguride	G02CB06
	Tolvaptan	C03XA01
	Vorinostat	L01XX38

INN/common name	Previous ATC	New ATC
ATC code changes:		
Benfluorex	C10AX04	A10BX06
Bupropion	N07BA02	N06AX12
Methoxyflurane	N01AB03	N02BG09
Tedisamil	C01EB12	C01BD06

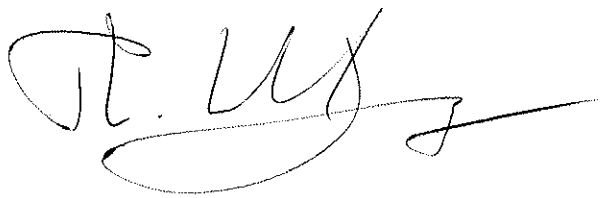
New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Alfa1 antitrypsin	0.6	g	P	B02AB02
Aliskiren	0.15	g	O	C09XA02
Ambrisentan	7.5	mg	O	C02KX02
Apomorphine	20	mg	P	N04BC07
Aripiprazole	15	mg	P	N05AX12
Betaine	6	g	O	A16AA06
Darunavir	1.2	g	O	J05AE10
Fesoterodine	4	mg	O	G04BD11
Maraviroc	0.6	g	O	J05AX09
Melatonin	2	mg	O	N05CH01
Methoxy polyethylene glycol-epoetin beta	4	mcg	P	B03XA03
Paliperidone	6	mg	O	N05AX13
Paricalcitol	2	mcg	O	A11CC07
Prulifloxacin	0.6	g	O	J01MA17
Rufinamide	1.4	g	O	N03AF03
Sitagliptin	0.1	g	O	A10BH01
Stiripentol	1	g	O	N03AX17
Telbivudine	0.6	g	O	J05AF11

Propriétés Pharmacologiques du benfluorex

Dr Philippe LECHAT
Professeur des Universités, Praticien hospitalier
Directeur de l'évaluation des médicaments et des produits biologiques
AFSSAPS

31 Décembre 2010



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-

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Introduction

Le benfluorex a été commercialisé en France de 1976 à 2009 sous le nom de Médiator après avoir obtenu son AMM en France en 1974. Il appartient à la famille des fenfluramines dont les principaux autres représentants ont été : La dl fenfluramine (Pondéral), avec une AMM française obtenue en 1965 et l'isomère d, la d-fenfluramine ou dex-fenfluramine (Isoméride) qui a obtenu son AMM en France en 1985. Isoméride et Pondéral ont été retirés du marché en 1997 suite à la mise en évidence d'effets indésirables graves à type de valvulopathies cardiaques et d'hypertension artérielle pulmonaire. Ces deux médicaments avaient les indications des médicaments de la classe des anorexigènes.
Le Médiator a été positionné sur le marché (avec une AMM correspondante) comme adjuvant au traitement des hypertriglycéridémies et comme adjuvant au régime chez les diabétiques en surcharge pondérale**, mais pas comme anorexigène.**

Historique du développement des anorexigènes

Ce sont les composés amphétaminiques qui ont été décrits les premiers comme ayant des propriétés anorexigènes, c'est-à-dire capables de réduire l'appétit. C'est en 1937 que Davidoff et Reifenstein décrivent pour la première fois les propriétés anorexigènes de l'amphétamine chez l'homme, et que Ehrich et al en font la démonstration expérimentale chez le rat.. Ces observations chez l'homme seront ensuite confirmées par Nathanson et al en 1939.
A peu près à la même époque, les expériences d'Hetherington et al publiées en 1940 montrent que les lésions de l'hypothalamus ventromédian chez le rat étaient susceptibles de provoquer une hyperphagie et d'entrainer l'obésité.
Ces travaux pionniers ont inauguré le développement de la physiologie et de la pharmacologie de la faim et de la satiété aboutissant au développement de nombreux médicaments anorexigènes mis sur le marché dans le monde pour le traitement de l'obésité.
Dans le numéro 17 du journal Thérapie de 1962, Jacques-R Boissier présente une revue de la pharmacologie des anorexigènes en développant la physiologie de l'appétit et de la faim ainsi que les méthodes pharmacologiques d'investigations des médicaments anorexigènes.

Il énonce donc en 1961 : « Tous les anorexigènes peuvent être considérés comme des phényléthylamines substituées. Il existe une filiation chimique directe entre ces substances et les deux phényl-éthylamines naturelles que sont l'adrénaline et l'éphédrine. Ceci explique que tous les anorexigènes développeront à des degrés divers deux actions latérales : action sympathomimétique et action stimulante au niveau du système nerveux central ». Les fenfluramines, développées plus tard sont aussi des composés phényl-éthylamines substituées, y compris le benfluorex.

Les Amphétamines citées en 1962 par JR Boissier sont les suivantes :

- L'amphétamine (racémique), la l amphétamine et la d amphétamine.

Il rappelle que ces composés possèdent essentiellement des actions sympathomimétiques et stimulantes du système nerveux central. L'isomère dextrogyre (d) est le plus pshychoanaleptique et l'isomère levogyre (l) le plus sympathomimétique. Il énonce « ceci explique que, à côté d'une action anorexigène indéniable, il se développe très souvent des effets secondaires indésirables

- La métamphétamine (dont les actions pharmacologiques sont identiques à celles de

l'amphétamine), - la phénylpropanolamine : Son action anorexigène s'accompagne d'une faible stimulation centrale mais de fortes réactions cardiovasculaires (tachycardie, hypertension artérielle) limitant l'intérêt de son effet anorexigène en pratique.

- Les phénylmorpholines : Deux substances appartiennent à ce groupe, la phenmétrazine et la phendimétrazine. C'est la phenmétrazine qui a été le plus étudiée. Elle est douée d'une action anorexigène avec des actions centrales et cardiovasculaires nettement inférieures à celles observées avec l'amphétamine. Sa toxicité est nettement plus faible chez la souris. Cependant, chez l'animal, l'anorexie s'accompagne de symptômes d'excitation du SNC, d'hypertension et de modifications pathologiques de l'ECG. Les dangers de la phemétrazine ont fait l'objet à l'époque de nombreuses publications avec , comme avec les amphétamine, la fréquence des manifestations psychotiques.
- La Benzphétamine. Son action anorexigène chez l'animal est comparable à celle de la phenmétrazine.
- La phentermine (2 methyl-amphétamine) : Elle ne contient pas de carbone assymétrique, il n'y a donc pas d'isomères optiques. Son action anorexigène est comparable à celle des composés précédents et son action centrale identique à celle de la phenmétrazine.
- La chlorphentermine : Cette substance, dérivée de la précédente par fixation d'un chlore sur le noyau en para, était utilisée sous forme de chlorydrate. Son action anoréxigène est comparable à celle des précédentes. Son action stimulante est très inférieure à celle de l'amphétamine, presque nulle aux doses anorexiantes. L'action sympathomimétique, très inférieure à celle des amphétamines, existe cependant.
- Amphépramone (diéthylpropion) : La dose anorexigène efficace est la moitié de celle de la d-amphétamine. Bien qu'ayant quelques propriétés de réduction de la motilité chez la souris, les études cliniques ont montré des phénomènes d'excitation, mais moindres qu'avec l'amphétamine.

Mécanisme d'action analysé par JR Boissier en 1962 :
Le mécanisme de l'action anorexigènes de l'amphétamine se situe au niveau du système nerveux central par une action au niveau hypothalamique. Le centre de l'appétit serait déprimé. L'injection d'amphétamine au niveau du centre hypothalamique de l'appétit et non pas au niveau du centre ventro-médian de la satiété, entraine l'arrêt de la prise de nourriture. Une action pschychotrope intervient également, provoquant chez le sujet traité, une sensation de bien-être et de force qui lui permet d'accepter le régime restrictif qui lui est proposé et d'adopter un nouveau rythme alimentaire contraire à ses habitudes et à ses gouts.

Modèles animaux expérimentaux
Les modèles animaux sont basés sur l'évaluation de la prise de nourriture chez l'animal, soit en administration aigue soit chronique. D'après Le Douarec (Thérapie 1979), la comparaison des résultats obtenus tend à recommander de travailler chez le chien et le rat. La reproductibilité des résultats'un laboratoire à l'autre est estimée satisfaisante. Les variations de poids ne sont prises en compte que lors des administrations chroniques.
Plusieurs méthodes ont été aussi développées pour analyser le comportement alimentaire : Test d'amassement chez le rat décrit initialement par Blundell (1971), mesure de la durée des repas, des intervalles entre chaque repas et comportements fondamentaux des animaux, test de discrimination (choix) ou d'aversion (Roskowsky 1963), test sur la boite à levier de de Skinner (activation d'un levier qui délivre un pellet d'aliment), modèles expérimentaux d'obésité et d'hyperphagie (rat obèse hypothalamique, souris obèse à l'aurothioglucose). Le Douarec conclue cependant dans son article de Thérapie 1979 que la souris, obèse ou

anormale ne semble pas un animal de choix à cause surtout de sa relative insensibilité aux anorexigènes.

Relation structure activité :
Tous les anorexigènes dérivent sans exception de la phényl-éthylamine. L'existence d'un azote basique par un double chainon carboné semble induire automatiquement des propriétés stimulantes du système nerveux central.
Quelques règles sont énoncées par JR Boissier :

- la présence d'un oxygène, surtout alcoolique secondaire, sur le carbone en alpha du noyau augmente les propriétés sympathomimétiques (éphédrine, phénylpropanolamine, amphépramone)
- Une double substitution sur le carbone en beta du noyau diminue l'action stimulante (phényl-ter-butylamines)
- Il en est de même lorsque l'azote est substitué par un radical lourd (benzphétamine)
- Une substitution, surtout chlorée, en para sur le noyau, diminue considérablement l'action stimulante, mais diminue légèrement l'action anorexigène (chlorphentermine).
- La substitution de l'azote ou du carbone par des radicaux méthyle augmente considérablement, lorsquelle est isolée, l'action pshycho-analeptique (amphétamine, méthamphétamine).

Il ajoute : Ces règles ne sont qu'indicatives et ne doivent pas être considérées comme absolues.

Dans cette revue de JR Boissier, est mentionnée la toxicité pulmonaire de la chlorphentermine, dérivé chloré en para du noyau phényl, à type d'histiocytose pulmonaire. En fait, il s'agit d'une phospholipose par accumulation de phospholipides par inhibition de la phospholipase par la chlorphentermine.

Peu de temps avant cette publication de JR Boissier de 1962, apparait en 1960, la publication d'un résumé du congrès de la Société Américaine de pharmacologie et de thérapeutique tenu à Seattle, par Albert Weissman et al sur un analogue fluoré (en position para sur le cycle phényl et non pas chloré en position para comme avec la chlorphentermine) de l'amphétamine, le chlorydrate de (dl-beta-p-trifluoromethylphenyl) isopropylamine. **Ce composé n'est autre que la dl-nor-fenfluramine. Des différences entre les isomères de position de la dl-norfenfluramine ont donné trois isomères différents selon la position de la substitution du cyle phényl en ortho, meta ou para. la substitution en meta donne la plus grande puissance de l'effet anorexigène (Beregi et al 1970).** Sa pharmacologie se caractérise par un effet anorexigène sans stimulation notable du système nerveux central. La conclusion des auteurs est la suivante : "It is concluded that P-1727 (numéro de code attribué dans cette publication) retains much of the anorectic potency of amphetamine in rats without concomitant behavioral stimulation, as measured by operant conditioning techniques".
Ces résultats confirment ainsi les propositions de JR Boissier sur les effets de la substitution du noyau phényl.

C'est à partir de cette publication princeps d'A Weissman que le développement de composés trifluorés de la phenyl-ethylamine s'est effectué, donnant naissance au groupe des fenfluramines et notamment la dl fenfluramine, la d-fenfluramine et le dl-benfluorex .

La pharmacologie comparée des amphétamines et des fenfluramines a été présentée en particulier en 1979 par JC Le Douarec et H Schmitt dans un numéro entier de la revue thérapie en 1979. Il n'est pas cependant pas fait mention dans cette revue, du benfluorex, bien qu'il soit sur le marché depuis 1976.
Ce médicament a été en effet positionné et développé dès le départ par les laboratoires Servier, non comme un anorexigène mais comme un médicament des troubles métaboliques (hypertriglycéridémie et diabète).

Pharmacologie comparée des fenfluramines et des amphétamines

Amphétamines

Les effets des composés amphétaminiques sont une stimulation du système nerveux central et un effet de type sympatho-mimétique en périphérie. La stimulation du SNC induit entre autres stimulation, une stimulation de l'éveil, de l'humeur, une réduction de la sensation de fatigue, une augmentation de la confiance en soi et de la capacité de se concentrer et un effet anorexigène. Tous ces effets des amphétamines sur le SNC résultent d'une augmentation de la libération de noradrénaline, dopamine et sérotonine à partir des terminaisons mono-aminergiques centrales. L'effet anorexique de l'amphétamine résulte des effets centraux sur la libération de dopamine.
Les effets de stimulation de la libération des monoamines cérébrales par l'amphétamine aboutit progressivement à une déplétion des stocks de ces mono-amines et à une réduction de l'effet pharmacologique lors des administrations répétées (tachyphyllaxie bien connue des composés amphétaminiques).
L'effet sympathomimétique indirect périphérique induit une stimulation cardiaque avec tachycardie et hypertension artérielle.
Les anorexigènes amphétaminiques ont également des effets complexes sur le métabolisme glucidique et lipidique. Dès 1972, Charbonnier et al rapportait les effets du clobenzorex sur les lipides plasmatiques et la glycémie.
L'isomère D, la dex-amphétamine est 3 à 4 fois plus puissante que l'isomère L en ce qui concerne les effets excitateurs sur le SNC. En revanche, c'est l'isomère l qui est plus le puissant comme sympathomimétique indirect en périphérie.

Fenfluramines

Les fenfluramines ont en fait été développées dans un but d'obtenir une meilleure sélectivité sur l'effet anorexigène des dérivés substitués de la phénylethylamine. L'hypothèse initiale étant qu'il devrait être possible de séparer les effets anorexigènes des effets stimulants du système nerveux central. Ceci était vérifié avec la chlorophenethylamine, substituée en para avec un atome de chlore (cf supra). Les équipes de recherche des laboratoires Servier se sont ainsi basées sur la publication initiale de Weisman présentant pour la première fois en 1960 la phényléthylamine substituée en position para sur le cycle phényl par un trifluorométhyl (CF3) comme étant anorexigène sans stimulation du système nerveux central.
A partir de cette amine primaire, très proche donc de la nor-fenfluramine qui elle est substituée avec CF3 en position meta, les chercheurs des équipes Servier ont donc passé en revue un nombre considérable de produits (280 au total) pour finalement sélectionner la fenfluramine, la dex-fenfluramine et le benfluorex pour leur équilibre entre propriétés

anorexigènes et les autres propriétés , notamment celles sur le système nerveux central et les propriétés sympathomimétiques périphériques.

Les fenfluramines ont des propriétés anorexigènes en diminuant la prise alimentaire et en stimulant la satiété par une action sur les neurones sérotoninergiques du système nerveux central par inhibition du recaptage neuronal de la sérotonine et stimulation des récepteurs sérotoninergiques centraux. Les effets anorexigènes de la fenfluramine sont 3 à 5 fois moins importants que ceux de l'amphétamine.
Les fenfluramines n'ont que très peu les propriétés des amphétamines dérivant de la stimulation de la libération de la dopamine et de la noradrénaline. La fenfluramine est plutôt sédative expérimentalement alors que les amphétamines sont stimulantes globalement sur le système nerveux central . Les fenfluramines, comme la chlorphentermine, sont également dépourvues des propriétés sympathomimétiques indirectes périphériques de l'amphétamine (Le Douarec et Schmitt , Thérapie 1964, H Schmitt et le Douarec, Thérapie 1979).

Les tests évaluant le comportement alimentaire chez le rat avaient abouti notamment à la conclusion que l'amphétamine agit plutôt sur l'appétit alors que la fenfluramine agit plutôt sur la satiété (Blundell 1976).
La fenfluramine a des actions périphériques sur le métabolisme : Elle augmente la captation du glucose par le muscle strié en présence d'insuline et favoriserait ainsi l'utilisation des substrats énergétiques.
La D-fenfluramine est plus active et plus puissante que l'isomère L.

A noter que dès 1974, Lullman-Rauch et Reil ont décrit les mêmes altérations tissulaires pulmonaires à type de phospholipose chez le rat et le cobayes suite à l'administration de fenfluramine. Ces lésions étaient similaires à celles observées avec la chlorephentermine sur les poumons et sont de mécanismes différents (inhibition de la phospholipase) de l'hypertension artérielle pulmonaire bien connue avec les anorexigènes (cf paragraphe suivant).

Données pharmacocinétiques de la Fenfluramine (dl-fenfluramine)

Administrée par voie orale, la fenfluramine est rapidement (Cmax atteint en 4 heures) et complètement absorbée au niveau du tractus gastro-intestinal.
La principale voie de métabolisation hépatique se fait par N-dééthylation pour former son métabolite principal actif, la dl-norfenfluramine qui sera désaminée et hydroxylée pour former le m-trifluorométhyl-phényl propane-diol puis l'acide m-trifluorométhyl benzoïque. Celui-ci sera conjugué avec la glycine pour former l'acide m-trifluorométhyl hippurique. Les autres métabolites sont mineurs et ne représentent que 1 à 2 % de la dose administrée.
La fenfluramine est distribuée dans tout l'organisme et franchit la barrière hémato-encéphalique.
L'excrétion dans les urines se fait sous forme inchangée et sous forme métabolisée. Elle est fonction du pH urinaire :
- Dans l'urine acide, environ 23% de la dose est excrétée sous forme inchangée et environ 17% sous forme de norfenfluramine. le reste étant constitué d'acide m-trifluorométhyl hippurique.
- Dans l'urine alcaline, environ 2% de la dose est excrétée sous forme inchangée et en norfenfluramine.

- Dans l'urine neutre, 3 à 10% peut être excrétée sous forme inchangée et 3 à 14% en norfenfluramine.
Jusqu'à 5% de la dose est éliminée dans les fèces en fenfluramine et en norfenfluramine.
La fixation aux protéines plasmatiques est de l'ordre de 30%.
La demi-vie d'élimination plasmatique est de 24,2 heures.

Données pharmacocinétiques de la D-fenfluramine

Après administration orale, l'absorption de la d-fenfluramine est rapide et pratiquement totale. Le pic de concentration plasmatique est atteint 4 heures après la prise. La biodisponibilité absolue est de 83 % environ.
La fixation aux protéines plasmatiques est de 40,7 %. La d-fenfluramine se distribue rapidement et largement dans tout l'organisme (substance hautement lipophile). Son volume de distribution est de 913 +/- 378,9 litres. Elle traverse facilement la barrière hémato-encéphalique.
La principale voie de métabolisation hépatique est la N-dééthylation conduisant au métabolite principal actif, la d-norfenfluramine qui est désaminée et hydroxylée pour former le m-trifluorométhyl-phénylpropane-diol puis l'acide m-trifluorométhyl benzoïque. Celui-ci sera conjugué avec la glycine pour former l'acide m-trifluorométhyl hippurique. Les autres métabolites sont mineurs et ne représentent que 1 à 2 % de la dose administrée.
La demi-vie d'élimination de la dexfenfluramine est de 18,3 heures et celle de la d-norfenfluramine est de 32 heures. Plus de 90% est éliminée dans les urines en 3 à 4 jours, essentiellement sous forme de métabolites. Le taux de dexfenfluramine et de d-norfenfluramine dans l'urine est augmenté à pH acide et diminué à pH alcalin. Toute la dose est éliminée en 168 heures. Moins de 1% de la dose administrée se retrouve dans les fèces.

Rôle des métabolites dans l'action pharmacologique des fenfluramines

Le Douarec, en 1971, a affirmé le rôle central de la norfenfluramine dans l'activité de la fenfluramine. Nous savons aussi par son témoignage que la norfenfluramine a été envisagée comme médicament anorexigène et testée comme telle chez l'homme. Les premiers essais cliniques ont rapidement été interrompus devant une toxicité trop importante de la norfenfluramine (proceedings du congrès des Bahamas sur les anorexigènes, 1971).

Goudie et al. en 1974 (psychopharmacologia) ont confirmé chez le rat les propriétés anorexigènes de la nor-fenfluramine, associées à des effets sédatifs lors de son administration aigue mais à des effets stimulants sur le système nerveux central chez le rat lors de son administration chronique. Ces données confirment les observations initiales de A Weissman dès 1960. Goudie et al concluent qu'une partie au moins des effets de la fenfluramine est due à celle de son métabolite principal la nor-fenfluramine : « The data reported in this paper provide evidence which implicates Norfenfluramine as a mediator of the actions of fenfluramine ».

En 1975, Broekkamp et al. (Journal of pharmacy and pharmacology, 1975, vol. 27) confirment le rôle de médiateur principal de la norfenfluramine dans les effets anorexigènes de la fenfluramine.

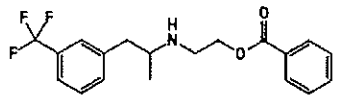
La publication de T Menzini du groupe de S Garattini (1991), a comparé les effets anorexigènes de la d-fenfluramine et de son métabolite principal la d-norfenfluramine chez le rat, le cobaye et la souris. Il en ressort que la d-Norfenfluramine est plus active que la fenfluramine dans les trois espèces, la plus sensible étant le cobaye et la moins sensible étant la souris. Le métabolite d-norfenfluramine joue un rôle majeur dans l'effet anorexigène de la fenfluramine chez le cobaye, y contribue chez le rat et n'ajoute rien chez la souris.

Pharmacologie du Benfluorex

Le benfluorex (initialement S992) a été sélectionné par les équipes de recherche des laboratoires Servier (Le Douarec et al, Beregi et al) lors de leur screening pharmacologique des composés phénylethylamine trifluorés substitués car il présentait un effet anorexigène plus important que celui de la fenfluramine après prise orale, chez le chien et chez le rat. Il était de surcroit 10 fois moins toxique expérimentalement chez l'animal (J Duhault et C Malen) mais a été développé pour être utilisé chez l'homme à des doses plus de 10 fois supérieures (450 mg/j) à celle de l'isoméride (30 mg/j) et 8 fois supérieures à celles du pondéral (60 mg/j). Dès ces premières investigations, la question se posait de savoir si l'activité du benfluorex résultait de son effet propre ou par l'intermédiaire de ses métabolites.

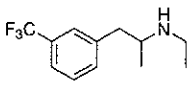
Le benfluorex a une action anorexigène (de type sérotoninergique comme la fenfluramine) et une action périphérique (comme la fenfluramine) sur le métabolisme lipidique et glucidique. Il diminue la production hépatique de glucose et agirait sur la néoglucogénèse, améliorant la sensibilité à l'insuline et l'insulino-résistante musculaire, d'où son indication comme « adjuvant au régime adapté chez les diabétiques avec surcharge pondérale ».
C'est sur ses propriétés métaboliques périphériques que le benfluorex a été développé et positionné dans ses indications thérapeutiques.

Benfluorex



Formule chimique : benzoate de méthyl-1 (trifluorométhyl-3 phényl) – 2 éthylamino -2 éthyle, chlorydrate

Fenfluramine



La dénomination commune internationale attribuée par l'OMS en 1971 a toujours été « benfluorex », attestant son appartenance à la catégorie des substances anorexigènes.

Cependant,le code ATC (classes thérapeutiques) de la classification de l'OMS du benfluorex a toujours été différent de celui de la fenfluramine et dexfenfluramine. Il correspondait avant le retrait à « Autres médicaments du diabète » alors que les fenfluramines ont toujours été

classées en «anorexigènes ».

L'effet anorexigène s'il apparait indiscutable se traduit lors des traitements chroniques chez l'homme par une réduction modeste du poids, comme cela a été le cas en fait, d'une manière générale avec tous les anorexigènes (perte de 1 ou 2 kg par rapport au placebo), en partie par développement d'un phénomène de tachyphyllaxie, bien démontré avec l'amphétamine (par épuisement des stocks de neuromédiateurs centraux, la sérotonine plus spécifiquement pour les actions des fenfluramines). Cependant, une grande variabilité inter-individuelle existe et certains patients peuvent présenter des pertes de poids plus importantes.

Dans l' étude de Moulin (benfluorex versus placebo), la perte de poids n'est pas significative par rapport au placebo.
Chez la souris diabétique ob/ob aucune réduction de poids ni de prise de nourriture n'est observée par rapport aux souris témoins. Mais, comme l'énonçait Le Douarec en 1979, les modèles expérimentaux de souris obèses sont très peu sensibles à l'action des anorexigènes.

Données pharmacocinétiques du benfluorex

Après administration par voie orale, il est en fait complètement et très rapidement métabolisé par des estérases plasmatiques et intestinales en S422. Ce métabolite primaire est alors lui-même dégradé en deux métabolites secondaires le S1475 **et le S585 la dl-norfenfluramine** (qui se sépare elle-même en ses deux isomères L et D). Cette dernière est elle-même secondairement désaminée et hydroxylée pour former le m-trifluorométhyl-phénylpropane-diol puis l'acide m-trifluorométhyl benzoïque. Celui-ci sera conjugué avec la glycine pour former l'acide m-trifluorométhyl hippurique éliminé par voie urinaire.
Les concentrations circulantes dans le plasma de benfluorex sont trop faibles pour être détectées même avec les techniques récentes de dosage incluant la LC-MS-MS (limite de quantification = 0.4 ng/ml dans l'étude de bioéquivalence soumise par les laboratoires Merck Génériques pour leur dossier de générique de benfluorex en 2006).
Les activités des métabolites S422 et S1475 sont a priori inexistantes aux concentrations plasmatiques obtenues chez l'homme aux doses thérapeutiques (concentrations inférieures à 100 nanoM pour la Camx du S-422 après 150 mg , 3 fois / j de benfluorex chez le sujet sain pendant 10 jours). In vitro le S422 n'est actif sur le métabolisme des acides gras et du glucose qu'à des concentrations supérieures à 10 microMolaires (voire milimolaires) (Kohl et al, Mazière et al, Bailey et al) alors que le S1475 est pratiquement inactif (Kohl et al).
De plus, la demi-vie d'élimination plasmatique de la Nor-fenfluramine est de 20 ± 6.2 h et celle du S est de 4 ± 1.2h dans l'étude de bioéquivalence déposée par les laboratoires Merck Génériques / Mylan dans le cadre du dépôt d'AMM d'un médicament générique de benfluorex en 2005. Ainsi, c'est dl-norfenfluramine qui va s'accumuler lors des administrations répétées et non pas le S422. Les niveaux de concentrations plasmatiques à l'équilibre seront ainsi plus élevés en dl-norfenfluramine qu'en S-422 (cf tableau annexe 2).
Le benfluorex peut donc être considéré comme un précurseur du métabolite actif la nor-fenfluramine.
En 1993 les laboratoires Servier ont réalisé une étude pharmacocinétique chez le sujet sain. nt les niveaux d'exposition des produits parents et des métabolites de la fenfluramine, de la d-fenfluramine et du benfluorex, administrés aux doses thérapeutiques usuelles soit 30 mg/j de d-fenfluramine, 60 mg/ j de fenfluramine et 450 mg/j de benfluorex pendant 10 jours.
Les données pharmacocinétiques montrent qu'à l'état d'équilibre et aux doses thérapeutiques, le niveau d'exposition (Cmax et AUC) pour la Norfenfluramine est

comparable après administration de benfluorex, fenfluramine et d-fenfluramine. Dans le cas de la d-fenfluramine, l'exposition relative (AUC) à la d-norfenfluramine représente environ 50% de l'exposition de la dexfenfluramine,. Cette valeur est de 37 % pour la fenfluramine. A l'inverse, pour le benfluorex, la d-norfenfluramine ne représente qu'environ 4% de l'exposition aux autres métabolites S422 et S1475.

Dans la mesure ou c'est le métabolite actif la d-norfenfluramine qui apparait rendre compte de la majorité de l'effet anorexigène, les différences de doses développées entre les trois fenfluramines « parentes » correspondent à l'ajustement des doses nécessaires à administrer pour obtenir une efficacité thérapeutique anorexigène similaire (en relation donc avec un niveau de production similaire du métabolite actif la d-norfenfluramine).

Mécanismes des actions périphériques pulmonaires et cardiaques des substances fenfluraminiques (Fenfluramines, norfenfluramine et benfluorex) : interactions avec les récepteurs sérotoninergiques périphériques (cardiaques et pulmonaires)

Des récepteurs sérotoninergiques de type 5HT1 se retrouvent au niveau pulmonaire et 5HT2 au niveau des valves cardiaques.
La famille des récepteurs 5-HT2 englobe trois types de récepteurs transmembranaires couplés à la protéine G: 5-HT_{2A}, 5-HT_{2B} et 5-HT_{2C}.
La présence de sérotonine extracellulaire est transduite par ces récepteurs via $G\alpha_q$ (sous-unité α de la protéine G)- PLCβ (phospholipase Cβ) et induisant une augmentation du calcium cytosolique et l'activation de la protéine kinase C (PKC). Néanmoins, la transduction du signal par ces récepteurs peut emprunter différentes voies qui dépendent du type de cellules dans lesquelles ils sont exprimés et du niveau de l'expression de ces récepteurs.
Ces différentes voies peuvent être divisées en trois catégories :

- génération d'un second messager
- mitogénèse
- anti-apoptose

Les conséquences majeures de la transduction par les récepteurs 5-HT_{2B} sont les réponses mitotiques et anti-apoptotiques qui ont un rôle essentiel dans le développement et tout particulièrement dans le développement cardique.

La *fenfluramine et la d-norfenfluramine* ont une faible affinité pour les récepteurs sérotoninergiques de type 5-$HT_{1D/1B}$. La d-norfenfluramine a une faible affinité pour le récepteur 5-HT_7 mais en revanche, la fenfluramine et la d-norfenfluramine ont une plus forte affinité pour les récepteurs 5-HT_{2A}, 5-HT_{2B} et 5-HT_{2C} : ce sont des agonistes partiels pour 5-HT_{2A} et des agonistes complets pour 5-HT_{2C}.
La d-nor-fenfluramine a une plus grande affinité pour les récepteurs 5HT2B que pour les récepteurs 5TH1B. C'est un agoniste entier vis-à-vis des récepteurs 5HT1B et 5HT2B.
Les interactions des différentes substances pharmacologiques en cause avec les récepteurs sérotoninergiques sont encore compliquées par le fait que les propriétés agonistes partielles des différentes substances peuvent venir réduire les actions des agonistes entiers que présentent certains de leurs métabolites comme la nor-fenfluramine sur les récepteurs 5HT1B et surtout 5HT2B.
Cependant, aucune donnée expérimentale n'a documenté l'impact de la présence des différents métabolites sur les effets de la d-nor-fenfluramine in vivo.

Récepteurs sérotoninergiques, fenfluramines et hypertension artérielle pulmonaire
Les dérivés fenfluraminiques peuvent induire des Hypertensions Artérielles Pulmonaires (HTAP) par une interaction complexe et spécifique avec les actions de la sérotonine au niveau du tissu artériel plumonaire. D'autres médicaments retirés du marché ont été reconnus responsables de l'apparition d'HTAP, comme l'aminorex (retiré du marché en 1968 en Autriche, Allemagne et Suisse ou il était commercialisé) et la phentermine (interdite en France en 1999 avec tous les amphétaminiques).

Les mécanismes et récepteurs en jeu dans les effets toxiques pulmonaires de la sérotonine ne sont probablement pas les mêmes qu'au niveau valvulaire cardiaque. Le développement d'une HTAP par l'action des fenfluramines fait intervenir une interaction complexe et spécifique au niveau artériel pulmonaire entre le transporteur transmembranaire de la sérotonine et les récepteurs 5HT1B des cellules musculaires lisses pulmonaires. Il existe une synthèse

importante de sérotonine au niveau pulmonaire par l'action de la tryptophane hydroxylase qui synthétise la sérotonine au niveau des cellules de l'endothelium pulmonaire à partir du tryptophane. La sérotonine ainsi formée au niveau de l'endothelium va stimuler les récepteurs sérotoninergiques des cellules musculaires lisses de l'artère pulmonaire et entrainer d'une part une vasoconstriction de l'artère et des artérioles pulmonaires et d'autre part une hypertrophie et prolifération des cellules musculaires lisses des artères pulmonaires, **entrainant ainsi une augmentation des résistances artérielles du territoire pulmonaire et donc une HTAP lors d'une stimulation chronique sérotoninergique.**

Les fenfluramines ainsi que la phentermine agissent en inhibant le transport transmembranaire de la sérotonine (par compétition de substrat au niveau du transporteur), ce qui induit une plus grande concentration de la sérotonine face aux récepteurs 5HT1B des cellules musculaires lisses. Il en résulte ainsi une hyperstimulation de ces récepteurs à l'origine du développement de l'HTAP. Les fenfluramines et leurs métabolites, la d-norfenfluramine en particulier stimulent également directement les récepteurs sérotoninergiques de types 5HT1B.

Les HTAP ont été beaucoup plus fréquemment observées avec la d-fenfluramide (l'isoméride)qu'avec qu'avec le benfluorex : Ainsi jusqu'au 31 Décembre 1997, 66 cas d'HTAP en relation avec la prise d'Isoméride avaient été notifiés à l'AFSSAPS par les centres de pharmacovigilance (n'incluant donc pas tous les cas notifiés auprès des laboratoires Servier) alors que 18 cas ont été rapportés avec le pondéral et un seul avec le médiator (jusqu'en décembre 1997 également par les CRPV).

Plueisrs explications peuvent en rendre compte :

- soit l'amplitude de l'effet de la d-norfenfluramine, métabolite actif commun, est réduite par la présence des différents métabolites du benfluorex ou surtout par la présence de l'isomère l de la nor-fenfluramine en tant qu' agonistes partiels. Cette hypothèse est soulevée par Rothman et al 2000 pour la fenfluramine et son interaction avec les récepteurs 5HT2 « In the case of fenfluramine, d-fenfluramine and l-fenfluramine have lower efficacy (40%) at the 5HT2B receptor than d-norfenfluramine (75%) and achieve blood levels twice that of norfenfluramine. This indicate that the parent drugs would partially antagonize activation of the 5HT2B receptors by d-norfenfluramine ». Ceci pourrait donc s'appliquer à la fenfluramine mais pas au benfluorex puisque ce dernier est d'emblée hydrolysé et transformé en S422 (inactif aux concentrations plasmatiques atteintes en thérapeutique) puis à la d et l norfenfluramine. Seule l'interaction entre ces deux énantiomères pourrait donc expliquer une réduction de l'effet de la d-norfenfluramine.
  Le résultat de l'interaction entre agonistes dépend des différentes affinités et des différentes activités des agonistes vis-à-vis des recepteurs 5HT1B au niveau des artères pulmonaires et 5HT2b au niveau cardiaque.
- Plus probablement, le niveau des ventes d'isoméride a en fait été beaucoup plus important que celui du benfluorex pendant les années de la commercialisation de l'isoméride (de 1985 à 1997). 7 millions de patients environ en France ont reçu l'isoméride pendant cette période alors que le nombre total de patients ayant pris du benfluorex en France a été d'environ 5 millions sur une période trois fois plus longue (cf figure en annexe 4). Le nombre de patients exposés à l'isoméride a donc été beaucoup plus important dans les années 1985-1997 que celui des patients exposés au benfluorex, ce qui peut expliquer pourquoi les HTAP ont été détectées surtout d'abord avec l'isoméride. Le pondéral a été mis sur le marché le premier en 1965, mais le niveau de ses ventes a aussi été beaucoup plus faible par rapport à celui de l'isoméride, puisque le nombre de patients traités par pondéral est estimé autour de 2 Millions de 1972 à Octobre 1992.

- Pour certains cas d'HTAP, les patients avaient pris successivement de l'isoméride puis du benfluorex après le retrait de l'isoméride. Dans ces cas les HTAP ont plutôt été rapportées à l'isoméride et non pas au benfluorex.
- Le fait que le benfluorex n'a pas été présenté comme anorexigène (mais quand même utilisé comme tel en partie) a probablement réduit la détection de sa responsabilité dans la survenue de certains cas d'HTAP et a peut être réduit par ce fait le nombre des notifications de cas d'HTAP.par les médecins.
- Le fait que le benfluorex soit à prendre en trois prises par jour peut avoir réduit son observance par rapport à celle de l'isoméride (deux prises / j) pouvant rendre compte lors des traitements chroniques d'une exposition plus faible en nor-fenfluramine avec le benfluorex par comparaison avec l'isoméride.
- Enfin, la commercialisation du pondéral a démaré avec un dosage à 30 mg seulement pour être remplacé plus tard par le pondéral retard dosé à 60 mg. Ceci peut expliquer le moindre nombre de cas d'HTAP notifiés avec le pondéral par rapport à l'isoméride (moindre dosage et plus faible nombre de patients traités).

Valvulopathies

Récepteur sérotoninergiques 5-HT-$_{2B}$ et valvulopathies.

La famille des récepteurs 5-HT2 englobe trois types de récepteurs transmembranaires couplés à la protéine G: 5-HT$_{2A}$, 5-HT$_{2B}$ et 5-HT$_{2C}$.
La présence de sérotonine extracellulaire est transduite par ces récepteurs via Gα_q (sous-unité α de la protéine G)- PLCβ (phospholipase Cβ) et induisant une augmentation du calcium cytosolique et l'activation de la protéine kinase C (PKC). Néanmoins, la transduction du signal par ces récepteurs peut emprunter différentes voies qui dépendent du type de cellules dans lesquelles ils sont exprimés et du niveau de l'expression de ces récepteurs.
Ces différentes voies peuvent être divisées en trois catégories :

- génération d'un second messager
- mitogénèse
- anti-apoptose

En plus de réguler les fonctions cellulaires (e.g contraetion-relaxation du muscle lisse), les conséquences majeures de la transduction par les récepteurs 5-HT$_{2B}$ sont les réponses mitotiques et anti-apoptotiques qui ont un rôle essentiel dans le développement et tout particulièrement pour le cœur.

La stimulation du récepteur 5-HT-$_{2B}$, présent sur les valves mitrales et aortiques humaines, est estimée responsable de l'induction de valvulopathies cardiaques chez l'Homme (Fitzgerald LW et al., Mol.Pharmacol. 2000;57: 75-81) par stimulation du développement et de l'activité des fibroblastes présents au sein du tissu valvulaire. La stimulation des fibroblastes induit la production et l'accumulation de protéines de type collagène induisant ainsi une infiltration fibreuse des valves et des cordages.

Jusqu'au début des années 2000, le mécanisme de développement des valvulopathies était inconnu, les études de pharmacologie expérimentale ont graduellement permis d'élucider ce mécanisme.
C'est en 2000 que la norfenfluramine a été identifiée comme possédant une action agoniste sur les récepteurs 5-HT-$_{2B}$ (Fitzgerald LW et al., Mol.Pharmacol. 2000;57: 75-81). La fenfluramine elle-même et la d-fenfluramine sont également des agonistes (pleins ou partiels) des récepteurs 5HT2B.(Rothman, 2000).

La susceptibilité individuelle varie d'un patient à l'autre expliquant que les patients qui développent une HTAP ne développent pas forcément une valvulopathie associée et réciproquement.
De plus, la cinétique de développement des lésions cardiaques et pulmonaires est aussi différente. Les lésions valvulaires peuvent apparaître au bout de 3 mois d'exposition aux fenfluarmines alors que le développement d'une HTAP peut prendre plusieurs années.
Les premiers cas de valvulopathies induites par la prise de dérivés fenfluraminiques datent de 1997, raison de leur retrait du marché aux USA.

Type et fréquence des lésions valvulaires

Les lésions observées sont un épaississement de la valve aortique et pour la valve mitrale ou tricuspide, un épaississement de la valve avec épaississement des cordages et rétraction de l'appareil valvulaire entrainant une régurgitation de la valve atteinte (mitrale, aortique ou tricuspidien).
L'aspect anatomopathologique est celui d'une valve épaissie, blanchâtre recouverte d'une sorte de plaque recouvrant la valve et entourant les cordages, sans altération propre du tissu valvulaire lui-même.

Ces lésions ressemblent à celles observées chez les patients présentant des tumeurs carcinoïdes secrétant de fortes quantités de sérotonine, ou lors de traitements chroniques avec les dérivés de l'ergot de seigle, type méthysergide dont le métabolite la méthyl ergonovine est le plus puissant agoniste connu des récepteurs 5HT2B. Les lésions valvulaires observées en présence de tumeur carcinoide touchent cependant préférentiellement la valve tricuspide car la majeure partie de la sérotonine circulante veineuse va être métabolisée lors de son passage dans la circulation pulmonaire après avoir été recaptée par le transporteur des cellules endothéliales pulmonaires.

D'après la publication de 2003 de Hopkins-Paul-N (BMC-Cardiovascular-disorders), le risque d'apparition d'une fuite aortique avec les dérivés fenfluraminiques est multiplié par un facteur 19 (IC 95% 16 à 23) et celui de fuite mitrale par un facteur 6 (IC 95% 4 à 8.6).
Dans une méta-analyse publiée en 2002 dans l'American Heart Journal (Sachev-Molly et al), le risque de lésion valvulaire est estimé augmenté d'un facteur 2.2 lorsque la durée de traitement est supérieure à 3 mois.
Enfin, dans une série publiée en 2008, chez 5743 patients traités par fenfluramines (Dahl-Charles et al BMJ) dans un seul centre cardiologique américain, la prévalence de la régurgitation aortique était de 19.6% et de 11.8% pour la valve mitrale. La durée de la prise de fenfluramine a été retrouvée comme facteur favorisant. Une HTAP a été retrouvée fréquemment associée à la fuite mitrale mais pas à la fuite aortique. Avec un suivi de 30 mois, la fuite aortique s'est aggravée dans 15% des cas, est restée stable dans 63% et s'est améliorée dans 21% des cas. Les chiffres correspondant pour la fuite mitrale ont été de 25%, 47% et 28%. **Une chirurgie valvulaire a été effectuée chez 38 patients (0.66%), avec dans 25 cas des lésions très évocatrices d'une étiologie médicamenteuse type agoniste sérotoninergique.**

Actions métaboliques périphériques du benfluorex

Le benfluorex et ses métabolites ont une action périphérique sur le métabolisme du glycogène. Ils diminuent la production hépatique de glucose et agissent sur la néoglucogénèse, améliorant la sensibilité à l'insuline et l'insulinorésistance musculaire. Le benfluorex n'aurait pas d'action sur l'insulinosécrétion.

Action périphérique sur le métabolisme du glycogène.
Des études *in vitro* sur modèles cellulaires ont montré que benfluorex et son principal métabolite (S422) ont un double effet sur le métabolisme du glycogène.
1. Sur hépatocytes de rat en culture, on observe une augmentation de la synthèse de glycogène stimulée par l'insuline et une diminution de la glycogénolyse stimulée par le glucagon (Melin, 1991). La glycogénolyse hépatique est diminuée par une inhibition d'une enzyme : le glycogène phophorylase.
2. La production hépatique de glucose est diminuée avec un effet sur la néoglucogénèse par une inhibition de la PEPCK (phosphoenol pyruvate carboxykinase) (Tielens, 1993 ; Zorzano, 1996). Les travaux de Kohl et Pégorier (Kohl, 2002) ont permis de préciser cet aspect du mécanisme d'action. L'expression des gènes codant pour les enzymes de différentes voies métaboliques a été étudiée sur hépatocytes isolés.
Le benfluorex et son métabolite principal S422 ont un effet direct et dose-dépendant sur l'expression de la PEPCK, enzyme-clé de la néoglucogénèse. Cet effet est quantifié: l'expression étant réduite à un niveau correspondant à 24 % et à 12 % de la valeur contrôle, pour le principe actif et son métabolite respectivement, à la concentration de 100 micromolaire.
3. Le benfluorex exerce, de plus, un effet inhibiteur sur l'expression de la CPT I (carnitine palmityl tranférase), enzyme responsable du transport des acides gras à longue chaîne à l'intérieur de la mitochondrie, étape préalable à la β oxydation.
Ainsi, la réduction de la production hépatique de glucose serait liée pour partie à la réduction de la β oxydation, privant la voie de la néoglucogénèse de ses substrats énergétiques.

Action sur l'insulinosensibilité.
Etudes chez l'animal. Plusieurs études, portant sur des modèles animaux d'insulinorésistance et/ou de diabète, ont montré que le benfluorex améliore la tolérance au glucose et l'insulino-sensibilité en utilisant la technique du clamp euglycémique hyperinsulinique (Brindley, 1991; Portha, 1993; Serradas, 1993; Storlien 1993). Le principe de cette technique repose sur une perfusion d'insuline exogène à débit continu associée à une perfusion variable de glucose, adapté de façon à maintenir la glycémie constante. Si la dose d'insuline est suffisante pour inhiber la production hépatique de glucose, la quantité de glucose perfusé est le reflet de la sensibilité à l'insuline, plus elle sera importante, plus la sensibilité est élevée.
Le benfluorex améliore l'insulino-résistance musculaire avec une augmentation du transporteur de glucose GLUT-4 (Sevilla, 1999; Storlien, 1993 ; Zorzano 1996) et de l'oxydation du glucose (Bailey, 1992).
Le benfluorex n'a pas d'effet direct sur la sécrétion d'insuline à l'état basal dans des conditions de stimulation (induction par le glucose ou l'arginine) chez le rat diabétique (Portha, 1993; Serradas, 1993).
Etudes chez l'homme. Chez l'homme, l'effet insulino-sensibilisateur du benfluorex a été étudié dans 3 études de clamp hyperinsulinique euglycémique (Bianchi, 1993 ; De Feo, 1993 et Ricchio, 1993).

Deux de ces études ont étudié la production hépatique de glucose; une étude (De Feo) a montré une diminution de cette production; l'autre étude (De Ricchio) n'a pas mis en évidence de variation.
Une étude complémentaire de Bianchi réalisée en 1996 n'avait pas montré d'amélioration de la consommation de glucose sous benfluorex.

Conclusions. Sur la base de ces éléments, aucune certitude sur le mécanisme d'action de cette molécule n'a pu être mis en évidence. L'ensemble des résultats a conduit à mettre en place deux études pivot visant à confirmer l'efficacité hypoglycémiante du benfluorex chez les patients diabétiques de type 2 (Moulin 2006, Del Prato 2003). L'effet hypoglycémiant dans l'étude Moulin s'est traduit par une réduction de 0.82% dans le groupe benfluorex versus +1% dans le groupe placebo après 18 semaines de traitement. L'étude REGULATE a par la suite comparé l'efficacité du benfluorex à celle de la pioglitazone.
Cependant, sur l'ensemble des données de ces études cliniques chez les patients diabétiques, compte tenu de la relative faible amplitude de l'effet sur la glycémie, des critiques méthodologiques, ainsi que la non fiabilité de certains résultats (cf inspections des centres de l'étude Moulin), l'indication du benfluorex comme médicament anti-diabétique n'a pas été retenue par l'AFSSAPS et seule l'indication du benfluorex comme adjuvant au régime chez le diabétique en surcharge pondérale a été maintenue.

Conclusion :

1. Les fenfluramines (fenfluramine, d-fenfluramine et benfluorex) ont été initialement développées par les laboratoires Servier pour séparer les effets anorexigènes des effet stimulants du système nerveux central qui sont ceux de l'amphétamine.

Ce sont des composés trifluorés, substitués en meta du cycle phényl, de la molécule de base des anorexigènes, la phényléthylamine.

Leur effet principal anorexigène passe par des mécanismes sérotoninergiques centraux (inihibition du recaptage de la sérotonine par les terminaisons nerveuses sérotoninergiques et stimulation des récepteurs sérotoninergiques centraux).
Les complications pulmonaires et valvulaires cardiaques observées lors des traitements au long cours par les fenfluramines sont dues à la stimulation des récepteurs sérotoninergiques 5HT1B (pour l'artère pulmonaire) et 5HT2B pour les valves cardiaques, avec l'inhibition du recaptage de la sérotonine qui joue également un rôle dans le développement de l'HTAP.

Ils possèdent aussi des effets périphériques sur le métabolisme lipidique et glucidique qui in fine n'ont pas été considérés comme thérapeutiquement suffisants pour un libéllé d'AMM comme médicament du diabète.

Une partie au moins de leurs effets provient de l'activité de leurs métabolites et en particulier de leur métabolite principal la d-nor-fenfluramine.

2. Le benfluorex est complètement métabolisé et ne circule dans le plasma qu'à des concentrations indétectables, car il est immédiatement transformé en son métabolite S422, puis en métabolite S1475 et en norfenfluramine.

Cette caractéristique métabolique du benfluorex conduit les laboratoires Servier eux-mêmes à

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écrire, en 1999, que le benfluorex est un précurseur (*« a pro-drug »*) de son métabolite S422, sans attribuer toutefois à ce dernier la moindre activité pharmacologique et alors même que le S422 est de surcroît transformé partiellement en norfenfluramine.

Répétons que la norfenfluramine a des propriétés anorexigènes puissantes et représente l'amine de base qui a servi au développement des autres composés, notamment les fenfluramines.

Après administration de dexfenfluramine (ISOMERIDE®), de fenfluramine (PONDERAL®) et de benfluorex (MEDIATOR®) aux doses préconisées en thérapeutique, les niveaux des concentrations plasmatiques de la norfenfluramine (exposition : Cmax et AUC) sont similaires : 25-30 ng/ml pour la Cmax de d-norfenfluramine (cf tableau de l'annexe 2).

Les métabolites soit sont inactifs (S-1475) soit inactifs (S-422) aux concentrations plasmatiques obtenues lors de l'administration des doses de 450 mg / j en trois prises. De plus la demi-vie du S 422 est beaucoup plus courte (4h) que celle de la norfenfluramine (20h), cette dernière atteignant ainsi des niveaux de concentrations à l'équilibre trois fois supérieurs à celles du S-422 en termes d'AUC 0-24h..

Les différences entre les doses préconisées pour les trois fenfluramines (dexfenfluramine 30 mg/j, fenfluramine 60 mg/j et benfluorex 450 mg/j) correspondent en réalité aux doses nécessaires pour atteindre une même concentration plasmatique de norfenfluramine et, ce faisant, pour obtenir un effet anorexigène comparable.

Le benfluorex doit donc être considéré comme un précurseur de la substance véritablement active : la nor-fenfluramine.
Et d'ailleurs, il est remarquable de relever la conclusion de Goudie et al en 1974 sur le rôle de la norfenfluramine, peu avant la mise sur le marché du médiator : « The data reported in this paper provide evidence which implicates Norfenfluramine as a *mediator* of the actions of fenfluramine »...

Mis en forme : Police :Gras

Annexe 1

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Annexe 2

Données pharmacocinétiques comparatives chez le sujet sain entre fenfluramine, d-fenfluramine et benfluorex

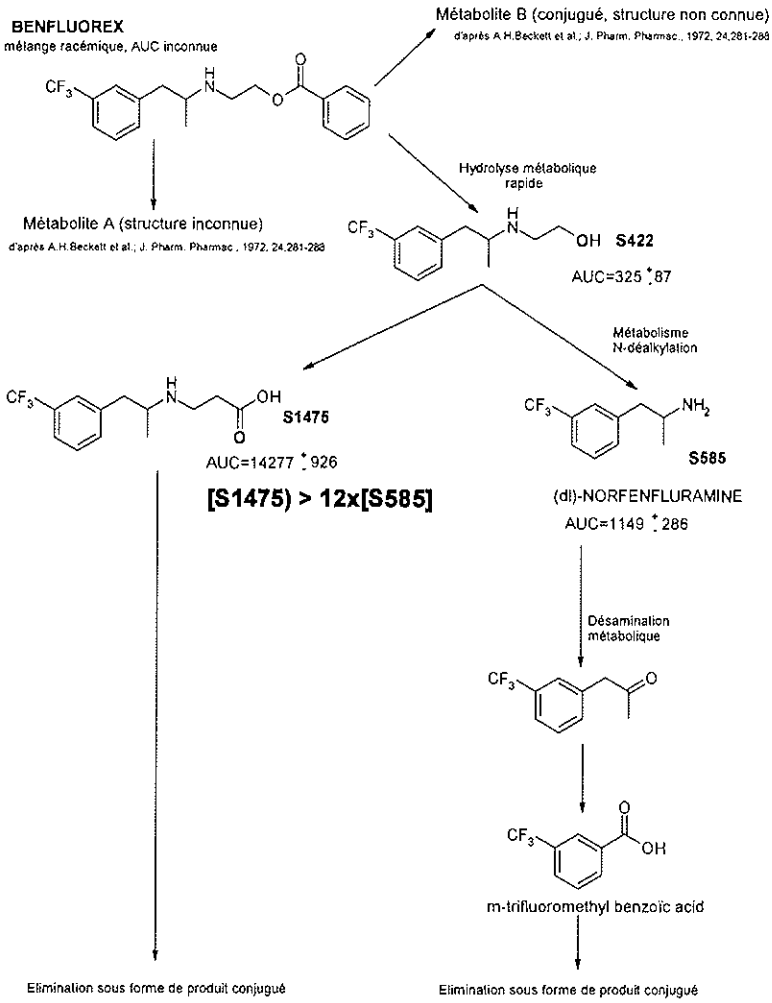
Tableau 1

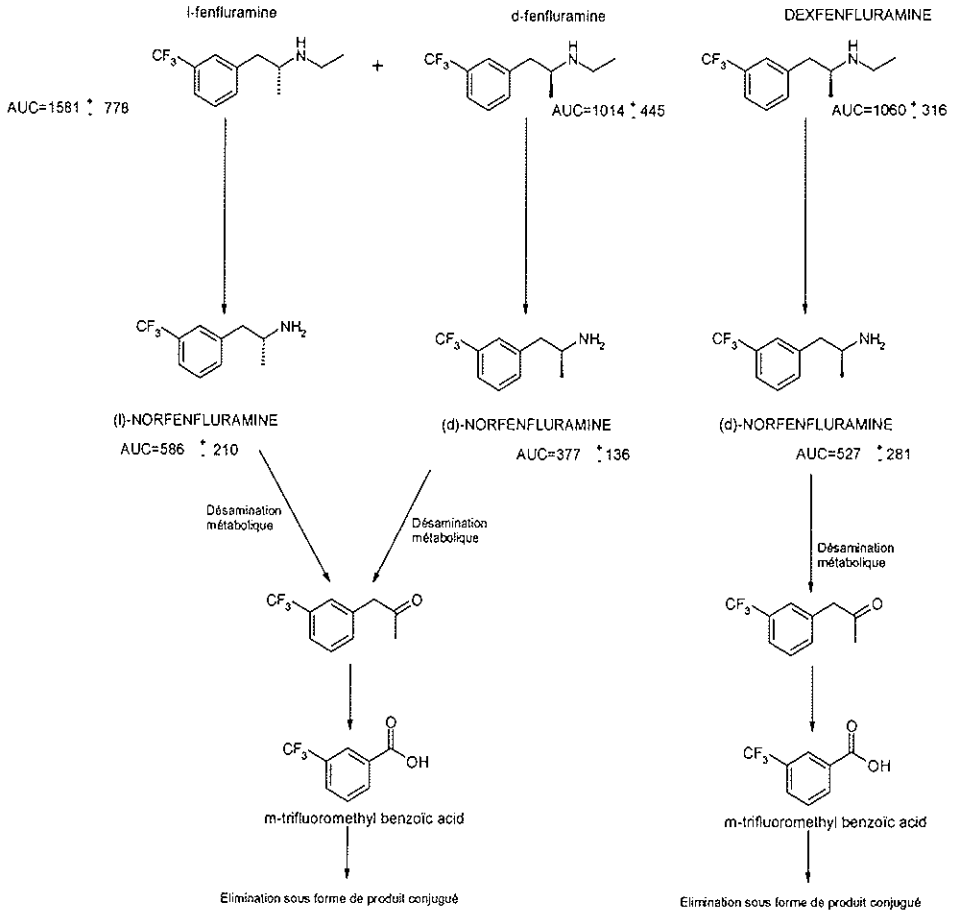
Paramètres cinétiques à l'état d'equilibre chez le volontaire sain après traitement par benfluorex, dexfenfluramine et fenfluramine

		AUC 24 (ng.ml-1.h)	Cmin (24 h) (ng.ml-1)	Cmax (ng.ml-1)
Benfluorex 3 x 150 mg	S 422	325 ± 87	7 ± 2	22 ± 7
	S 1475	14277 ± 926	125 ± 52	1361 ± 233
	dl-norfenfluramine	1149 ± 286	43 ± 8	59 ± 15
Dexfenfluramine 2 x 15 mg	d-fenfluramine	1060 ± 316	34 ± 7	70 ± 15
	d-norfenfluramine	527 ± 281	18 ± 10	26 ± 13
Fenfluramine 60 mg	d-fenfluramine	1014 ± 445	33 ± 12	65 ± 26
	l-fenfluramine	1581 ± 778	54 ± 24	97 ± 47
	d-norfenfluramine	377 ± 136	14 ± 5	21 ± 8
	l-norfenfluramine	586 ± 210	21 ± 9	32 ± 13

Annexe 3

METABOLISME DU BENFLUOREX, FENFLURAMINE ET DEXFENFLURAMINE CHEZ L'HOMME

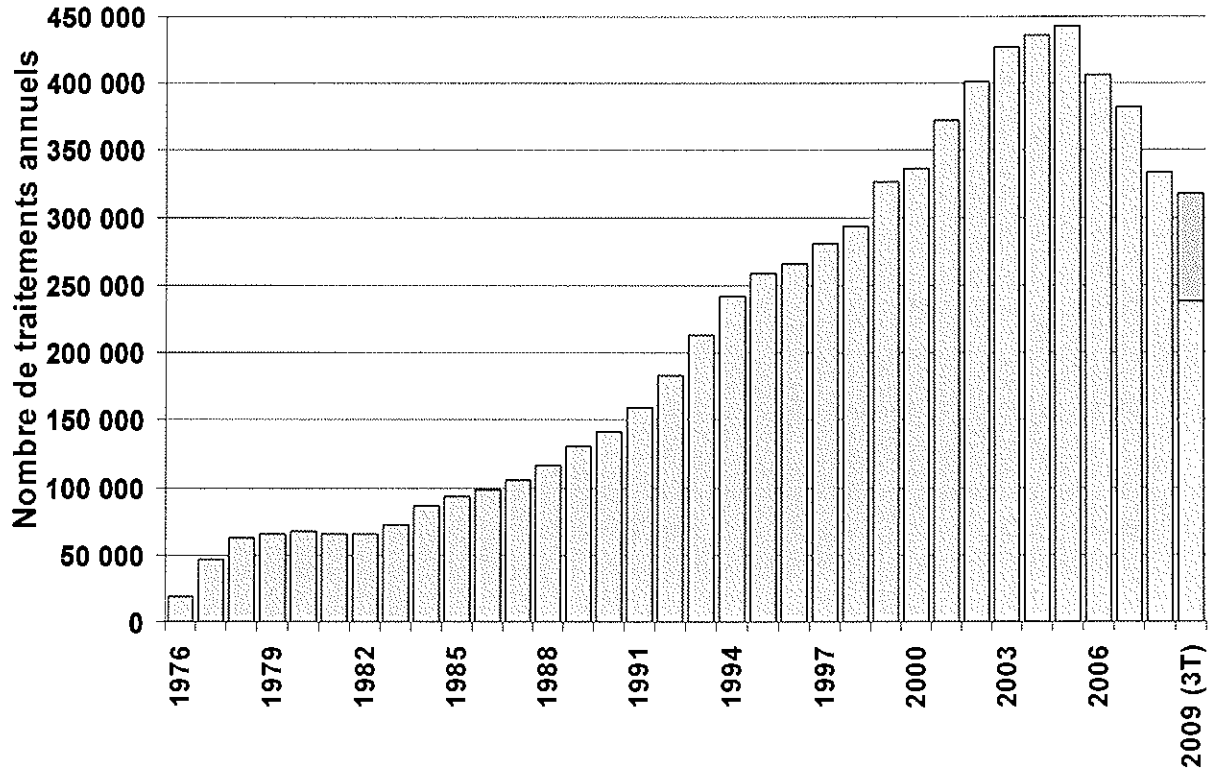




AUC 24 (ng.ml-1.h) administration benfluorex (3x150 mg), dexfenfluramine (2x15 mg) et fenfluramine (60 mg) pendant 10 jours chez les sujets sains
Pour le Benfluorex [S585] <12 x [1475] et (dl) norfenfluramine ≈ 50 % (d)-norfenfluramine + 50 % (l)-norfenfluramine

Annexe 4 :

Nombre de traitements annuels de Médiator (Données Servier communiqués à l'AFSSAPS)



Annexe 1-37

Le tableau VIII représente les anorexigènes utilisés et montre bien cette appartenance au groupe des phényl-éthylamines. On retrouve en effet dans chacun des produits le squelette :

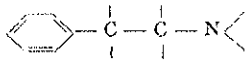
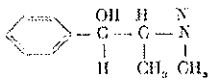
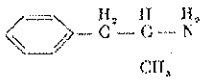


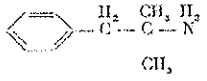
TABLEAU VIII



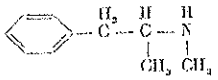
Ephédrine



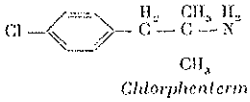
Amphétamine



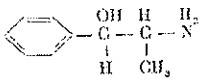
Phentermine



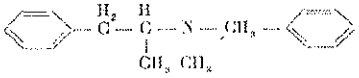
Méthamphétamine



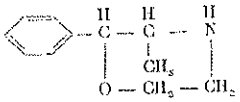
Chlorphentermine



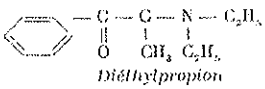
Phénylpropanolamine



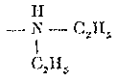
Benzphétamine

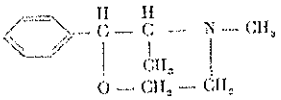


Phenmétrazine

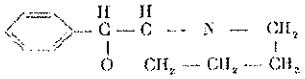


Diéthylpropion

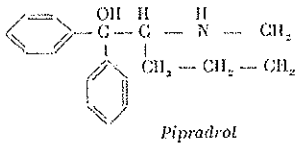




Phendiméträzine



Acétophénane

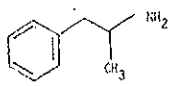


Pipradrol

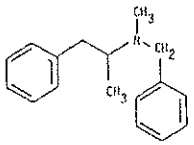
JR Boissier Thérapie 1960

Annexe 1-37

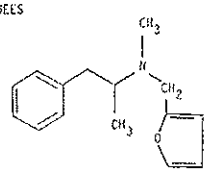
AMPHETAMINE



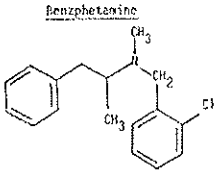
AMPHETAMINES N-SUBSTITUEES



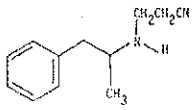
Benzphetamine



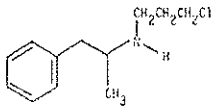
Furfenorex



Clobenzorex



Fenproporex

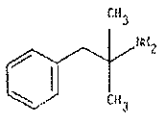


Mefenorex

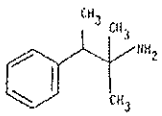
FIG. 1 (*ci-dessus*). — Structures chimiques et noms génériques des amphétamines N substituées.

FIG. 2 (*ci-contre*). — Structures chimiques et noms génériques des phénylisopropylamines substituées sur la chaîne latérale.

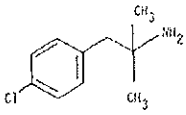
PHENTERMINES



Phentermine

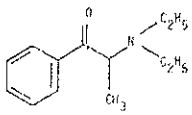


Pentorex

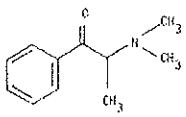


Chlorphentermine

ANFEPRAMONES



Anfepramone



Metanfepramone

c) *Phénéthylamines et phénylisopropylamines cyclisées.*

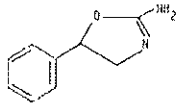
Il y a trois représentants dont deux sont disponibles en France *(figure 3)*.

d) *Phénylisopropylamines halogénées sur le noyau.*

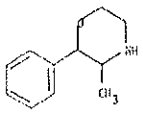
Seule la fenfluramine fait l'objet d'une spécialité pharmaceutique *(figure 4)*.

e) *Autres structures.*

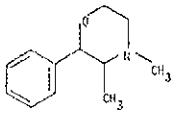
La diphéméthoxidine seule, stimulant central, appartenant à cette catégorie est disponible sur le marché français *(figure 5)*.



Aminoxaphen

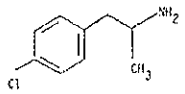


Pheneetrazine

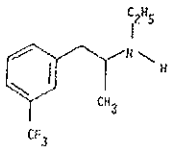


Phendimetrazine

FIGURE 3

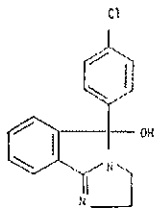


p-chloroamphétamine

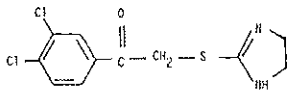


Fenfluramine

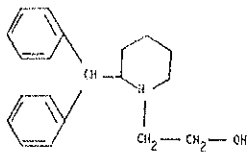
FIGURE 4



Mazindol



Dita



Diphéméthoxidine

FIGURE 5

FIG. 3. — Structures chimiques et noms génériques des phénethylamines cyclisées.

FIG. 4. — Structures chimiques et noms génériques des phénylisopropylamines halogénées sur le noyau.

FIG. 5. — Structures et noms génériques ou de code des structures non amphétaminiques.

2. Classification par les mécanismes d'action.

Les progrès réalisés au cours de la dernière décade dans le domaine des amines cérébrales concernant leur localisation, leur métabolisme et leurs effets, ont tout naturellement été appliqués à l'étude du mécanisme d'action des anorexigènes qui font l'objet de l'article suivant (Prof. H. Schmitt).

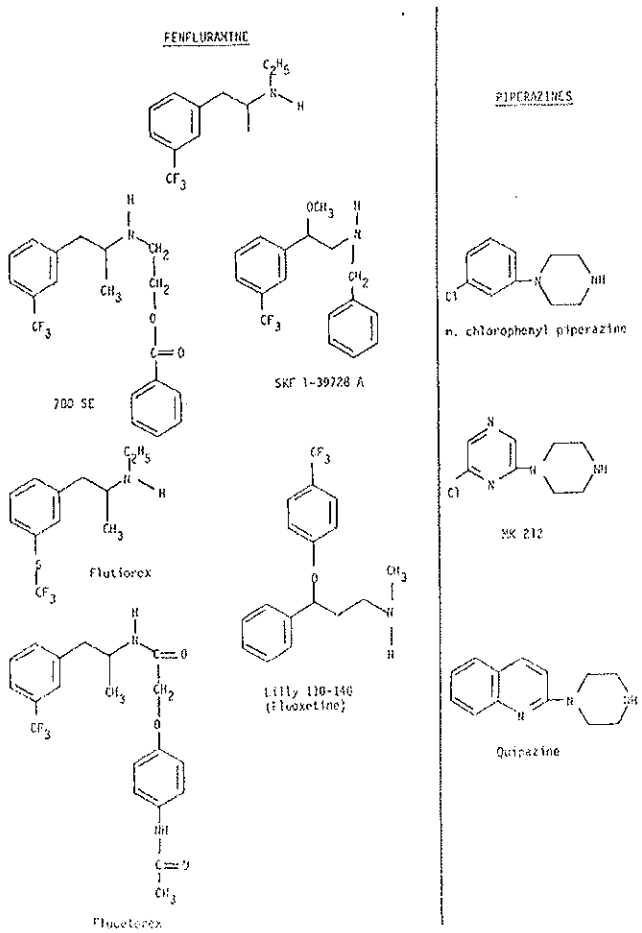


Fig. 6 - Structures et noms génériques ou de code des anorexigènes interférant avec la sérotonine cérébrale.

Le Douarec Thérapie 1979 : Méthodes expérimentales d'études , structures chimiques et classification.

BENFLUOREX

V2 prodrug

-II-

PHARMACOKINETICS AND METABOLISM

CLINICAL STUDIES

PHARMACOKINETICS AND METABOLISM

The pharmacokinetic and metabolism parameters were measured in healthy human volunteers. In this study, similar results were obtained with men and women, therefore all data were pooled.

This report summarizes the results obtained from various studies carried out between 1971 and 1996.

1. ABSORPTION

^{14}C-benfluorex was rapidly absorbed into plasma : the plasma concentration peak was reached one to two hours after administration of the compound and reached a value of 2.6 □g. equivalent. ml^{-1} (table 1, figure 1) (1, 2). The blood/plasma ratio was 0.4 over the first ten hours after administration. Later, the ratio increases, which suggests the formation of more lipophilic metabolites.

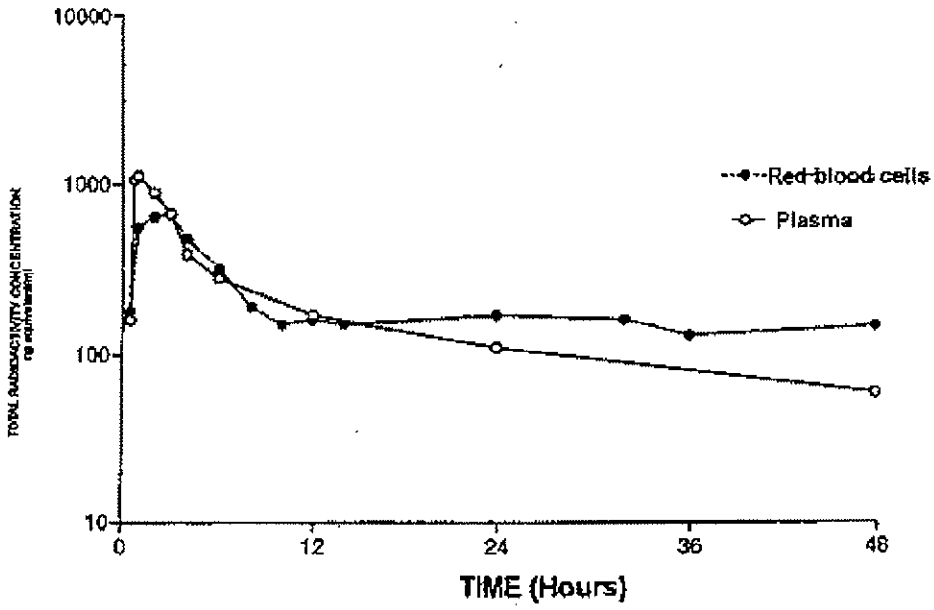
Urinary elimination is greater than 90 %, expressed as a percentage of the radioactivity administered, and in cumulative values for a period of more than 72 hours. This indicates that the drug is well absorbed from the gastrointestinal tract.

Table 1
Pharmacokinetic parameters measured after oral administration of 14C-benfluorex (Mean ± standard deviation) (1)

Parameter	*Human*
Dose (mg)	109
Cmax (□g equiv/ml)	2.6 ± 0.2
Tmax (h)	1.4 ± 0.3
AUC (mg equiv/ml)	23.8 ± 3.9
Vd/F (L)	124 ± 6
Vd/F (% body weight)	1.8 ± 0.1
t1/2 (h)	0.2 ± 0.2
terminal t1/2 (h)	34.0 ± 11.0
AUC (mg equiv/h/ml)	23.8 ± 3.9
Urine (1) (%)	94.0 ± 6.3
Faeces (1) (%)	0.5 ± 0.1
Total excreted (%)	94.5 ± 6.0

(1) % of the dose eliminated for a period greater than or equal to 72 hours
F = biovailability
Vd = volume of distribution

Figure 1
Concentration of total radioactivity in the plasma and in red blood cells



2. TISSUE UPTAKE AND DISTRIBUTION

The data concerning the volume of distribution are approximate for two reasons : a) the drug was metabolised completely and b) was the only measurement carried out. According to table 1, the volume was relatively low (124 litres) which suggests low uptake of radioactive metabolites in the tissues and confirms their polar nature.

The rapid hydrolysis of the unchanged drug makes difficults the measure of plasma proteins binding. Furthermore the binding of metabolites has not been systematically studied. However, one study has shown that protein binding of S 585, the most lipophilic metabolite, is low (17 %) (3). It is highly unlikely that any more polar metabolites bind to plasma proteins in a stronger way .
In general, therefore, plasma protein binding is not a major feature of this compound.

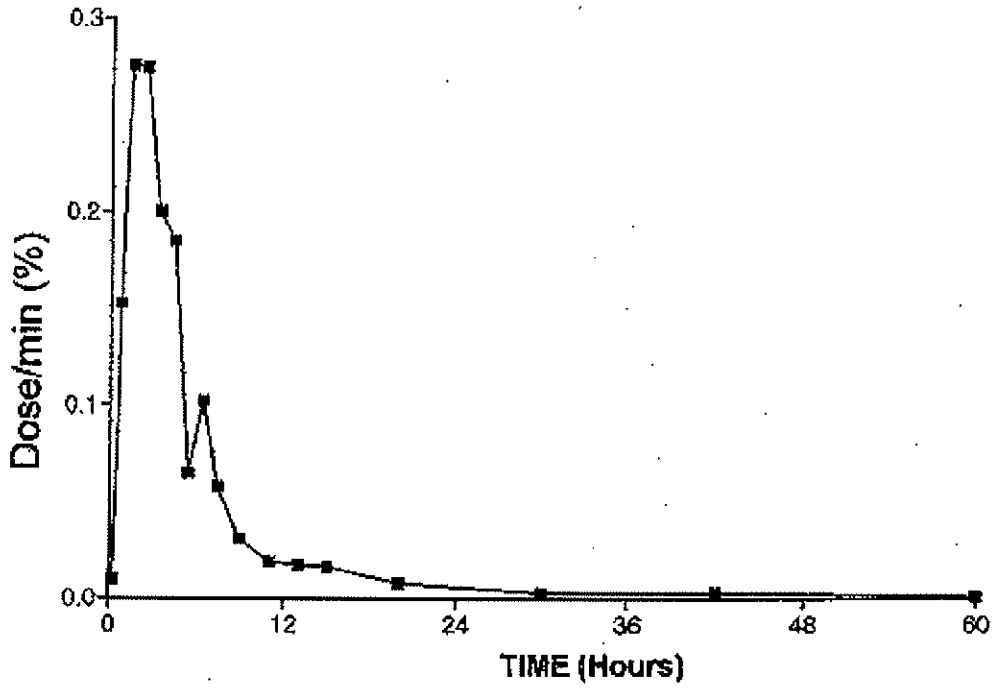
3. ELIMINATION

After the absorption phase, radioactivity is eliminated with a biphasic profile : the half-life of the product was found to be approximately 0.2 hours for the initial phase and 34 hours for the terminal phase (1) (table 1). After, the first 72 hours the radioactivity was found to be near to the limit of detection in all subjects (approximately 0.05 mg equivalent/ml^{-1}). The values of half-life radioactivity during the terminal phase varied between subjects : the values range between 18.6 and 44.9 hours. However, the measurement of the area under the curve, which is the most important pharmacokinetic parameter since it allows to measure levels at the steady state, was similar in all studied subjects (19.8 - 26.3 mg equivalents/h/ml).

Urinary elimination

Urinary elimination of radioactivity was rapid in healthy subjects : 90 % of the dose administered was detected during the first 24 hours. The urinary excretion peak of total radioactivity (0.275 % of the dose/min) coincided with the plasma concentration peak (figure 2). The corresponding calculated clearance was similar to normal renal blood flow (approximately 120 ml/min). These results confirm a weak protein binding and show that neither mortal absorption nor secretion take place in the renal tubules. Then radioactivity declined slowly. After 72 hours elimination was practically completed (87-99 % of the dose administered).

Figure 2
Percentage of radioactivity excreted in urine in healthy volunteers after oral administration of benfluorex (2.5 mg/kg) in solution (n=4)



Faecal elimination

Faecal elimination of radioactivity was low (< 0.5 %). This result confirms that the drug and its metabolites are completely absorbed from the gastrointestinal tract.

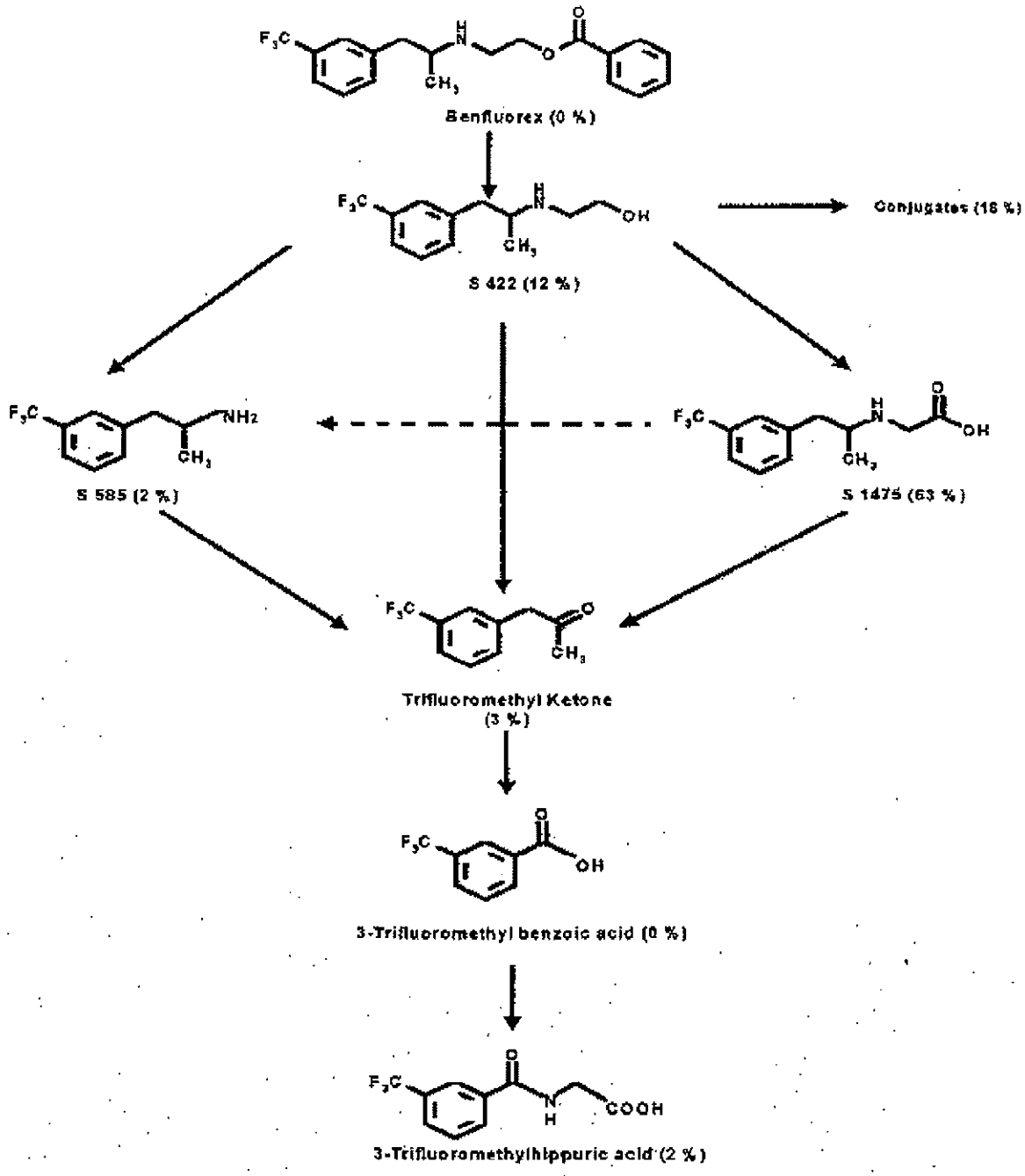
4. METABOLISM

In previous studies, it has been demonstrated the rapid metabolism of benfluorex by circulating esterases, and so no traces of the compound have been found in various body fluids (4) no trace of the product was found in various body fluids. In the original studies (5, 6), radioactive material was not available. Subsequently, radioactive labelling of the compound have allowed a more systematic approach. The identification and quantification of the different metabolites was therefore possible. The results of these various studies (non radioactive and radioactive) are in agreement. Thus, this report also cites the most recent studies and it is based on data obtained from studies using the labelled compound.

Urine

As previously reported, benfluorex could not be detected in the various body fluids. It should be therefore considered to be a prodrug. In humans, at least nine metabolites were detected in the urine (7). Four main steps are : a) hydrolysis of the drug by plasma esterases into a primary metabolite, followed by b) conjugation, c) oxidation of the aliphatic nitrogenic side chain and d) deamination to yield more polar compounds (figure 3).

Figure 3
Metabolic pathways suggested for benfluorex in humans
(% of the dose eliminated between 0 and 24 hours) (1)



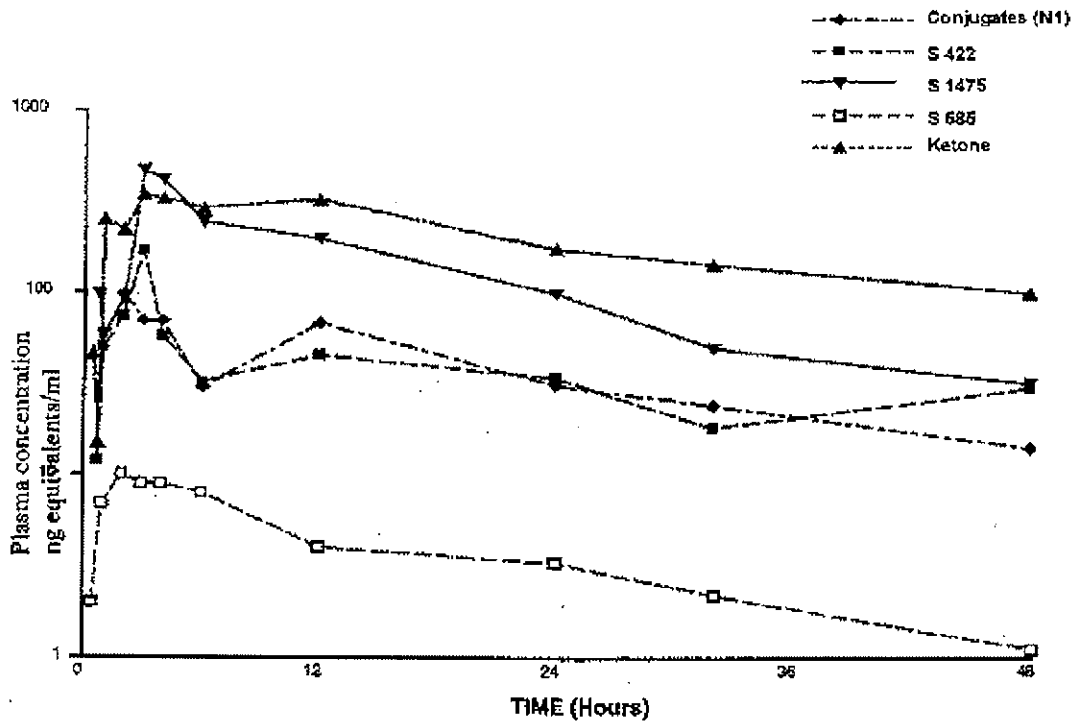
All the major metabolites (> 95 %) have been identified using mass spectrometry and their chromatographic properties have been compared to synthetic standards. Benfluorex undergoes rapid hydrolysis to a primary metabolite, S 422 (approximately 12 %).

If the results obtained before and after enzymatic hydrolysis in urine are considered, it is clear that this metabolite combines to the glucuronide and sulphate conjugates (approximately 18%) (1, 8). S 422 is then oxidised either into a) a carboxylic acid, the S 1475, the main metabolite in humans (approximately 63 %), or b) a primary amine S 585, which represents only 2% of the dose. It is therefore likely that a small quantity of metabolite S 1475 was conjugated. Nevertheless, further studies are required to confirm this hypothesis.
These substances are then deaminated to yield more polar metabolites ; fristly trifluoromethylbenzylketone (ketone) (approximately 3 %), and secondly : trifluoromethylhippuric acid (TFH) (approximately 2 %) a glycine-conjugated compound obtained by oxydation of trifluoromethylbenzoic acid (TBB). All the metabolites identified in the urine represent more than 95 % of the radioactive dose administered.

Plasma

Single dose
Because of the difficulties of mesuring the low levels of the more polar metabolites of benfluorex in plasma, relatively little work has been undertaken to investigate levels of the circulating metabolites.
Oral administration of a single dose of radiolabelled benfluorex (approximately 110 mg) to a healthy volunteer allows to estimate the levels of circulating metabolites of benfluorex (figure 4). The major metabolite was the same as the one found in urine : the carboxylic acid derivative (S 1475). The plasma peak (approximately 400 ng/ml) was found between 3 and 4 hours after oral administration and represents 40 % of the radioactive plasma components. The terminal half-life of this compound is approximately 14 hours. Another polar compound, the deaminated ketone derivative, was also detected in relatively large quantities with a peak of 300 ng/ml three hours after administration. The primary metabolite of benfluorex, S 422, had a peak at 170 ng/ml. Metabolite N1 (approximately 100 ng/ml) is the glucose conjugate of S 422. The levels of S 585 remained low (approximately 33 ng/ml).
These data were obtained after separation by thin-layer chromatography, followed by scraping of the plates and counting.

Figure 4
Concentrations of metabolites of ^{14}C-benfluorex in the plasma of healthy volunteers after oral administration



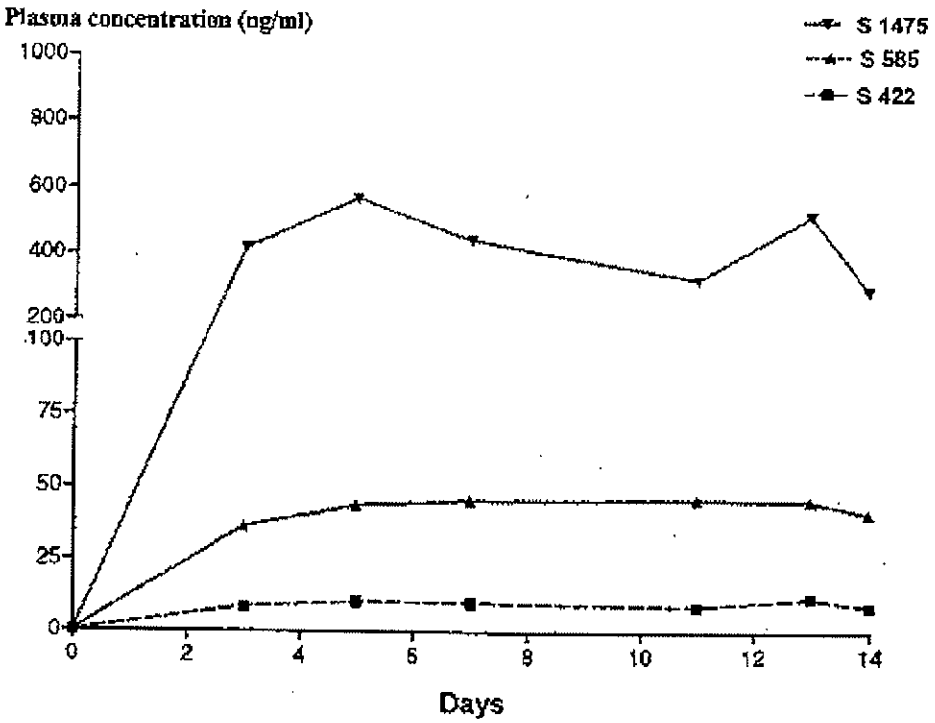
Repeated doses

Figure 5 shows the results of quantification by HPLC of the metabolites in six healthy volunteers after repeated administration of a dose (150 mg), three times per day, over a period of 14 days (9).

The steady state for the principal metabolite, S 1475 (approximately 1000 ng/ml), was reached after four to five days of administration. For S 422 (approximately 18 ng/ml) and S 585 (approximately 50 ng/ml) the steady state was reached later, seven to ten days after the start of treatment.

Level of S 585 remained relatively constant for the entire duration of the treatment whereas some fluctuations appeared for the other metabolites. This was due to differences in the half-life elimination times. The more rapid elimination of S 1475 (elimination half-life : 3 hours) compared to S 422 (elimination half-life: 7 hours) is difficult to explain from a kinetic point when the metabolic route is considered. Nonetheless, three hypotheses are possible : (a) S 1475 is formed directly from benfluorex, (b) S 1475 has a longer half-life as suggested by radioactive studies, (c) S 422 has an "artificially" prolonged half-life due to slow release from the tissues or to recirculation of the product from conjugates. From currently available results it is not possible to confirm these hypotheses.

Figure 5
Mean plasma concentrations of metabolites of benfluorex after the administration of 3 x 150 mg of benfluorex tablets over a period of 14 days (n = 6)



5. PARTICULAR SITUATIONS AND DRUG INTERACTIONS

Precautions should be taken in the prescription of this drug in patients with renal disorders. In fact, as described previously, the elimination of the two main metabolites, S 1475 and the glucuronide of S 422, is essentially urinary. Furthermore, although the conversion of benfluorex into its metabolites occurs in plasma by hydrolysis, subjects suffering from liver failure should be followed up carefully.

No studies have looked at the specific problems of the interaction of benfluorex with other drugs. However, the results of the bioavailability studies do not indicate any problems. In addition, no interactions were reported during clinical or pharmacovigilance studies over a long period of widespread use.

6. SUMMARY

Benfluorex is rapidly metabolised and it can be considered to be a prodrug of S 422. This is then metabolised into at least eight other metabolites. The main metabolites were identified and quantified in urine as products of oxidation and deamination. The extensive radioactivity elimination in urine combined with a lack of a significant quantity of metabolites in faeces shows that the drug is well absorbed and that no other accumulation occurs.

The specific measurement of metabolites in plasma after chronic administration shows that the steady state is reached in less than one week and remains constant, suggesting no induction or inhibition of metabolism. After stopping treatment all metabolites are eliminated during a few days period ; no accumulation phenomena occurred.

REFERENCES

1- RICHARDS R. The metabolism and kinetics of Fenfluramine, its optical isomers and a structural analogue, Benfluorex,1985.

2- TOZER R, MCGOWAN ME, CAMPBELL DB. The kinetics of ^{14}C-780E in the rat, dog, monkey and human - a comparative report. Servier Internal Report, PMH078031004, 1976.

3- CAMPBELL DB. Pharmacokinetics of amphetamine and Fenfluramine after therapeutic dosage and overdosage. Ph. D London University Thesis, 1978.

4- BECKETT AH, SHENOY EVB, BROOKES LG. Absorption, metabolism and elimination of N-(2-benzoyloxyethyl)-norfenfluramine (JP992) in man. J. Pharm. Pharmacol, 1972;24:281-288.

5- BECKETT AH, SHENOY EVB, BROOKES LG. Determination of N-(2-benzoyloxyethyl)-norfenfluramine (JP992) and its metabolites in urine. J. Pharm. Pharmacol, 1971;23:950-955.

6- OGUNBONA FA. The importance of hydrolysis and n-oxidation in the *in vitro* metabolism of N-(2-benzoyloxyethyl)-norfenfluramine. Servier Internal Report, No. 780K.03, 1973.

7- RICHARDS RP, MAC GOWAN M, CAMPBELL DB. The plasma and urinary metabolites of benfluorex in man. Servier Internal Report, NP02464, 1978

8- CHARPENTIER J. Blood kinetics of S992 metabolites after venous administration in the dog. Servier Internal Report, M 0992.10.009, 1976

9- GORDON BH, VIS PW. The pharmacokinetics of the metabolites of benfluorex in chronic administration : comparison of a sustained release formulation (500 mg) with the control form (3 x 150 mg) in human volunteers. Servier Internal Report, 93-5792-001 on file, 1993.

Annexe 1-39

LES LABORATOIRES SERVIER
22, rue Garnier - 92200 NEUILLY-SUR-SEINE
Tél. : 01.46.41.60.00

MEDIATOR® 150 mg

Dossier VNL 10008

Dossier complémentaire
en réponse à la demande du 18.06.99
de l'A.F.S.S.A.P.S.

- Juin 1999 -

BENFLUOREX

-II-

PHARMACOKINETICS AND METABOLISM

CLINICAL STUDIES

1. PHARMACOKINETICS AND METABOLISM

The pharmacokinetic and metabolism parameters were measured in healthy human volunteers. In this study, similar results were obtained with men and women, therefore all data were pooled.

This report summarizes the results obtained from various studies carried out between 1971 and 1996.

1.1. Absorption

^{14}C-benfluorex was rapidly absorbed into plasma : the plasma concentration peak was reached one to two hours after administration of the compound and reached a value of 2.6 µg. equivalent.ml^{-1} (table 1, figure 1) (1, 2). The blood/plasma ratio was 0.4 over the first ten hours after administration. Later, the ratio increases, which suggests the formation of more lipophilic metabolites.

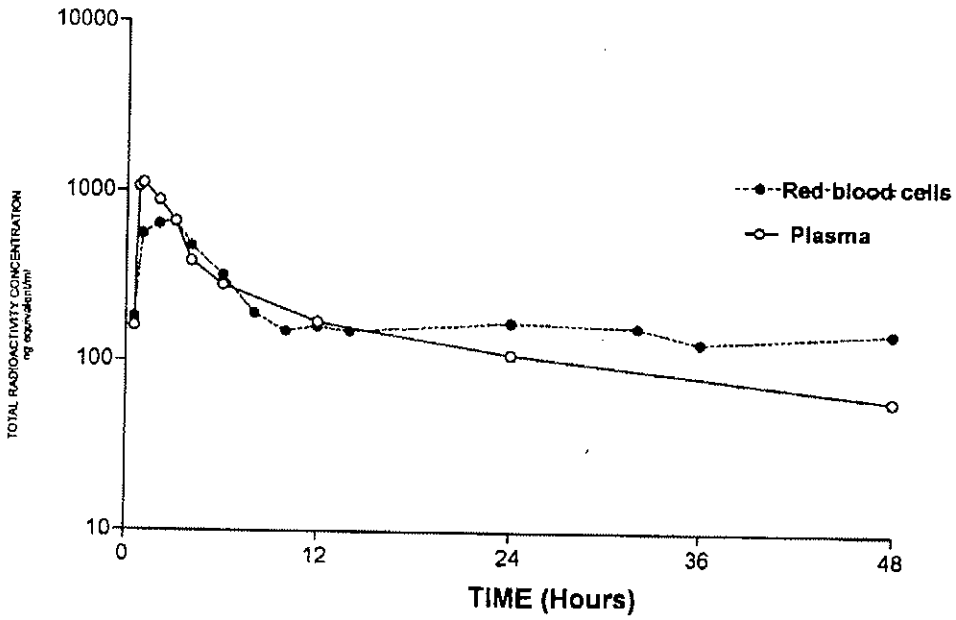
Urinary elimination is greater than 90 %, expressed as a percentage of the radioactivity administered, and in cumulative values for a period of more than 72 hours. This indicates that the drug is well absorbed from the gastrointestinal tract.

Table 1
Pharmacokinetic parameters measured after oral administration of 14C-benfluorex (Mean ± standard deviation) (1)

Parameter	*Human*
Dose (mg)	109
Cmax (µg equiv/ml)	2.6 ± 0.2
Tmax (h)	1.4 ± 0.3
AUC (mg equiv/ml)	23.8 ± 3.9
Vd/F (L)	124 ± 6
Vd/F (% body weight)	1.8 ± 0.1
t1/2 (h)	0.2 ± 0.2
terminal t1/2 (h)	34.0 ± 11.0
AUC (mg equiv/h/ml)	23.8 ± 3.9
Urine (1) (%)	94.0 ± 6.3
Faeces (1) (%)	0.5 ± 0.1
Total excreted (%)	94.5 ± 6.0

(1) % of the dose eliminated for a period greater than or equal to 72 hours
F = biovailability
Vd = volume of distribution

Figure 1
Concentration of total radioactivity in the plasma and in red blood cells



1.2 Tissue uptake and distribution

The data concerning the volume of distribution are approximate for two reasons : a) the drug was metabolised completely and b) was the only measurement carried out. According to table 1, the volume was relatively low (124 litres) which suggests low uptake of radioactive metabolites in the tissues and confirms their polar nature.

The rapid hydrolysis of the unchanged drug makes difficults the measure of plasma proteins binding. Furthermore the binding of metabolites has not been systematically studied. However, one study has shown that protein binding of S 585, the most lipophilic metabolite, is low (17 %) (3). It is highly unlikely that any more polar metabolites bind to plasma proteins in a stronger way .
In general, therefore, plasma protein binding is not a major feature of this compound.

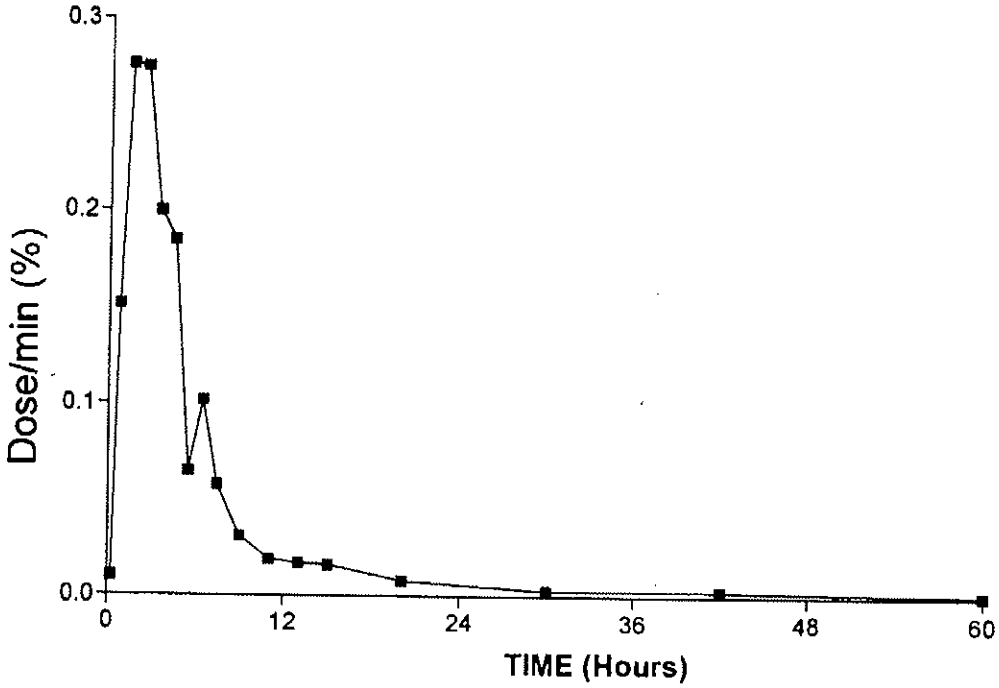
1.3 Elimination

After the absorption phase, radioactivity is eliminated with a biphasic profile : the half-life of the product was found to be approximately 0.2 hours for the initial phase and 34 hours for the terminal phase (1) (table 1). After, the first 72 hours the radioactivity was found to be near to the limit of detection in all subjects (approximately 0.05 mg equivalent/ml^{-1}). The values of half-life radioactivity during the terminal phase varied between subjects : the values range between 18.6 and 44.9 hours. However, the measurement of the area under the curve, which is the most important pharmacokinetic parameter since it allows to measure levels at the steady state, was similar in all studied subjects (19.8 - 26.3 mg equivalents/h/ml).

1.3.1 Urinary elimination

Urinary elimination of radioactivity was rapid in healthy subjects : 90 % of the dose administered was detected during the first 24 hours. The urinary excretion peak of total radioactivity (0.275 % of the dose/min) coincided with the plasma concentration peak (figure 2). The corresponding calculated clearance was similar to normal renal blood flow (approximately 120 ml/min). These results confirm a weak protein binding and show that neither mortal absorption nor secretion take place in the renal tubules. Then radioactivity declined slowly. After 72 hours elimination was practically completed (87-99 % of the dose administered).

Figure 2
Percentage of radioactivity excreted in urine in healthy volunteers after oral administration of benfluorex (2.5 mg/kg) in solution (n=4)



1.3.2 Faecal elimination

Faecal elimination of radioactivity was low (< 0.5 %). This result confirms that the drug and its metabolites are completely absorbed from the gastrointestinal tract.

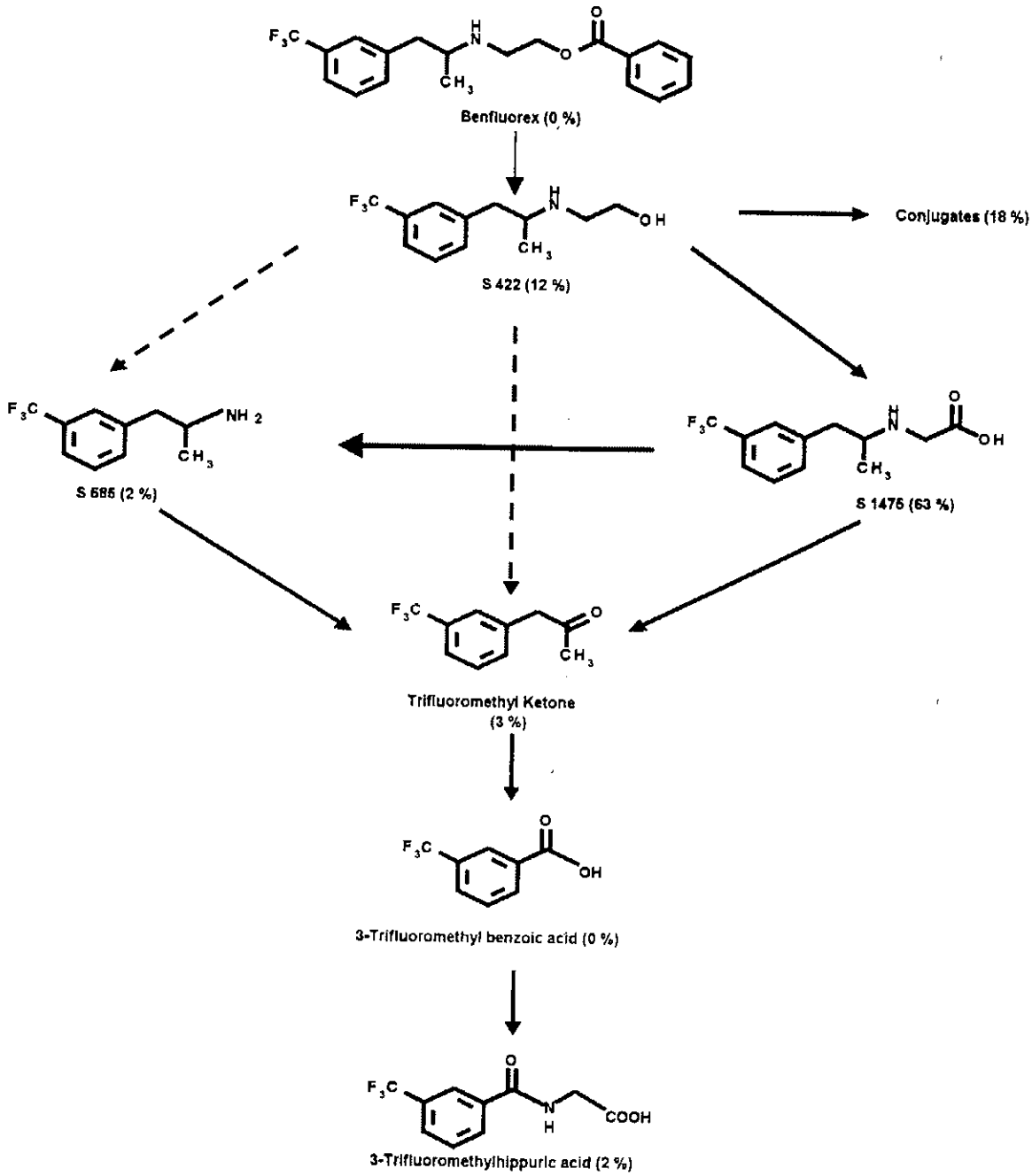
1.4 Metabolism

In previous studies, it has been demonstrated the rapid metabolism of benfluorex by circulating esterases (4). In the original studies (5, 6), radioactive material was not available. Subsequently, radioactive labelling of the compound have allowed a more systematic approach. The identification and quantification of the different metabolites was therefore possible. The results of these various studies (non radioactive and radioactive) are in agreement. Thus, this report also cites the most recent studies and it is based on data obtained from studies using the labelled compound.

1.4.1 Urine

In humans, at least nine metabolites were detected in the urine (7). Four main steps are : a) hydrolysis of the drug by plasma esterases into a primary metabolite, followed by b) conjugation, c) oxidation of the aliphatic nitrogenic side chain and d) deamination to yield more polar compounds (figure 3).

Figure 3
Metabolic pathways suggested for benfluorex in humans
(% of the dose eliminated between 0 and 24 hours) (Richards, 1985)



All the major metabolites (> 95 %) have been identified using mass spectrometry and their chromatographic properties have been compared to synthetic standards. Benfluorex undergoes rapid hydrolysis to a primary metabolite, S 422 (approximately 12 %).

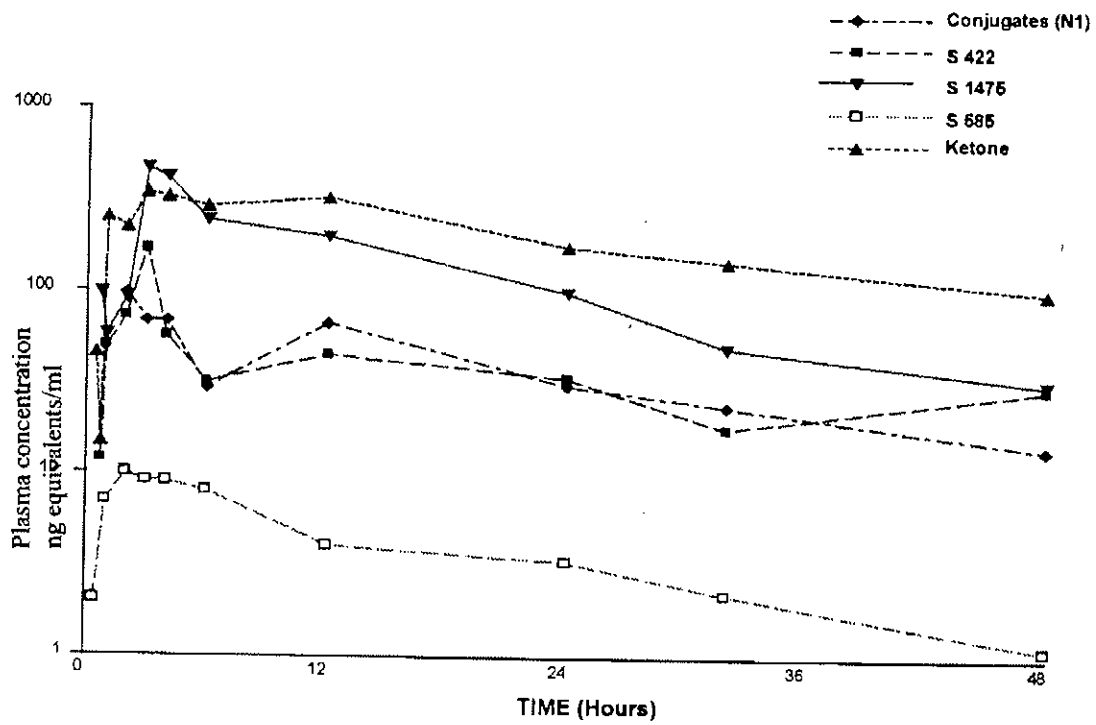
If the results obtained before and after enzymatic hydrolysis in urine are considered, it is clear that this metabolite combines to the glucuronide and sulphate conjugates (approximately 18%) (1, 8). S 422 is then oxidised either into a carboxylic acid, the S 1475, the main metabolite in humans (approximately 63 %), or to a lesser extent to a primary amine S 585 ((dl)-norfenfluramine), which represents only 2% of the dose. It is therefore likely that a small quantity of metabolite S 1475 was conjugated. Nevertheless, further studies are required to confirm this hypothesis.
These substances are then deaminated to yield more polar metabolites ; fristly trifluoromethylbenzylketone (ketone) (approximately 3 %), and secondly : trifluoromethylhippuric acid (TFH) (approximately 2 %) a glycine-conjugated compound obtained by oxydation of trifluoromethylbenzoic acid (TBB). All the metabolites identified in the urine represent more than 95 % of the radioactive dose administered.

1.4.2 Plasma

1.4.2.1 Single dose

Because of the difficulties of mesuring the low levels of the more polar metabolites of benfluorex in plasma, relatively little work has been undertaken to investigate levels of the circulating metabolites.
Oral administration of a single dose of radiolabelled benfluorex (approximately 110 mg) to a healthy volunteer allows to estimate the levels of circulating metabolites of benfluorex (figure 4). The major metabolite was the same as this one found that this one found in the urine : the carboxylic acid derivative (S 1475). The plasma peak (approximately 400 ng/ml) was found between 3 and 4 hours after oral administration and represents 40 % of the radioactive plasma components. The terminal half-life of this compound is approximately 14 hours. Another polar compound, the deaminated ketone derivative, was also detected in relatively large quantities with a peak of 300 ng/ml three hours after administration. The primary metabolite of benfluorex, S 422, had a peak at 170 ng/ml. Metabolite N1 (approximately 100 ng/ml) is the glucose conjugate of S 422. The levels of S 585 (dl)-norfenfluramine) remained low (approximately 33 ng/ml).
These data were obtained after separation by thin-layer chromatography, followed by scraping of the plates and counting.

Figure 4
Concentrations of metabolites of ^{14}C-benfluorex in the plasma of healthy volunteers after oral administration



1.4.2.2 Repeated doses

The pharmacokinetics of benfluorex and the quantification of the metabolites have been examined in six healthy volunteers after repeated administration of a dose (150 mg), three times per day, over a period of 14 days (9).

The steady state for the principal metabolite, S 1475 (approximately 1361 ng/ml), was reached after four to five days of administration. For S 422 (approximately 22 ng/ml) and S 585 (dl)-norfenfluramine (approximately 59 ng/ml) the steady state was reached later, seven to ten days after the start of treatment.

Level of S 585 remained relatively constant for the entire duration of the treatment whereas some fluctuations appeared for the other metabolites. This was due to differences in the half-life elimination times. The more rapid elimination of S 1475 (elimination half-life : 3 hours) compared to S 422 (elimination half-life: 7 hours) is difficult to explain from a kinetic point when the metabolic route is considered. Nonetheless, three hypotheses are possible : (a) S 1475 is formed directly from benfluorex, (b) S 1475 has a longer half-life as suggested by radioactive studies, (c) S 422 has an "artificially" prolonged half-life due to slow release from the tissues or to recirculation of the product from conjugates. From currently available results it is not possible to confirm these hypotheses.

1.5 Particular situations and drug interactions

Precautions should be taken in the prescription of this drug in patients with renal disorders. In fact, as described previously, the elimination of the two main metabolites, S 1475 and the glucuronide of S 422, is essentially urinary. Furthermore, although the conversion of benfluorex into its metabolites occurs in plasma by hydrolysis, subjects suffering from liver failure should be followed up carefully.

No studies have looked at the specific problems of the interaction of benfluorex with other drugs. However, the results of the bioavailability studies or in vitro studies in human hepatocytes do not indicate any problems. In addition, no interactions were reported during clinical or pharmacovigilance studies over a long period of widespread use.

1.6 In vitro metabolism

Benfluorex is metabolised by isolated human hepatocytes but not human liver S9 or liver microsomal fractions. The metabolism of benfluorex, by human hepatocytes, to three metabolite components, S 422, S 1475 and (dl)-norfenfluramine, correspond with the same principal metabolites of benfluorex identified following oral administration of benfluorex (150mg) to healthy volunteers.

The principal metabolites of benfluorex (S 422, S 1475 and (dl)-norfenfluramine) do not inhibit any of the CYP-marker substrate activities at a concentration equal to the reported Cmax plasma level.
Cytochromes P450 1A1, 1A2, 2C9, 2C19, 2E1 and 3A4 (heterologously expressed in bacculo- virus or lymphoblastoid systems) do not support the metabolism of benfluorex. These results indicate a non-cytochrome P450-dependent primary route of benfluorex metabolism.

1.7 Summary

Benfluorex is rapidly metabolised to form an alcohol derivative S 422. This compound is then metabolised into at least eight other metabolites. The main metabolites were identified and quantified in urine as products of oxidation and deamination. The extensive radioactivity elimination in urine combined with a lack of a significant quantity of metabolites in faeces shows that the drug is well absorbed and that no other accumulation occurs.
The specific measurement of metabolites in plasma after chronic administration shows that the steady state is reached in less than one week and remains constant, suggesting no induction or inhibition of metabolism. After stopping treatment all metabolites are eliminated during a few days period : no accumulation phenomena occurred.

REFERENCES

1- RICHARDS R. The metabolism and kinetics of Fenfluramine, its optical isomers and a structural analogue, Benfluorex, 1985.

2- TOZER R, MCGOWAN ME, CAMPBELL DB. The kinetics of ^{14}C-780E in the rat, dog, monkey and human - a comparative report. Servier Internal Report, PMH078031004, 1976.

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8- CHARPENTIER J. Blood kinetics of S992 metabolites after venous administration in the dog. Servier Internal Report, M 0992.10.009, 1976

9- GORDON BH, VIS PW. The pharmacokinetics of the metabolites of benfluorex in chronic administration : comparison of a sustained release formulation (500 mg) with the control form (3 x 150 mg) in human volunteers. Servier Internal Report, 93-5792-001 on file, 1993.

Annexe 1-40

PRATIQUES

OU LES CAHIERS DE LA MÉDECINE UTOPIQUE

Les médicaments du trimestre - Vers des Centres de santé intégrés - Requiem pour une médecine - La médecine au quotidien - Vaccination rougeole-rubéole - Le shériff est dans l'ambulance

REVUE DU SYNDICAT DE LA MÉDECINE GÉNÉRALE
FÉVRIER 1977 - 12 F

13

Annexe 1-40

DU CÔTÉ DE L'INDUSTRIE PHARMACEUTIQUE

Les laboratoires Français de Thérapeutique, vous connaissez ? Ils font comme par hasard partie du groupe Boehringer-Ingelheim (avec les laboratoires Badrial).

Un parfait exemple de traficotage de marché !

La mode est aux antiagrégants plaquettaires.. Les prescriptions augmentent... Il vaut mieux donc multiplier les produits, pour mieux se partager le gateau...

Notons encore que le PERIDAMOL coûte 18,75 F pour 30 comprimés, et la PERSANTINE 75, toujours pour 30 comprimés, 25,45 F. Cette baisse de 6,70 F n'est pas une mauvaise chose, mais nous oblige à nous interroger rétrospectivement sur le prix de la PERSANTINE 75...

Le groupe Boehringer-Ingelheim, qui par ailleurs cherche à apparaître comme un informateur scientifique du corps médical, n'est qu'un honteux fabricant de devises. AU PILORI !

SUR LA SELLETTE

1. — *Les laboratoires Diamant et le groupe Hoechst-Roussel,* pour le « nouveau » produit IDARAC (Floctafenine), « antalgique périphérique ».

Pour planter le décor, rappelons que les laboratoires Diamant font partie du colossal groupe « franco-allemand » Hoechst-Roussel avec entre autres : Roussel, Cassenne, I. S. H., Houdé, etc.

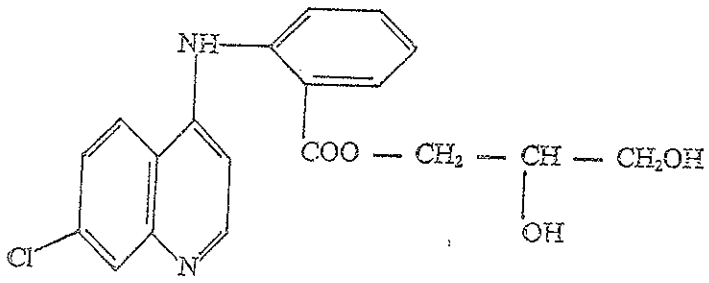
Précisons que pour 1975 les premiers produits du groupe (ventes par les officines ayant atteint plus de dix millions de francs de chiffre d'affaires) sont les suivants :

1 - Glifanan (Roussel)
2 - Dibencozan (I. S. H.)
3 - Dupéran (Cassenne)
4 - Diammaglobulines (Diamant)
5 - Adalgur (Roussel)
6 - Angioxine (Roussel)
7 - Baronorme (Roussel)
8 - Indusil (Diamant)
9 - Staporos (Roussel)
10 - Glyo 6 (Houdé)
11 - Dinintel (Diamant)
12 - Intensain (Diamant)
13 - Rubitracine (Roussel)
14 - Rythmodan et Sédo (Roussel)
15 - Myocoril (Houdé)
16 - Synalar (Cassenne)
17 - Stimugène (Cassenne)

On voit ainsi tout l'intérêt porté aux antalgiques par ce groupe : quatre produits parmi les cinq premiers.

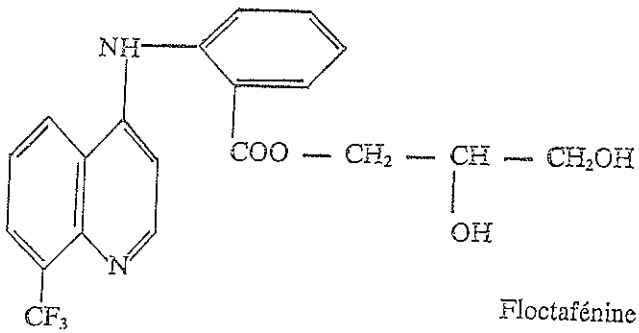
Annexe 1-40

Le GLIFANAN est maintenant un « vieux » produit (D. C. I. de 1961) comprimés à 200 mg de glafénine, boîte de 18 comprimés, 10,85 F :



Glafénine

Le tout jeune IDARAC lui, est fait de 200 mg de floctafénine, boîte de 20 comprimés, 12,80 F :



Floctafénine

Comme on peut s'en rendre compte, la différence sur le plan chimique est loin d'être majeure !...

Le sera-t-elle sur le plan clinique ?

On peut en douter, notamment en lisant le chapitre des précautions d'emploi :

« Il est prudent d'éviter l'administration d'Idarac chez les sujets ayant présenté des incidents de type allergique à la glafénine. »

Et en remarquant l'absence d'étude comparative avec son jumeau GLIFANAN dans les documents fournis par le laboratoire.

Devinette :

IDAFLAN et GLINARAC sont dans un bateau.
GLINARAC tombe à l'eau.
Qu'est-ce qu'il reste ?
Des diamants pour HOECHST-ROUSSEL...

Annexe 1-40

2. — *Les laboratoires Servier* pour le MÉDIATOR.

Cinquième au classement par le chiffre d'affaires, ils sont le champion français de la « promotion médicale », c'est-à-dire de la publicité, de la relance postale, de la visite médicale etc. (1er rang pour les dépenses consacrées à ce domaine en 1975).

Chaque médecin a d'ailleurs pu mesurer cette suprématie, en soupesant et en tâtant les luxueux papiers reçus en surabondance durant ce trimestre à propos du MÉDIATOR.

« *Il arrive qu'un nouveau médicament soit une découverte...* » C'est là le mot d'ordre clef de ces laboratoires en vue de faire prescrire MÉDIATOR. De quoi faire hésiter un régiment d'incrédules...

Et cela d'autant plus que les indications sont quasi universelles : « Contre les hyperlipidémies, qu'il s'agisse d'hypercholestérolémie, d'hypertriglycéridémie, d'hyperlipidémie mixte. »

« Chez les diabétiques, dans le diabète patent... en traitement d'appoint important, dans le diabète asymptomatique. »

« Chez tous les athéroscléreux potentiels ou avérés. »

Ça en fait du monde tout ça !

Ça en fait des centaines et des centaines de milliers de boîtes à vendre !

Et pas pendant deux jours !

Pendant des années !... Et à 28,10 F la boîte, ça fait du 84,30 F le mois de traitement !...

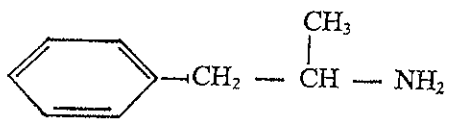
Pour cet enjeu financier si important, les laboratoires Servier méritent bien de passer un moment sur la sellette...

Finalement c'est quoi le Médiator ?

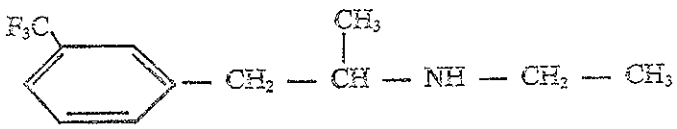
Du Benfluorex ; et « benfluorex », c'est toujours écrit le plus petit possible, dans un coin de page, comme si la terminaison OREX de cette dénomination commune internationale (déposée en 1971) gênait son propriétaire (le suffixe OREX correspond aux anorexigènes dans la nomenclature de l'O. M. S.).

« *Médiator nous a demandé plus de dix ans de recherche* » nous dit Servier... Mais pourquoi donc ne nous dit-il pas que son MÉDIATOR, sur le plan chimique, est un dérivé de l'amphétamine, et un dérivé d'un autre produit de son laboratoire, l'anorexigène PONDÉRAL ?

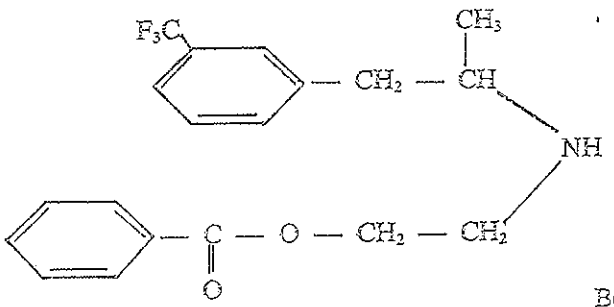
Qu'on en juge :



Amphétamine



Fenfluoramine (PONDERAL *)



Benfluorex (MEDIATOR *)

Donc : MÉDIATOR = PONDÉRAL + l'acide benzoïque branché en bout de chaîne.

Chacun sait que la chimie ne peut pas tout expliquer. Quelquefois l'action d'un produit est totalement modifiée du fait d'un changement minime dans la molécule. C'est peut-être le cas du benfluorex.

Mais tout de même... Pour un produit « *à vocation internationale* » qui se veut être prescrit des années en continu, il est indispensable que les prescripteurs soient prévenus dès le départ de ce tout petit détail. Pour mieux surveiller les réactions des malades par exemple...

Les laboratoires Servier sont trop expérimentés en matière de lancement de produit pour ne pas y avoir pensé.

Alors... dissimulation volontaire ?...

Ça agit comment, ce produit ?

Là, nous renvoyons le lecteur à la documentation des laboratoires Servier dans laquelle sont réunis des exposés très détaillés sur le cycle de Krebs, le Co-enzyme A, et bien d'autres choses encore (« *les lipides brûlent au feu des glucides* »).

Les discours biochimiques impressionnent toujours les prescripteurs ignorauts que nous sommes. Ça fait savant, ça fait sérieux, ça fait honnête...

Mais en fin de compte, honorés confrères, il ne faut pas se laisser impressionner par la grandeur des mots. Les malades ne

sont pas traités par des démonstrations biochimiques sur papier glacé, mais par des produits efficaces.

Le mode d'action du MÉDIATOR n'a pas grand intérêt pratique si l'on n'a pas répondu auparavant à la question suivante :

Ce produit est-il utile, est-il efficace ?

Là, bien sûr, dans les documents présentés, il y a des courbes. Elles montrent que chez les quelque dizaines (voire centaines) de malades étudiés, la glycémie, les lipides baissent plus ou moins selon les conditions d'expérimentation. Et finalement nous dit Servier :

« *C'est à vous qu'il appartient maintenant de juger du progrès que représente* Médiator *chez vos malades hyperlipidémiques, ou présentant un trouble de la tolérance au glucose, donc menacés ou déjà atteints par l'athérosclérose.* »

ALORS LA, NON !

Cette phrase du « *dévoué confrère* » est une mystification, une subtile escroquerie, reposant sur une idée fausse, répandue autant dans le corps médical, que dans la profession pharmaceutique.

Non ! nous les médecins de base, les prescripteurs de quartier, nous ne pouvons absolument pas « juger » un tel produit. Ni d'ailleurs un spécialiste de ville, un hospitalier, ou un Professeur Duduche.

De tels produits, pour des indications aussi floues que le diabète, les hyperlipidémies, l'athérome... etc., ne peuvent être jugés valablement qu'avec une méthodologie statistique et épidémiologique sur plusieurs années. Toute autre évaluation individuelle, à petite échelle, ou de courte durée, NE PEUT AVOIR AUCUNE VALEUR.

L'expérience des antidiabétiques oraux à ce propos est particulièrement instructive. Ils sont prescrits en grande quantité depuis 20 ans ; ils font régulièrement baisser la glycémie ; mais il semble de plus en plus probable qu'en fin de compte, ces produits augmentent la mortalité des diabétiques par maladie cardio-vasculaire (voir à ce sujet : « Diabète : qu'ajouter au régime ? » in *Concours médical*, 20/11/1976, 98-42).

Alors, pour MÉDIATOR, on n'est pas pressé...

On attendra encore quelque temps, voire quelques années...

Mais dans quelques années, quand on commencera à savoir un petit bout de la vérité, ça en fera déjà des millions de boîtes de MÉDIATOR vendues !... Et avec tout cet argent, les laboratoires Servier auront bien vécu... et aussi inventé « benflobis », pour lequel il faudra dix ans de plus pour affirmer quelque chose... et... avec tout cet argent...

Qui médit a tort... ?
Peut-être pas.
En tout cas, question information, en l'absence d'organisme d'information indépendant, on est loin du compte !...

Le 23 décembre 1976

Dr James LARNAQUE.

Après n'avoir reçu les visiteurs médicaux que pour leur faire lire le texte diffusé à l'initiative de notre syndicat et pour en discuter, je leur ai fermé ma porte depuis un an. Et pourtant :

— JE NE VAIS PAS PLUS MAL.
— J'UTILISE MOINS DE MÉDICAMENTS.
— JE CONNAIS MIEUX LES MÉDICAMENTS QUE J'UTILISE.

Alors...

Ils m'avaient dit : « Vous redemanderez bientôt à nous revoir... Comment serez-vous informé ?... »

Je n'ai pas eu de syndrome de manque. J'achète à la pharmacie les médicaments d'urgence dont j'ai besoin. Cela ne grève pas mon budget. J'achète les ouvrages et publications dont j'ai besoin.

L'information sur les nouveaux médicaments me vient par quatre voies :

— les publicités insérées dans les revues (non négligeable)
— les additifs au dictionnaire *Vidal*
— les conseils de mes correspondants
— les lectures d'articles ou livres de thérapeutique.

J'accède au médicament de manière plus active. Je me fais une idée du médicament avant de l'utiliser. Comme conséquence, le nombre de substances (et surtout des spécialités) inclues dans mon arsenal thérapeutique a diminué en même temps que s'améliorait la connaissance que j'avais de ces substances.

Supprimer le contact avec les visiteurs médicaux, c'est supprimer l'une des sources de cette éternelle rengaine (l'autre étant l'E. P. U. officiel) : « Vous ne pouvez pas ignorer... » « Tout bon médecin doit savoir... » distillée à leur manière par les visiteurs médicaux. Donc plus d'appel à la mauvaise conscience systématique, frustrante et incitatrice à la consommation.

Ma conclusion : la visite médicale est non seulement inutile, mais encore elle est toxique.

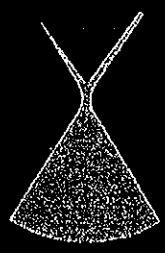
F. PIEDNOIR.

Annexe 1-41

HENRI PRADAL

DICTIONNAIRE CRITIQUE DES MÉDICAMENTS

1978 - 1979



EDITIONS DU COULOIR DE GAUBE - SARL
BP 77, 65110 CAUTERETS

MAX

MAXILASE III.A.3

Enzymes à visées antiœdémateuses

voir : RIBALGILASE

MÉDIATOR III.C.3

Antisurcharges alimentaires

Pour qui sait examiner une formule développée — mais encore faut-il avoir l'occasion de tomber dessus — le benfluorex, principe actif du Médiator, est un dérivé de la molécule du Pondéral, coupe-appétit bien connu commercialisé par le même laboratoire. « Il arrive qu'un nouveau médicament soit une découverte », comme on peut lire sur les publicités du Médiator. C'est reconnaître que bien des médicaments « nouveaux » n'apportent rien : phrase dangereuse, surtout lorsqu'on veut vendre une amphétamine modifiée par adjonction d'un radical organique en en faisant « le traitement logique des surcharges lipido-glucidiques athérogènes »...

Chaque comprimé est dosé à 0,150 g de chlorhydrate de benfluorex. L'excipient contient de l'amidon de maïs, de la carboxyméthylcellulose sodique, de la cire blanche, du stéarate de magnésium, du mono-oléate de glycérol, du polysorbate, de la polyvidone, de la silice colloïdale, du sucre blanc officinal, du talc, de l'oxyde de titane, le tout en quantité suffisante pour un comprimé dragéifié terminé à 0,700 g .

Quand on relit la littérature concernant le Pondéral, publiée en tout cas avant que ne sévisse « la censure scientifique » dont se plaint en public son fabricant, on constate qu'il s'agit d'« une thérapeutique rationnelle de l'obésité » puisque « Pondéral augmente l'assimilation périphérique du glucose et accélère la métabolisation des lipides tout en diminuant leur synthèse ». Le rapprochement de ce texte (*Vidal 1974*, page 1306) avec les phrases décrivant le mécanisme d'action du Médiator permet de constater que la parenté des deux médicaments n'est pas que chimique. La similitude des axes promotionnels, qui a dû échapper à bien des prescripteurs, aurait-elle pour but d'installer sur l'orbite des antigraisses un coupeur d'appétit appartenant à une catégorie de plus en plus décriée et en voie de ne plus être remboursée par la Sécurité Sociale ? Quoi qu'il en soit, si le Médiator était capable, par une sorte de miracle, d'agir aussi bien sur les surcharges lipidiques que sur les surcharges glucidiques dont on connaît l'importance dans la genèse de l'athérosclérose, dans son extension et dans son aggravation, ce serait le médicament du siècle. Il

se vendrait dans le monde entier (ce qui n'est pas le cas) et ne serait pas oublié des principaux traités de pharmacologie.

La somnolence (qui était un effet secondaire curieux du Pondéral) se retrouve avec le Médiator. L'anorexie est évidemment très marquée, personne ne peut s'en étonner. Les douleurs abdominales, les nausées, les vomissements ne sont pas rares. Des vertiges et des intolérances cutanées ont cutanées ont été signalés.

Les dérivés de l'amphétamine ne doivent pas être associés aux IMAO (Marplan, Niamide, etc.), aux antidépressions tricycliques (Concordine, Laroxyl, etc.). La prise simultanée d'hormones thyroïdiennes est déconseillée.

Le Médiator est contre-indiqué en cas de grossesse et de pancréalite chronique. Sa parenté avec les amphétamines devrait rendre très prudent en cas d'hypertension artérielle, d'insuffisance cardiaque, et chez les sujets anxieux ou présentant des antécédents de suicide.

Peut-être le Médiator peut-il rendre des services dans le diabète avéré avec troubles lipidiques ? Il s'est montré capable de modifier certaines courbes d'hyperglycémie provoquée dans certains états prédiabétiques. On pourrait admettre ainsi qu'il intervient favorablement dans certaines hyperglycémies génératrices d'hypertriglycéridémie. Tout cela est du domaine de la spéculation intellectuelle et ne doit pas faire oublier l'importance primordiale du régime alimentaire dans les états de surcharge, ni la supériorité incontestée des normolipémiants comme le clofibrate (Athérolip et Lipavlon, Dabical, Clarésan et Clofibral).

Le fabricant recommande, en traitement d'attaque, un comprimé à chacun des 3 principaux repas. Par la suite, la posologie peut être abaissée à 2 comprimés quotidiens, parfois 1 seul.
Laboratoire Servier : 45 Orléans-Gidy, BP 2019, 45010 Orléans Cédex.

MÉDIOSTAT — II.C.1

Antihypertensions réserpiniques

voir : TENSID

MÉDOCOCCINE — II.A.1

Antalgiques externes

BRITISH MEDICAL JOURNAL VOLUME 283 3 OCTOBER 1981

PAPERS AND SHORT REPORTS

Pulmonary hypertension and fenfluramine

J G DOUGLAS, J F MUNRO, A H KITCHIN, A L MUIR, A T PROUDFOOT

Abstract

Pulmonary hypertension developed in two women who had been taking fenfluramine for over eight months for weight reduction. On withdrawing the drug symptoms and electrocardiographic evidence of pulmonary hypertension disappeared in both cases. In one patient, however, the evidence recurred after rechallenge with fenfluramine.

These findings are strong evidence that fenfluramine may cause pulmonary hypertension. Hence any patient taking the drug should report immediately any deterioration in exercise tolerance.

Introduction

Fenfluramine is an anorectic drug widely prescribed for obesity. Adverse effects include dry mouth, drowsiness, lethargy, nausea, diarrhoea, nightmares, and depression, particularly after sudden withdrawal.[1,2] Aminorex fumarate, which is chemically related, has been associated with pulmonary vascular hypertension[3,4] but there are no reports implicating fenfluramine. We describe two patients in whom pulmonary hypertension was associated with fenfluramine.

Case 1

A 26-year-old nurse presented in May 1975 with a two-month history of increasing breathlessness and tiredness. She had had two episodes of exertional syncope together with mild exertional chest pain and by the time of admission was unable to walk more than 50 m on the flat. In 1964 and 1969 she had been admitted for diarrhoea secondary to chronic ulcerative pancolitis and since then had received courses of iron for recurrent anaemia. For nine months before admission she had been taking fenfluramine 160 mg daily, having completed an 18-month course only six months before the start of the second course. One month before—that is, about four weeks after her symptoms began—she had also started an oral contraceptive (norethisterone 1 mg and mestranol 0·05 mg per tablet). She had not taken any oestrogen or progesterone preparation before.

On admission she weighed 61 kg and had bilateral ankle oedema. Jugular venous pressure was raised 3 cm and a right ventricular heave was noted. The pulmonary second sound was greatly accentuated, and a soft ejection systolic murmur was audible at the lower left sternal edge. The electrocardiogram showed right axis deviation with P pulmonale and changes compatible with right ventricular hypertrophy and strain (fig 1). A chest x-ray picture showed prominence of the main pulmonary arteries but the heart shadow was normal. Lung volume measurements were normal but the $Tc_{L}o$ was reduced to 5·01 mmol/min/kPa (14·96 ml/min/mm Hg) (predicted normal 8·79 ± 1·44 mmol/min/kPa; 26·24 ± 4·30 ml/min/mm Hg). A perfusion lung scan using ^{99m}Tc macroaggregates and a ventilation scan using ^{133}Xe were normal. Right heart catheterisation showed the pulmonary artery pressure to be raised at 50/20 (mean 32) mm Hg, but the mean "wedge" pressure was only 9 mm Hg. Pulmonary angiography showed slight enlargement of the main pulmonary arteries with possible exaggerated tapering of the pulmonary vasculature but with no abrupt vessel cut-off.

Fenfluramine and the oral contraceptive were stopped and she was given thiazide diuretics. Three weeks later her symptoms had disappeared and she was able to go dancing. The pulmonary second heart sound was less accentuated and no cardiac murmurs were audible. One year after presentation her chest x-ray picture had returned to normal and the electrocardiogram was within normal limits (fig 1). Repeat right heart catheterisation showed a pulmonary artery pressure of 19/5 (mean 11) mm Hg.

Case 2

A 45-year-old housewife weighing 98·4 kg was referred for weight reduction in August 1978. One year before she had been given fenfluramine and lost 4·5 kg without obvious ill effects. She had regained weight, however, despite simple dietary restriction. Systematic inquiry and clinical examination showed nothing abnormal, blood pressure was 130/80 mm Hg, and a chest radiograph and electrocardiogram (fig 2) were normal. The serum thyrotrophin concentration

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oedema, many factors make it unreliable, such as differences in body position, level of inspiration, tube-to-object distance, current and voltage, and the existence of prior lung disease. Furthermore, we have noticed that the *x*-ray appearances may lag behind the clinical state of the patient, as judged by respiratory function, by as much as 36 hours during both the development and the resolution of pulmonary oedema. A more accurate diagnosis may be made by using lung functions such as the alveolar-to-arterial oxygen-tension gradient or the shunt fraction, which would be easy to measure with a pulmonary artery catheter in place.

Secondly, although the patients in the Brighton study had normal serum albumin concentrations, this is only one determinant of the colloid osmotic pressure, accounting for 65-70%.[2] The remaining 30-35%, comprises the other serum proteins and any colloidal fluids used in therapy. Moreover, temperature elevation, pH, position of the patient, and anticoagulant therapy may all affect the colloid osmotic pressure, and the application of a tourniquet to collect the blood sample will increase the measured value. Therefore it would be more accurate to measure the actual colloid osmotic pressure from an arterial or central venous blood sample. The colloid osmotic pressure has been shown to fall, often dramatically, in patients with acute myocardial infarction with circulatory shock,[3 4] and the majority of patients with normal hydrostatic (pulmonary capillary wedge) pressures but with low colloid osmotic pressure have developed pulmonary oedema.

Thirdly, one has to interpret the measured hydrostatic pressures with care. If the transducer is placed at the level of the sternal angle, and the catheter tip is in the dependent region of the lung, as it often is, there may be a hydrostatic pressure difference of 20 cm H_2O, equivalent to about 15 mm Hg. The value obtained for the pulmonary artery end-diastolic pressure would be an underreading by this amount for the dependent region of the lungs, and it is there that the oedema often forms. Furthermore, the use of the pulmonary artery end-diastolic pressure as an index of left atrial filling pressure may not be accurate in these clinical circumstances. It has been shown that the pulmonary vascular resistance rises early in the formation of pulmonary oedema with different causes, and this creates a gradient between the pulmonary artery end-diastolic and the pulmonary capillary wedge pressure.[5] Therefore if clinical pulmonary oedema is present, the pulmonary artery end-diastolic pressure may give a higher reading than the left atrial filling pressure. In this situation the pulmonary capillary wedge pressure would be a more accurate representation of the left atrial filling pressure.

I completely agree with the authors that careful pressure monitoring is important in the management of these patients, and therefore feel that attention to detail in these respects may improve the outcome for these critically ill patients.

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Pulmonary hypertension and fenfluramine

SIR,—I read with interest the paper by Dr J G Douglas and others (3 October, p 881), in which the authors seek to demonstrate a parallel between fenfluramine and aminorex in the pathogenesis of pulmonary hypertension. Cardiopulmonary pathology resulting from the use of aminorex appeared as an epidemiological phenomenon shortly after the drug was marketed. Aminorex is an aminooxazoline, unlike fenfluramine, which is a phenylethylamine; contrary to the authors' statement, the compounds are not chemically related.

On the two cases reported, I should like to offer the following observations. In the first case the patient was a non-obese woman (61 kg) taking a large dose (160 mg/day) of fenfluramine nearly three times that usually recommended for mild obesity (60 mg/day). The admission to hospital occurred four weeks after she first started to take oral contraceptives. The disappearance of her symptoms was temporally related to administration of the thiazide diuretic as well as withdrawal of the oral contraceptive and fenfluramine. In the second case the woman was also being treated for hypothyroidism. The findings on cardiac catheterisation indicated a global cardiac insufficiency, with left and right heart failure. She received bendrofluazide and this may well have been the major contribution to the improvement in her symptoms, rather than withdrawal of the drug.

Oral contraceptives have been implicated in the aetiology of pulmonary hypertension in young women,[1 2] and pulmonary hypertension has been described in obese patients without significant alveolar hypoventilation, reflecting left ventricular insufficiency.[3-5] In both cases reported, a known aetiological factor for pulmonary hypertension and an immune disease (ulcerative pancolitis, hypothyroidism with thyroid antibodies) was present.

The relevance to man of the observations in dogs by Engelhardt *et al*[6] is doubtful, and Prime[7] showed the stability of pulmonary pressure in man following administration of fenfluramine for up to three months. It is noteworthy that no cases of this nature have been previously published since the drug was first marketed in 1963, and the relationship between pulmonary hypertension and fenfluramine in the two cases described is by no means clear.

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Tricyclic antidepressant poisoning and prolonged external cardiac massage during asystole

SIR,—I am grateful to Drs D A Orr and M G Bramble for their article emphasising the potential for resuscitation from tricyclic antidepressant overdose even after prolonged periods of asystole (24 October, p 1107). I am, however, somewhat concerned that their comment, "Asystole caused by a drug overdose does not carry the same prognosis as asystole secondary to acute myocardial infarctions," might suggest less heroic efforts in resuscitating patients with organic heart disease. We know that life-threatening arrhythmias complicating angina pectoris or acute infarction do not necessarily predict long-term survival and need not correlate with the extent of myocardial damage—possibly the best long-term prognostic factor.[1]

I have personally resuscitated a patient with acute myocardial infarction after two hours of asystole. His subsequent course in hospital was uneventful and he has returned to a vigorous lifestyle without brain damage. The presence of extensive cardiopulmonary disease, advanced age, malignancy, etc might well suggest less heroic resuscitation measures; however, since the majority of patients we will see with asystole or other malignant arrhythmias will probably have ischaemic heart disease, not tricyclic drug overdose, we must be committed, within reason, to salvage as many of these lives as possible. The Seattle experience certainly indicates the potential for aggressive resuscitation efforts.[2] We must also not forget other young adults with "healthy myocardiums"—for example, victims of mitral valve prolapse, coronary artery spasm, electrocution, and others who die suddenly—whose potential for recovery mandates intensive efforts in resuscitation. These efforts may save many useful lives, and even ultimately unsuccessful efforts at resuscitation might provide badly needed organ donors to salvage other young lives from the suffering of blindness, renal failure, congestive heart failure, and other diseases amenable to transplantation therapy.

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Non-steroidal anti-inflammatory drugs and frusemide-induced diuresis

SIR,—I was interested in the three case reports of Drs A C Yeung Laiwah and R A Mactier (12 September, p 714) relating to use of ibuprofen and naproxen in older patients with congestive heart failure and diuretic therapy. They describe the antagonistic effect on the diuretic by these non-steroidal anti-inflammatory drugs. They rightly point out that this effect is likely to be seen in patients in whom renal prostaglandins assume clinical importance (for example, those with compromised renal function, systemic lupus erythematosus, severe cardiac failure, etc). They conclude that non-steroidal anti-inflammatory drugs should be avoided in such patients.

Although no one will disagree with this suggestion, it is worthy of note that one such non-steroidal anti-inflammatory drug, sulindac, may not have this deleterious effect. Sulindac is considered a pro-drug since it is absorbed in its inactive sulphoxide form. Only the reduced sulphide is effective in inhibiting prostaglandin synthesis. Although it is well recognised that the precise relationship between prostaglandins and renal function is controversial,[1] Ciabattoni and colleagues have shown that the renal prostaglandin system is probably not inhibited by sulindac in humans at doses which inhibit platelet cyclo-oxygenase.[2] Likewise, sulindac has a paradoxical effect in Bartter's syndrome, a condition that responds to other non-steroidal

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ORIGINAL ARTICLES

Transcutaneous ultrasound measurement of blood-flow in internal mammary artery to coronary artery grafts

D. P. DE BONO N. J. SAMANI T. J. SPYT T. HARTSHORNE
A. J. THRUSH D. H. EVANS

Transcutaneous doppler ultrasound was used to examine internal-mammary-artery (IMA) blood-flow in 26 patients with IMA coronary bypass grafts. The ungrafted right IMA could be seen in all of 19 patients, the grafted left IMA in 16 of 26, and the grafted right IMA in 3 of 7.

The velocity profile recorded from the proximal part of the grafted IMA is distinct from that of an ungrafted artery, with a systolic peak which reflects graft capacitance in the face of high intramyocardial resistance, and a diastolic peak which represents graft conductance when intramyocardial resistance is low. Total graft blood-flow can be estimated from the mean velocity and the measured vessel diameter; resting flows ranged from 22 to 79 ml/min. In recently grafted patients, resting graft blood-flow correlated with myocardial "run-off" estimated from preoperative arteriograms; graft blood-flow increased appropriately with exercise.

This simple, non-invasive technique to measure IMA graft blood-flow may find applications for routine postoperative follow-up of patients with IMA grafts and for studies on the physiology and pharmacology of coronary artery blood-flow.

Lancet 1992; **339**: 379–81.

Introduction

The internal mammary (or internal thoracic) artery is now the preferred source for bypass grafts to the left anterior descending coronary artery.[1,2] In some patients, the right internal mammary artery (IMA) may also be used as a graft to the right or circumflex coronary arteries. A simple, repeatable, and non-invasive technique to assess IMA graft blood-flow would be useful for clinical follow-up of patients with such grafts, and for the study of coronary physiology and pharmacology. Duplex ultrasound has been extensively used to measure blood-flow in peripheral and cerebral blood vessels;[3] we describe use of this technique in the assessment of IMA graft function.

Patients and methods

26 consecutive patients (25 men, 1 woman) were studied as part of routine follow-up in a cardiology clinic at intervals from 6 weeks to 12 months after coronary artery bypass surgery in which at least one IMA was grafted. Informed consent was obtained and the study was approved by the local ethics of medical research committee.

The proximal IMA was imaged with transcutaneous ultrasound by use of a 7·5 MHz mechanical sector probe with 3 MHz offset doppler (Diasonics, Bedford, UK). The two transducer positions used were lateral to the upper sternal margin just below the clavicle, and above the clavicle with the ultrasound beam angled downwards and forwards. For intracoronary doppler studies we used a monorail 20 MHz catheter tip transducer (Schneider, Beulach, Switzerland) during routine coronary angiography.

Preoperative coronary arteriograms were recorded on 35 mm cine-film and reported according to the Green Lane (Auckland) semi-quantitative analysis scheme,[4] which assigns a "myocardial score" for the distribution of individual vessels as well as incorporating an assessment of the degree of stenosis. From the original reports of the preoperative arteriograms we aggregated myocardial scores for all vessels supplied by the IMA graft downstream of the principal native vessel stenosis: for example, a sequential graft to the left anterior descending and two diagonal coronary arteries would aggregate the myocardial scores of all these vessels. The myocardial score was modified to take account of competing native coronary flow by multiplying the score by 1 in the case of total proximal occlusion, by 0·5 if proximal occlusion was by a single stenosis of or below 70% normal vessel diameter, and by 0·75 if the proximal stenosis showed more than 70% occlusion but was not complete. This "run-off" score was compared with measured IMA graft flow.

Statistical comparisons were made with the Mann Whitney test, Wilcoxon's test for paired observations, and Spearman's correlation coefficient. Results are presented as median (range) for flow data, and as mean (standard deviation) for vessel diameter and flow per beat, for which data distribution was close to a normal distribution.

ADDRESSES: **Departments of Cardiology** (Prof D. P. de Bono, MD, N. J. Samani, MRCP), **Surgery** (T. J. Spyt, FRCS), **and Medical Physics** (T. Hartshorne, A. J. Thrush, MSc, D. H. Evans, PhD), **University of Leicester, Leicester, UK**. Correspondence to Prof David de Bono, Clinical Sciences Wing, Glenfield General Hospital, Leicester LE3 9QP, UK.

We suggest that our patient had a dissection of the vertebral artery due to the violent neck movements associated with the scrambler. Although our patient anticipated temporary dysequilibrium and nausea from the scrambler, she had not thought that these might be longlasting effects. This very rare complication of amusement park rides might be prevented by avoiding excessive neck movements.

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Pulmonary hypertension and dexfenfluramine

SIR,—Dexfenfluramine is used as adjuvant therapy for obesity. Pulmonary hypertension has been described with D, L-fenfluramine but not with the pure D-isomer, dexfenfluramine.

A 30-year-old woman was admitted to hospital at 34 weeks' gestation. She had no history of cardiac or respiratory disease. She had taken dexfenfluramine for six months between July, 1989, and March, 1990, and stopped after reaching her desired body weight. In March, 1990, shortly before she became pregnant, and while on holiday 800 m above sea level, the patient complained of reduced exercise tolerance with dyspnoea and tiredness on the slightest exertion. Echocardiography before the onset of pregnancy had revealed a slightly dilated right ventricle.

The patient was admitted because of early uterine contractions but examination revealed severe dyspnoea and a respiratory rate of 28/min. There was loud pulmonary component of the heart sound and a pansystolic murmur at the left sternal border compatible with tricuspid regurgitation. She had a regular heart rate of 96/min, her blood pressure was 100/70 mm Hg, and she had increased jugular venous pressure. Arterial blood gas analysis was pH 7·53, pCO_2 2·79 kPa, pO_2 8·86 kPa, and an arterial oxygen saturation of 95% on room air. Electrocardiography demonstrated sinus rhythm and an incomplete right-bundle-branch block, and on chest radiography moderate enlargement of the right ventricle was seen. Electrocardiography disclosed advanced dilatation of the right ventricle. The pulmonary artery pressure was 84 mm Hg above right atrial pressure, and there was mild tricuspid valve incompetence. A ventilation-perfusion scan did not demonstrate pulmonary embolism.

Elective caesarean section was done under epidural anaesthesia, which was haemodynamically well tolerated. Pressures (mm Hg) during the procedure were: mean pulmonary artery (PAP) 44–59, mean systemic arterial 56–85, central venous 12–18, and pulmonary capillary wedge 15–25. Cardiac index ranged from 1·56 to 2·13 l/min per m^2. Calculated pulmonary vascular resistance (PVR) was 542–858 dyn/s per cm^5. Postoperatively her pulmonary hypertension worsened and did not respond to prostaglandin E_1 or diuretic therapy (PAP 52–77 mm Hg, PVR 551–1231 dyn/s per cm^5). On day 3 she had a cardiac arrest and on day 4 she died in right ventricular failure. Necropsy revealed right heart hypertrophy and plexogenic pulmonary arteriopathy.

Primary pulmonary hypertension predominantly affects women of childbearing age and often gets worse during pregnancy.[1] A relation between anorectic drugs and pulmonary hypertension has been known for a long time and three cases of pulmonary hypertension in women taking fenfluramine have been described. In two patients, pulmonary hypertension resolved upon withdrawal of the drug, but it reappeared in one of them after reingestion of fenfluramine.[2] Another case of pulmonary hypertension resistant to therapy was described after fenfluramine ingestion for several months.[3] Dexfenfluramine is thought to have few side-effects (sedation, lethargy, and dry mouth in the short term[4] and no extra risks during long-term therapy[5]). Fenfluramine and dexfenfluramine are related to amphetamine, and both sympathomimetic and serotoninergic effects of the pulmonary vascular system are to be expected. Serotonin was responsible for the development of pulmonary hypertension in animal studies with anorectic drugs.[6] Apart from two cases reported to the French Centre for drug control pulmonary hypertension associated with dexfenfluramine has not been recorded. In the fatal case reported here the evidence suggests that the sequence of dexfenfluramine intake, followed by a stay at moderate altitude, and subsequent pregnancy triggered irreversible primary pulmonary hypertension. The indication for dexfenfluramine has been questioned in a *Lancet* editorial[7] because the drug adds little to other weight-reducing measures. Even if anorectic agents only rarely cause or contribute to the development of pulmonary hypertension, it seems reasonable to advise that they are not tried until all other measures have been exhausted.

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SIR,—Drug-induced pulmonary hypertension has been associated with phenformin, but anorectic drugs such as aminorex and fenfluramine[1-5] have been more frequently involved. We report reversible pulmonary hypertension caused by dexfenfluramine.

A 26-year-old woman was referred to our hospital in October, 1990, with pulmonary hypertension, and no significant medical history before January, 1990. She had taken dexfenfluramine from December, 1989, to January, 1990, at a daily dose of 15–30 mg. She had never taken any other medication. She experienced exertional dyspnoea and palpitations toward the end of January, 1990. Because nasal plastic surgery was scheduled, she underwent a medical examination in February, 1990. An electrocardiogram showed signs of cor pulmonale; both pulmonary arteries were enlarged on standard chest radiography but computed angiography showed no pulmonary embolism. The surgery was done in April, 1990. Because her dyspnoea had worsened, she was re-examined in July, 1990. She had a pulmonary regurgitant murmur and a split second heart sound; chest radiography was normal; an electrocardiogram still showed signs of cor pulmonale. Catheterisation studies pointed to primary pulmonary hypertension, at which point the patient was referred here but she did not consult us until October, when she no longer had either dyspnoea or palpitations, and no abnormality of the respiratory or cardiovascular systems was found during physical examination. Chest radiography showed a mild enlargement of pulmonary arteries. Electrocardiogram, arterial blood gases, and lung function were normal, as was a perfusion lung scan, conventional pulmonary angiography, and phlebocavography. Catheterisation studies (cardiac output 7·4 l/min in October) were:

Date	Pulmonary artery	Capillary wedge	Right ventricular
July	82/27 (50)	5	85/0
October	34/5 (14)	5	32/0

Pressures (mm Hg) as systolic/diastolic (mean).

Use of aminorex in Germany, Switzerland, and Austria between 1967 and 1970 was followed by a 20-fold increase in the incidence of

pulmonary hypertension, which decreased when the drug was withdrawn. 2% of patients taking the drug had pulmonary vascular disease mimicking primary pulmonary hypertension. Suggested mechanisms were release of catecholamines or serotonin, the drug resembling adrenaline and amphetamine. Fenfluramine-induced pulmonary hypertension was described from 1981.[1-5] The pulmonary hypertension in the patient described here was probably due to dexfenfluramine. Other causes are unlikely: oral contraception had been stopped 2 years before the first symptoms; there was no evidence of autoimmune disorder;[1] and pulmonary angiography was normal. Re-challenge would have been unethical.

Our patient took dexfenfluramine for only 2 months and symptoms developed after 1 month. In fenfluramine-induced pulmonary hypertension the duration of treatment was 7 months to 6 years and first symptoms developed up to 1 year after the end of treatment. Pulmonary hypertension associated with fenfluramine[1-5] usually reversed when the drug was withdrawn, whereas in primary hypertension of unknown aetiology the clinical course is less favourable.[3] D,L-fenfluramine and D-fenfluramine (dexfenfluramine) share serotoninergic effects and may well therefore have some side-effects in common. The incidence of pulmonary hypertension among patients taking these widely used drugs must be very low, since so few cases have been reported. Nonetheless, patients taking dexfenfluramine or fenfluramine should be advised to report any shortness of breath.

Supported by a grant from AERE.

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Influence of ethanol on toxicity of paraquat and *Amanita phalloides*

SIR,—Dr Ragoucy-Sengler and colleagues (Dec 7, p 1461) reported the unexpected survival of three patients after severe paraquat intoxication. The outcome of paraquat poisoning is largely determined by the ingested dose. According to the Yamaguchi index (based on serum concentrations of potassium, bicarbonate, and creatinine and on time since ingestion of paraquat),[1] and to the Proudfoot curve (serum paraquat concentration/time after injection),[2] fatal outcome for these cases was predicted; they were all chronic rum drinkers who drank 80 g ethanol daily. Ragoucy-Sengler et al suggested that an ethanol-induced increase in cupro-zinc superoxide dismutase could protect against free-radical damage due to paraquat.

We draw attention to an equally puzzling protective effect of ethanol in poisoning with the mushroom *Amanita phalloides* (death cap). In mice injected with lethal doses of a lyophilisate from *A phalloides*, survival was greatly increased by single doses of ethanol applied 30 min before or 5 min after mushroom injection.[3] Hepatic histopathological damage (confluent necrosis) was largely prevented. Ethanol might interfere with the uptake of mushroom toxins into liver cells, either by blocking receptors or a transport system, or by causing structural disorders of membrane lipids limiting permeability and thus inhibiting entry of toxins into cells. The inhibition of toxicity by ethanol may help to explain inconsistencies in mushroom intoxication and in responses to therapy, as well as the fact that the mortality from death cap intoxication is much higher in children than in adults.[4]

These observations for paraquat and *A phalloides* suggest that the consumption of alcoholic beverages should be taken into account if the outcome of poisoning is other than expected for the toxin dose, and in evaluation of therapeutic measures. A common feature of the ethanol effect in different types of poisoning could be lipid peroxidation, which is known to take place through a free-radical-mediated mechanism after high doses of ethanol, leading to membrane derangement and diminished cellular toxin uptake. Accordingly, the seemingly paradoxical diminuition by ethanol of the damaging effects of other toxins may be a more general occurrence.

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Teratogenicity of misoprostol

SIR,—Dr Schönhofer (June 22, p 1534) and Dr Fonseca and colleagues (July 6, p 56) refer to five Brazilian newborn babies with congenital malformation after alleged maternal use of misoprostol as an abortifacient during the first trimester of pregnancy.

In Porto Alegre, Brazil, we have a nationwide teratogenic information system, the only one operating in the country, that provides counselling to women or their doctors about the teratogenic risks in relation to exposure. Since 1990, 29 pregnant women called our service seeking counselling after unsuccessful use of misoprostol as an abortifacient during the first trimester of gestation. The doses taken ranged from 1 tablet (200 µg) to 56 tablets, the mean number being 20 tablets. These pregnancies were followed by ultrasonography during the second and third trimesters. All patients were asked about the use of other drugs and a special questionnaire was administered to detect further genetic or environmental risks in each case. 3 of these 29 pregnancies ended in second-trimester spontaneous abortion, 3 mothers are still pregnant, and we have lost contact with 6 others. Of the remaining 17 livebirths, we examined 8 of the babies; in 4 cases we obtained information from the paediatrician and in 5 we had only verbal information from the mother.

No major malformations were found in these 17 babies. 1 of them had a preauricular tag. Although we are aware that further epidemiological studies are needed, our preliminary data do not support the hypothesis that misoprostol is teratogenic in man.

We thank Hernando Augusto Clavijo, Roberto Giugliani, Carmem Maria Vinhas Santos, Fernando Recis, Erica Tatto, Fabricio Costa, Vee Wong, Karim Boianovsky, and Fernando Thode for their collaboration.

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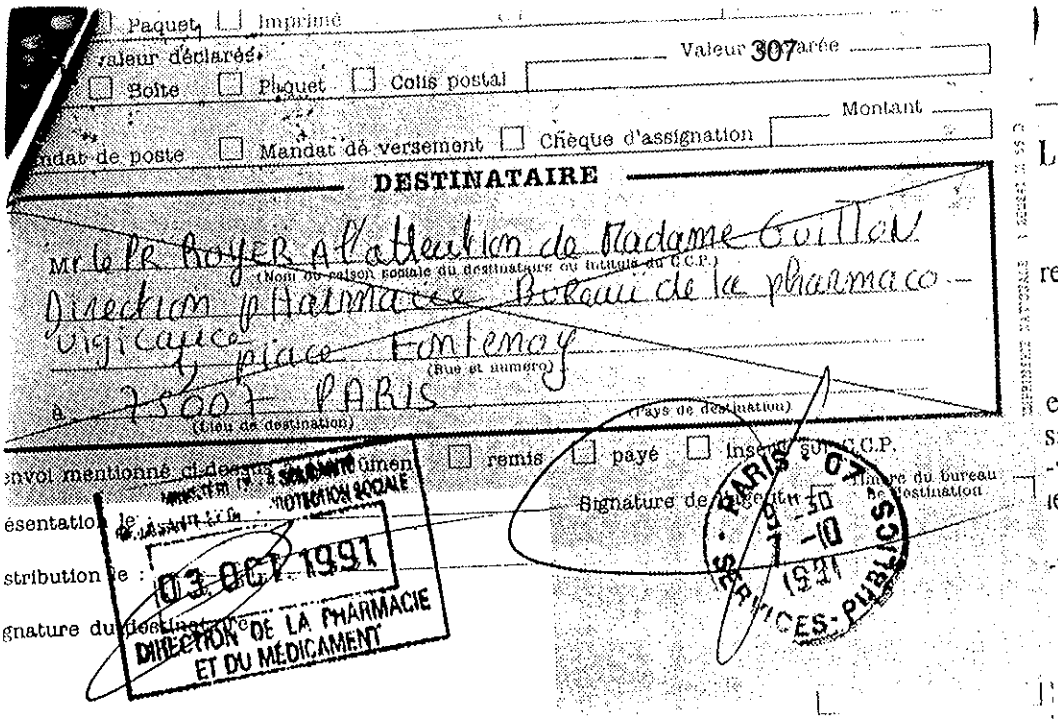
Azithromycin for cerebral toxoplasmosis

SIR,—A 30-year-old man had cerebral toxoplasmosis during the third week of intravenous pentamidine therapy for histologically proven *Pneumocystis carinii* pneumonia (his first AIDS opportunistic infection). A double-contrast computed tomographic (CT) scan showed ring-enhancing lesions, and serum antibodies were positive for *Toxoplasma gondii*. He was successfully treated with pyrimethamine/sulfadiazine but a rash developed. Substituting clindamycin for sulfadiazine did not help, and it became apparent that he was allergic to pyrimethamine. On suppression therapy with sulfadiazine alone he manifested allergy to this agent too. On stopping all medication, the toxoplasmosis relapsed, complete remission being again achieved by pyrimethamine/sulfadiazine but at the expense of life-threatening erythema multiforme. Secondary prophylaxis was instituted with doxycycline, but 10 weeks later the patient again relapsed with multiple ring-enhancing lesions. Clindamycin was added to



DE PARIS

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ERVICE DE PNEUMOLOGIE
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Mon Cher Collègue,

Plusieurs faits concernant Pondéral et Isomeride sont récemment survenus. Je voudrais par cette lettre les signaler au Comité National de Pharmaco-Vigilance.

1) Du fait de notre spécialisation dans la circulation pulmonaire, nous recevons de toute la France pour avis diagnostique et thérapeutique de très nombreux patients atteints d'hypertension artérielle pulmonaire primitive (HTAPP). Ces malades sont soumis à un interrogatoire précis et prospectif appréciant en particulier chez eux la prise d'anorexigènes. Nous avons ces dernières semaines terminé l'examen des dossiers de 127 patients atteints d'HTAPP que nous avons explorés durant la période 1980-1991. Il s'avère que 20 femmes sur 79 ont utilisé des coupe-faim ; dans 9 cas il s'agissait d'Isomeride et/ou de Pondéral.

2) L'interrogatoire des derniers cas montre que l'apparition ou l'aggravation des signes fonctionnels de dyspnée parait coïncider dans le temps avec la prise d'anorexigènes, en l'occurence la prise d'Isomeride.

Ces observations ont été signalées au Docteur Laurent PERRET du Laboratoire Servier en lui précisant le nom des patientes pour qu'il puisse tenir à jour le registre des cas qui ont pu lui être signalés.

Je voulais signaler ces faits à votre commission, bien que, à nos yeux, ceux-ci ne permettent pas d'établir scientifiquement une relation de cause à effet.

Je suis à votre disposition pour vous donner tous les renseignements que vous jugerez nécessaires sur ces données et observations et pour participer à toutes les actions que les organismes publics voudraient entreprendre sur ce sujet.

Je vous prie de croire, Mon Cher Collègue, à l'expression de mes meilleurs sentiments.

Professeur P. DUROUX

Annexe 1-45

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Docteur L.PERRET

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18 SEP. 1991

Monsieur le Président
de la Commission Nationale de Pharmacovigilance
Bureau PH 13
Direction de la Pharmacie et du Médicament
Ministère de la Santé

Courbevoie, le 16 septembre 1991

Monsieur le Président,

Le Professeur Pierre DUROUX, Chef du Service de Pneumologie et de Réanimation Respiratoire à l'Hôpital Antoine-Béclère à Clamart, et ses collaborateurs ont récemment procédé à une étude rétrospective des observations d'hypertension artérielle pulmonaire examinées dans leur service durant la période 1980-1991.

Cette étude rétrospective a montré dans la population féminine une proportion importante de patientes ayant utilisé des médicaments contre leur obésité (20 cas sur 79). Dans 9 cas sur 20, il s'agissait de PONDERAL ou d'ISOMERIDE.

PONDERAL (DL-Fenfluramine) est sur le marché en France depuis 1962 et est largement diffusé dans le monde. Quelques cas d'hypertension artérielle pulmonaire ont été observés à partir de 1980 (publication de DOUGLAS et coll. en 1981) et nous avons en conséquence amendé l'information au prescripteur pour signaler ces observations.

.../...

ISOMERIDE (D-Fenfluramine) a été mis sur le marché en France en 1985. En l'absence d'observations de cas d'hypertension artérielle pulmonaire au cours du développement clinique, compte tenu de la dose moindre administrée, et du profil d'effets indésirables différent (certains effets indésirables du racémique pouvant être attribués au dérivé lévogyre), l'information destinée au prescripteur ne comporte pas (présentement) de mention d'hypertension artérielle pulmonaire.

Les observations du Professeur P. DUROUX et les notifications spontanées nous ont incité à étudier cette question sur un plan épidémiologique.

En première analyse, il apparaît que l'incidence de ces cas ramenée au volume de prescriptions du médicament est extrêmement faible. Le bilan présenté par le Professeur DUROUX est purement rétrospectif et n'a par conséquent qu'une valeur épidémiologique relative. L'interrogatoire des patientes (à la recherche de médicaments amaigrissants) est très orienté et il n'y a pas de groupe contrôle, ce qui introduit un biais d'observation important.

Il y a quelques jours, plusieurs journaux suisses ont publié des informations alarmistes et en partie erronées sur cette question. En juillet 1991, nous avons décidé, en concertation avec les autorités sanitaires suisses, de modifier l'information au prescripteur de notre spécialité ISOMERIDE à la suite d'un rapport de pharmacovigilance, et sans que l'imputabilité du cas ait pu être établie.

Nous souhaiterions vous présenter et discuter avec vous au cours d'une réunion, les faits tels qu'ils se présentent aujourd'hui, et sommes à votre disposition à la date que vous voudrez bien nous fixer.

Dans cette attente, nous vous prions de recevoir, Monsieur le Président, l'expression de notre haute considération.

L. PERRET
Directeur Recherche et Développement

Annexe 1-46

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

ANTOINE BÉCLÈRE

Clamart, le 27 Février 1992

Monsieur le Professeur LAGIER
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Cher Monsieur,

Je vous fais parvenir l'ensemble du dossier que nous avons à notre disposition concernant la Fenfluramine et la Dexfenfluramine ainsi que les différents cas d'hypertension pulmonaire rapportés.

Nous sommes pour notre part assez inquiets de la fréquence des cas observés, en particulier dans notre série d'hypertensions pulmonaire. Notre centre est un centre de référence concernant l'hypertension artérielle pulmonaire ; depuis 4 ans, nous avons pu étudier 80 cas de cette maladie dans la population de femmes de 20 à 60 ans qui sont susceptibles de prendre de l'Isoméride. Parmi ces 80 cas, 12 patients avaient pris de l'Isoméride avec, dans 9 cas, une constitution ou une aggravation manifeste des symptômes lors de la prise du médicament.

Il existe 2 autres cas récents publiés dans le Lancet que je vous joins à notre Abstract envoyé à VIENNE. D'autre part, je suis au courant de plusieurs autres cas en FRANCE dont 2 récents, un à LYON et un en Cardiologie au VAL-de-GRACE.

Il est difficile de ne pas suspecter une relation de cause à effet entre la prise de Dexfenfluramine et de Fenfluramine et la constitution ou l'aggravation de l'hypertension pulmonaire. Nous sommes d'autant plus inquiets que, dans notre série, il n'existe pas de régression à l'arrêt du médicament comme cela a d'ailleurs été rapporté lors de l'épidémie d'Aminorex en SUISSE vers les années 60.

Le rôle des anorexigènes est sûrement complexe. D'une part, parce qu'il s'agit d'une maladie extrêmement rare et d'autre part, parce que les anorexigènes interviennent sûrement comme facteur déclenchant d'une maladie sous-jacente plus que comme seul facteur causal. D'autres facteurs tels que génétiques sont sûrement impliqués dans cette maladie, mais une fois que la maladie est constituée, l'arrêt du médicament ne permet pas forcément la diminution des symptômes et de l'hypertension pulmonaire.

Annexe 1-46

Le problème nous apparaît donc relativement sérieux du fait de la gravité de cette maladie et de la fréquence de la prise de ces médicaments actuellement en FRANCE. Mr DUROUX avait alerté la Pharmacovigilance vers le mois de Septembre-Octobre 1991, nous n'avons eu aucune réponse des autorités compétentes pour savoir ce que devenait le dossier et ce qu'il avait été décidé de faire.

Dans le cas où le Service de Pharmacovigilance continuerait donc à autoriser la prescription libre de ce produit, nous essayerons pour notre part de faire une étude cas-témoins pour essayer d'évaluer avec plus de précisions l'augmentation du risque relatif par ce médicament. Si bien sûr ce médicament doit être retiré du marché dans les prochains mois, nous ne nous lancerons pas dans cette étude de cas-témoins et donc nous aimerions avoir votre sentiment sur l'attitude à avoir.

En espérant obtenir une réponse rapide sur toutes ces incertitudes et sur la conduite à tenir dans les prochaines semaines, je vous prie de croire, Monsieur, à l'expression de mes sentiments les meilleurs.

Professeur G. SIMONNEAU

P.S. : copie de la lettre du mois de Septembre 1991 de Mr DUROUX

Protocol
International Primary Pulmonary Hypertension Study
(IPPHS)

December 1, 1992

1. BACKGROUND

Primary pulmonary hypertension (PPH) is a very rare disease. Its annual incidence is not known with accuracy [1] but is estimated to be around 1 per 500,000 inhabitants in countries like France or the U.S. [2]. However, if only the age categories 20-50 are considered, the incidence appears twice as high. Since the disease is more frequent in females, the annual incidence in 20-50 years old females could be closer to 1:200,000 or more, a still very rare phenomenon.

PPH is a very much unknown disease and epidemiological data are scarce. Except for few large case-series [3,4], there are no published epidemiological studies of the disease. As a matter of fact, the role of factors, such as age and sex, is only partially known and there is no consensus on the role of a series of factors such as the use of oral contraceptives, tryptophan, herbal diets, pregnancy, co-morbid states, systemic diseases, and others [3, 5-7]. A number of drugs have been suggested to play a role [8,9,10]. Some anorexigens have been associated with PPH since the epidemic of this disease which occurred in the early 60's where a high percentage of cases exposed to aminorex was reported [11]. Cases of primary pulmonary hypertension (PPH) have recently been reported in users of fenfluramine derivatives [12,13]. Besides, the exposure to drugs is rarely unique. Reported cases of PPH in Europe had been exposed to a variety of drugs, "fasting pills", amphetamines, thyroid compounds, and others. Underreporting of PPH cases exposed to drugs is likely to have occurred, as is generally the case in pharmacovigilance [14]. On the other hand, the suspicion that certain factors may play a role in the development of PPH is known by cardiologists and pneumologists and it has been suggested that some subjects suffering from pulmonary hypertension (PH) might be (wrongly) diagnosed as Primary PH as soon as an exposure to one of these factors is found.

Although some recent studies point out in the direction of an immunological [15] or genetic origin [16], they still remain to be confirmed. The fact that an epidemic of PPH is presently going on in HIV-infected individuals [17], and that women seem at a clearly greater risk for the disease than men [3] militate in favor of a complex phenomenon where genetic and immunologic factors might play an important role.

Indeed, the diagnosis of PPH is one of exclusion. The definition of the disease is unclear and many unexplained pulmonary hypertensions (PH) are wrongly classified as PPH without the necessary investigation for the diagnosis to be made. Exclusion of other causes of PH includes a number of steps which have been recently defined [1].

2. OBJECTIVES

2.1 General objectives

To contribute to an epidemiological understanding of primary pulmonary hypertension.

To quantitatively assess the role of several known or suspected risk factors in the development of primary pulmonary hypertension

2.2 Specific objectives

To assess the role of sex, age, obesity, medical history, concomitant illnesses, drugs, behavioral factors and exposure to selected environmental factors.

3. OVERVIEW OF THE STUDY

In order to reach these objectives, a case-control study will be conducted in five European countries (France, The United Kingdom, The Netherlands, Belgium and Switzerland) and Canada. One hundred cases and up to four matched controls will be recruited altogether, over a period of 18 months to two years. Cases will be recruited through the reporting of PPH patients by specialized centres to a local team in each country. Controls will be selected by a coordinating centre among the patients seen by the general practitioner of the case (physician-based controls) or, by default, among the patients of a physician practicing near the case's residence. Cases and controls will be interviewed by non-medically trained interviewers, face to face. Interviewers will be blinded to the objective of the study. An international coordinating centre located in Montreal (McGill University Jewish General Hospital) will monitor the study, process the data, and conduct the analysis.

4. RESULTS OF THE FEASIBILITY STUDY

Mortality data from France (INSERM) and The Netherlands indicate that approximately 20 individuals per 10 million inhabitants die each year with a primary or secondary diagnosis of PPH. Since the disease is thought to be fatal in 65-90% of the cases and taking into account possible errors in diagnosis (in both directions), it is believed that this is a conservative estimate of the incidence of the disease. The five countries altogether represent almost 150 million inhabitants. Applying the above estimate to this denominator, it is estimated that 300 cases are diagnosed each year in the five countries. Thus, the objective of recruiting 100 cases in two years would correspond to 16.6% of all the cases diagnosed during that period. The objective could be attained in 1 year if 1/3 of the cases were recruited.

One hundred and ten (110) Divisions of Pneumology and/or Cardiology of University Hospitals in France have received a letter asking them to participate in the study (two mailings). Seventy-eight of them (71%) have accepted and 1 has refused. The remainder have not responded. All the major centres have actually consented to participate, including the referring centres and transplantation centres. Of the respondents, 22 had seen no cases in the past year, 28 had seen 1 to 2 cases per year, and 9 had seen more than 2 cases per year. Nineteen (19) did not report the number of cases that they had seen.

A field feasibility study has been conducted during the month of May 1992 (4 weeks) in the Aquitaine region of France (around Bordeaux). This region represents a catchment population of approximately 4.2 million inhabitants. The heads of the divisions of Pneumology (3), Cardiology (8), Internal Medicine (6), Chest Surgery (2) and Intensive Care units (4) of the five University and Military Hospitals have been contacted in the region. Three (3) large private clinics were also surveyed. Finally, 32 local hospitals were contacted. They were all visited whenever they declared that they had diagnosed a PPH case in the preceding 16 months. Seventeen (17) cases were found. After applying the algorithm for case-ascertainment (see below), 7 cases were considered as meeting the inclusion criteria for the study. All the centres participated with enthusiasm to the feasibility study. Extrapolating these results, when applied to the whole of France, this figure would lead to 72 potential "validated" cases per year in this country.

Forty-two (42) private cardiologists and 18 pneumologists were randomly selected among the list of cardiologists practicing in the Aquitaine region. They were contacted by telephone. The objectives of this survey were: (i) to validate the patterns of referral of PPH cases seen by private cardiologists; (ii) to

possibly identify more cases of PPH that would have been missed in the hospital centres. Forty-one declared that they would refer a case of PPH for treatment and/or confirmation of diagnosis to a University Hospital, 9 to a private clinic and 10 to local hospitals. It was confirmed that most of these cases would however end up in a University Centre. These centres were among the 23 surveyed. Two potential cases of PPH had been seen by the private cardiologists in the 16 months preceding the interview. These 2 cases were among the 17 found in the survey of the University Centres.

The medical extraction form was tested on several occasions. A preliminary version had been used for the validation of the 17 cases reported in the Aquitaine area. The final version (see below) has been tested on 5 cases newly diagnosed at the Clamart Centre in France and in the U.K. It was found efficient and easy to use.

The mode of recruitment of controls (see below) has been tested with the same patients in France and the U.K. The general practitioners of the cases have been contacted by telephone. They all agreed to help in the recruitment of controls. The scarcity of the disease and the difficulties encountered with the diagnosis and treatment of these patients was declared as the main reason for trying to help.

In view of the result of the feasibility study, the International Scientific Board concluded that: (i) the recruitment of a sufficient number of cases (100) during a rather short period of time was a feasible hypothesis; (ii) the University Centres and some large private clinics were shown to be sufficient for catching the number of cases needed; (iii) the medical extraction form was appropriate.

5. METHODS

5.1 General considerations

The case control design was selected in view of the rarity of the disease at hand. A prospective cohort study was deemed not feasible. Because record-linkage databases are not available on a sufficiently large scale in the countries where the study will be conducted, the only choice left was to rely on the recruitment of cases through the reporting by clinicians. Besides, the necessity of very well defined conditions and procedures for the recognition of cases made it mandatory to obtain validated medical information which are less likely to be found in automated databases.

5.2 Cases

5.2.1 Case definition

The algorithm developed by Rich et al. [1] has been retained for the diagnosis of PPH (Appendix A). Primary pulmonary hypertension is defined as the presence of a mean pulmonary artery pressure greater than 25 mmHg at rest.

Given the total lack of a single clinical feature or laboratory test for the diagnosis, the diagnosis of PPH is achieved by exclusion of the following secondary causes:

- congenital abnormalities of the lungs, thorax and diaphragm,
- congenital or acquired valvular or myocardial disease,
- pulmonary thromboembolism (because this may be clinically silent, objective proof of absence is necessary),
- sickle cell anaemia,
- history of intravenous drug use,
- AIDS (but not HIV infection per se),
- obstructive lung disease,
- interstitial lung disease,
- central hypoventilation with hypoxemia and hypercapnia,
- definite collagen vascular disease (Lupus and others),

- parasitic disease affecting the lungs,
- pulmonary artery or pulmonary valve stenosis,
- pulmonary venous hypertension,
- active liver diseases.

5.2.2 Case-ascertainment

In order to exclude the above conditions, the following diagnostic tests results are mandatory and will be abstracted or copied from the medical records or asked to the clinicians in charge:

- chest X-ray,
- pulmonary function tests,
- lung perfusion scan,
- echocardiogram,
- cardiac catheterization (right mandatory),
- arterial blood gases

The following tests are found useful (but not mandatory):

- liver function tests - preferably a biopsy or any other diagnostic liver function tests that would exclude chronic hepatitis for instance,
- Anti-nuclear antibodies (ANA)
- CBC,
- left catheterization,
- HIV serology,
- pulmonary angiogram,
- sleep studies - oximetry, polysomnography,
- high resolution CT-SCAN.

Case ascertainment will be achieved on the basis of the data collected from medical charts with the Medical Extraction Form (Appendix B).

Only the cases with the mandatory procedures listed above will be

retained for the study. In addition, cases should be diagnosed as PPH for less than 3 months at the time of reporting (incident cases).

5.3 Controls

Up to four controls per case will be recruited and matched on age, sex, physician and number of visits to the physician per year.

5.3.1 Type of controls

Physician-based controls were chosen [18]. Several issues were considered in the choice of controls:

a) Minimization of selection bias

If hospital controls had been chosen, one must have ensured that the illness for which they were hospitalized is unrelated to exposure. Because the exposure factors of interest extend far beyond the unique effect of one single factor, i.e. several risk factors for PPH will be examined, it would be almost impossible with hospital controls to ensure that the selected control illnesses would be independent of all the risk factors to be considered. This would have excluded most chronic conditions and a number of acute conditions as well.

It was felt that if randomly selected community controls were chosen, they would be less likely to be exposed to a number of risk factors (drugs, other morbid status) than the population who consults physicians. Since the use of anorectics, contraceptives, and other risk factors under study lead to visits to physician, controls might underrepresent those exposures.

In hospital-based and in community controls, referral bias might occur that would have potentially an important impact on the results (in an unknown direction a priori).

b) Minimization of information bias

Cases are unlikely to be hospitalized for a long time after the diagnosis is made, except for a few instances. It is only after a variable time that their condition worsens to the point that they are hospitalized for long duration. Thus, they are unlikely to be interviewed in the hospital since the needed time for reporting of the case, case validation and interview might take between 2 and 4 weeks. This could lead to a non-comparability of information if cases were interviewed at home and if hospital-controls were selected and then interviewed at the hospital. Physician-based controls would be preferable in this regards. This will not control for another type of recall bias, that is if cases are most likely to remember exposure to drugs and other factors than controls. This will be dealt with in more details further below in the section on "exposure assessment".

c) Feasibility

Arguments of feasibility would a priori militate in favor of hospital-based controls. However, because of all the restrictions to be applied on the type of illness to be selected, the age groups considered (PPH is most likely to occur between 20 and 40 of age), the conditions of interview, it was felt that the gain in feasibility in the recruitment of hospital- vs physician- based controls might be seriously impaired. It was felt that the feasibility would be even greater with physician-based controls.

5.4 Matching

Age and sex are known to be associated both with the outcome (PPH) and with exposure to suspected risk factors (O.C., pregnancy, exposure to other drugs, immunological susceptibility, and others).

Since the controls are selected through the physicians, matching on this variable will ensure for the control of unknown confounders that could be linked both to the probability of exposure (physician

practice) and to the probability of diagnosis (monitoring of patients by the physician).

It was felt necessary to match on the number of visits to the physician per year because controls will be selected out of the list of patients seen in a given period of 2 to 3 days by the physician. In effect, a list of all the patients seen by a physician in a long period (about one year) is often not available at the GP's office (except for computerized practices). Hence, the random selection of patients would not be possible. By selecting the controls among the patients seen in a short period, the probability of being selected will be higher for patients who visit the physician often. Therefore, a bias would be introduced whereby sicker controls would be overrepresented in the sample. Matching for the number of visits to the physician would help controlling for this bias.

Up to four matched controls per case will be included if they meet the matching variables and timing of the interview.

5.5 Inclusion / Exclusion criteria

5.5.1 Inclusion criteria

The following inclusion criteria will be applied to the study population:

- Both genders
- Age 18-70
- Resident in the country and the area of residence for more than 6 months at the index date (i.e. date of diagnosis of the case)

5.5.2 Exclusion criteria

The following exclusion criteria will be applied to the study population:

- Age less than 18 years old and greater than 70 years old

- Interviews impossible because of health condition, language or other technical conditions
- Subject refusing to participate in the study
- Subject absent of the country at the time of interview
- Conditions found to be associated with a decrease in the probability of exposure to anorectic agents and O.C. (contra-indications to the drug):
  - all contra-indications listed in each country's compendium
- Severe chronic disease: cancer, juvenile diabetes mellitus, others

6. RISK FACTORS ASCERTAINMENT AND QUESTIONNAIRES

There will be three sets of questionnaires:

- questionnaire A is the main questionnaire for risk factor ascertainment with four parts, (Part I, Part II, Part III, Part IV, see below),
- questionnaire B is an additional questionnaire for cases,
- questionnaire C is an additional questionnaire for the controls.

6.1 Main questionnaire (Questionnaire A)

The main questionnaire, as already mentioned, will be composed of four parts, mandatory ones (Part I-II) and optional ones (Part III-IV). Part I, II, III of the main questionnaire have been developed and tested with prevalent cases in France.

Part IV will be added only subsequently, in January 1993, and will then not be available for cases and controls recruited in the first months of the study.

Parts I and II will be administered to all cases and controls. Part III will be in a separate envelop handed to the cases and controls.

Part IV will be administered to all cases and to subset of controls. The first three parts will take approximately 40 minutes to be administered. The fourth will take approximately 20 additional minutes. The first three parts of the questionnaire deal with all suspected or known risk factors for PPH. They will address the following risk factors:

Part I:

- family history,
- age,
- gender,
- weight, height
- place of birth,
- smoking history (intensity / duration),
- obstetric history,
- (chemical) environment,
- alcohol / coffee intake,
- diving history,
- altitude,
- profession,
- medical history,
- diet (selected items)

Part II:

- drug history

  In the interview, exposure to drugs and diets will be assessed in three steps:

  a. open question: which drugs used in past four years?
  b. specific question: drug history in the last four years with suggestion of specific names of drugs (all therapeutic classes)
  c. packages or pictures of relevant drugs shown with a visual display

Part III:

- illicit drug abuse,
- HIV infection and other STDs

Part IV will be used to generate hypotheses regarding the etiology of PPH. It will address the following:

- history of childhood infections,
- history of infections in utero,
- exposure to selected environmental factors,
- history of exposure to drugs in utero

Questionnaires are described in more detail and included in Appendix C).

6.2 Additional questionnaires

Additional questionnaires for the cases (questionnaire B) will be aimed at describing the history of the disease (PPH), the onset of symptoms and subsequent medical developments. It will include also questions for the verification of inclusion criteria and exclusion criteria. Likewise, the additional questionnaire for the controls (questionnaire C) will be aimed at the verification of these inclusion and exclusion criteria.

7. OTHER METHODOLOGICAL ISSUES RELATED TO SUSPECTED RISK FACTORS

7.1 Protopathic bias

The possibility of a protopathic bias in the relationship between exposure to therapeutic agents and PPH has been documented. Some patients may have been prescribed a drug because they had developed dyspnea, a prodromic sign of PPH. This could lead to a spurious association with PPH. This bias will be carefully examined.

7.2 Diagnostic bias (selection bias)

Clinicians may be more likely to diagnose PPH in patients exposed

to a suspected risk factor than in unexposed individuals. This would result in an overrepresentation of cases exposed to this risk factor in the study sample compared to reality. A similar bias may occur, but to a lower extent, if PPH was diagnosed earlier in individuals exposed to suspected risk factors than in unexposed (regardless of the association between the exposure and the outcome). In this case, the probability of exposure to these factors in a given time window before the onset of symptoms would be increased. These problems will be considered through a careful examination of the reported cases, both exposed and unexposed. In particular, the time between the onset of symptoms and the diagnosis will be examined and considered between exposure groups. Also, the proportions of exposed cases will be compared between the probable PPH cases, the possible cases and the rejected ones. These potential biases will be considered in the conduct of analysis and the interpretation of results.

7.3 Reporting bias

The participating centres may be more inclined to report the cases exposed to a given risk factor than the unexposed ones. Conversely, it is possible that some centres would not report exposed cases because they would think that the association between exposure to the risk factor and PPH is known. This phenomenon, which has been documented in pharmacovigilance [4], is less likely to occur here, but will be considered nevertheless. In order to assess the importance of these biases, if any, participating centres will be regularly surveyed for their recruitment of PPH and the percentage of exposed vs unexposed cases will be evaluated. Each participating centre will be contacted by telephone every 3 months. Validated cases that were not spontaneously reported will be considered for the study. In the case of difficulty with including some non-reported cases with a lower (or higher) probability of exposure, the impact of this bias on the results of the study will be assessed and considered in the analysis and

interpretation of results.

8. SAMPLE SIZE AND STATISTICAL POWER

Sample size calculation was based on 3 major factors: 1) the prevalence of exposure in the control population, 2) power consideration and, 3) feasibility.

The sample size calculation had to take into account that there was more than one risk factor of interest. Thus, the most conservative estimate was retained. Calculations were based on anorexigens for the following reason: it is likely to produce one of the most conservative estimates because of the expected low prevalence of exposure in the control population.

According to sales figures, it was estimated that approximately 5% of the population in this age group is exposed at least once in the relevant time-window. Two-sided p values will be used. Alpha is set at .05 and the power at 0.80. The lowest detectable risk was based on clinical as well as feasibility considerations. According to the feasibility study, it has been estimated that 100 cases could be recruited during the study period. This number would allow us to detect a RR of 4.0. Such a sample size would produce a power greater than 0.80. It is likely that this number would also permit to study the effect of the other risk factors that may have a smaller RR than anorexigens but a greater prevalence in the control population. In addition, it would allow us to conduct stratified analyses in order to identify potential high risk groups.

9. STATISTICAL ANALYSES

Associations will be analyzed in three ways:

a. testing the significance of simple bivariate association between a given risk factor and the observed frequency of PPH (for each factor separately);

b. testing the significance of the contribution of a given risk factor or of a group of factors to the occurrence of PPH, after having adjusted for the effects of other risk factors (family history of PPH, oral contraceptive intake, smoking history, race etc.) using multiple regression approach which allows for the simultaneous analysis of all factors;

c. stratified analyses in order to identify high risk group. The selection of the stratifying variables is based on clinical relevance and plausibility. A priori, the stratifying variables of interest are age group and sex. However, these may be revised depending on the distribution of the study population.

Bivariate analyses: Since all hypotheses concerning bivariate associations will not a priori specify the direction, two-tailed tests will be used. The chi-square test will be used to assess the significance of the heterogeneity of the distribution of the risk factor between cases and controls. A crude odds ratio (OR) will be reported and 95% confidence intervals will be obtained with the test-based method.

Multivariate logistic regression: The relative risk (RR) for PPH within each exposure group will be estimated by the odds ratio (OR). The adjusted OR for each independent predictor will be obtained from an unconditional logistic regression model. The matching variables, sex, age group and number of visits to the GP will be included in the model to assess residual confounding. Because PPH is a rare illness, it is not likely that more than one

case will originate from the same GP. As a result, GP will not be included in the multivariate logistic regression.

Stratified analyses: Stratification of the data by age group and sex will allow us to identify high risk groups. An OR specific to each level of the stratifying variable will be obtained. Homogeneity of the stratum-specific ORs will be assessed by the Breslow-Day test.

Significance level will be set at .05. Data manipulation, bivariate and stratified analyses will be conducted using the SAS statistical package. Unconditional multivariate logistic regression will use the EGRET statistical package.

10. ORGANIZATION OF THE STUDY

The framework for the organization of the study in each country includes six steps:

(i) Recruitment of participating centres. As already done in the feasibility study in France, the head of the Cardiology and Pneumology divisions of all the University Hospitals in the five countries will receive a letter signed by two leading clinicians (one cardiologist and one pneumologist), by the Chair of the IPPHS and sometimes a local epidemiologist, asking for their collaboration in the identification of cases of PPH.

All participating centres will receive a folder containing an outline of the study, the present study protocol, reminders of the inclusion and exclusion criteria, the algorithm for PPH diagnosis of Appendix A and pre-stamped and pre-addressed postcards for the reporting of cases (Appendix D). They are also invited to an educational session on PPH and the IPPHS.

(ii) Reporting of cases by the hospital centres. Pre-stamped cards (Appendix D) will be made available to each centre for the reporting of a case. Each case will be assigned an identification number. Centres will only have to post the card (or fax it) to the local team. The places where the reporting of cases will be received are: Hôpital Bichat (Prof. M. Aubier, France); Hammersmith Hospital (Prof. C. Oakley, United Kingdom); Limburg University (Dr. H. Petri, The Netherlands); Institut d'Hygiène et d'Épidémiologie (Dr. X. Kurz, Belgium). A place will have to be named for Switzerland. Copies of the cases will be faxed to the International Coordinating Centre in Montreal.

(iii) Telephone screening. A physician in each local team (preferably a cardiologist or a pneumologist) will telephone the clinician who reported the case and fill out a screening form where questions will be asked regarding the procedures applied to verify the case. All the mandatory procedures listed in section 5.2.2 will have to have been performed to accept the case (screening form with Appendix E). Clinicians will be informed of the criteria chosen by the panel for the diagnosis of PPH to be made.

(iv) Case ascertainment. If the case is retained, a physician from the local team will visit the reporting centre for the extraction of data from medical charts with the Medical Extraction Form from Appendix B. When in doubt, a referee expert will be asked to review the case (one has been identified in each country). All cases will subsequently be reviewed by an independent panel of three experts. This panel will be blinded as to the source of the case and exposure status. It will classify the cases into 3 groups: (a) accepted cases; (b) possible cases; (c) rejected. It is expected to recruit 100 accepted cases. The possible cases will be kept for comparative studies and control potential biases (see above). In Appendix F are summarized the steps to be followed for

the recruitment and validation of cases. Forms will be sent to the International Coordinating Centre (Montreal) for coding, verification and processing.

(v) Recruitment of controls. The recruitment of controls will follow the chart represented in Appendix G. This will consist in three steps:

1. A list of patients seen by the case's-GP will be generated. This will require the following steps:
   - Identification of the GP by the case: name of the GP obtained by phone or at the hospital (consent form to be mailed and signed by the case is with Appendix I);
   - Information of the GP by telephone and mail (simultaneously). An agreement by the GP to participate;
   - Mailing of a pad (Appendix H) to the GP for the listing of all patients seen in 1 week. Each sheet on the pad is made of two parts: on the left side, space is allowed for the name and telephone number of the patients; on the right side, information is registered by the GP for each patient on sex, age, number of visits in the last 12 months, together with the sequential number of the patient.

2. Selection of controls
   In order to protect confidentiality, only the right side of the sheets are sent (or faxed) by the physician to the local research team. The GP keeps the left side, with the patients IDs. An epidemiologist from the local team identifies 6 controls for the case (4 + 2 replacements). The epidemiologist informs the GP of the sequential number selected and offers him/her: (a) either that s/he (the GP) would contact the selected controls to inform them of the

study and of the fact that an epidemiologist will call them if they agree; (b) or that the epidemiologist would write to (or call) the control, in the name of the GP. Solution (a) would be much preferable (in the feasibility study, the three GPs preferred to contact their patients themselves).

3. The epidemiologist contacts the control patients by telephone and finalises the conditions of their recruitment and the conditions of interview (consent formS to be filled by the patients with Appendix I).

(vi) Interviews. It has been decided that the number of interviewers should be kept to a minimum. Interviews will be conducted by 3 interviewers in France, 2 in the United Kingdom, 1 (bilingual) in Belgium, 1 in The Netherlands. One of the French interviewers will conduct the interviews in Switzerland.

As an example, if 50 cases and 200 controls were recruited in France, then each French interviewer will interview 25 cases and 100 controls. Since cases and controls will, by definition, live in the same area, this will represent 25 sets of interviews of 5 subjects. It is felt that these interviews can be conducted over a period of 2.5 days, including preparation and transportation. Thus, two half-time interviewers will be recruited, one for each half of the country (North and South). The same basis will be used for other countries at the pro rata of recruitment of cases.

Interviewers will be non-medically trained individuals who will be blinded vis-à-vis the objectives of the study. They will receive an initial training and will be regularly supervised for their work. Blinding vis-à-vis the status of the subjects (cases and controls) seems impossible to achieve in regard of the content of the additional questionnaires. The interviewers will be however trained to counteract this factor. Interviews will be conducted

face to face, preferably at the subject's home or in a quiet environment.

(vii) Blood samples (this section is not funded yet). Cases and controls will be asked if they volunteer for a collection of blood. If so, a trained nurse will be sent to collect the blood. It is estimated that 50% of cases (50 cases) and 25% of controls (100 controls) will accept. This blood will be frozen at -70° C and stored for future studies on immunological and genetic factors.

11. ETHICAL CONSIDERATIONS

The study being sponsored by a pharmaceutical company which has an interest in some of the factors investigated, several measures were taken to ensure for the independence of the study. Firstly, the members of the Scientific Board were selected independently by the Chair of the IPPHS. They are all scientists affiliated with academic institutes with no personal interest in the result of the study. Secondly, the following clause regarding publication has been introduced in the contract between SERVIER and the Centre for Clinical Epidemiology of the McGill University Jewish General Hospital where the study will be coordinated:

> PUBLICATION OF RESULTS
>
> In accordance with the International Scientific Board of the study, "the Centre reserves the right to disseminate information or to publish any and all material resulting from the IPPHS without need for approval by ADIR (SERVIER). The Centre shall provide ADIR (SERVIER) with a copy of any proposed publication intended for any third party forty five days in advance of the proposed publication date. ADIR (SERVIER) will not be entitled to require any modification but it would be its privilege to make suggestions to the authors.

These suggestions will be submitted to the international Scientific Board of the Study. ADIR (SERVIER) at its election shall be entitled to receive in any such publication an acknowledgement of its sponsorship of the IPPHS."

The issue of potential early stopping of the study in the case of an obvious increased risk associated to drugs was discussed by the International Scientific Board, together with the method to determine such an increase if any. It was decided that it should not be the decision of the panel to stop the study, since the authorities of each country will receive all the relevant information about exposed cases. The authorities of each country will have all the data necessary for them to take a decision regarding those drugs. It is felt that the policy decisions should be totally separated from the scientific ones. The International Coordinating Centre will conduct a descriptive analysis at 50 cases recruited or after one year of recruitment in order to identify a potentially major association and will report to the ISB. The protocol will be submitted to local Ethical Committees in each country, including the country where the International Coordinating Centre is located (the Montreal Jewish Hospital).

12. TIMETABLE

The projected timetable for a study period of 2 years is included in Appendix J.

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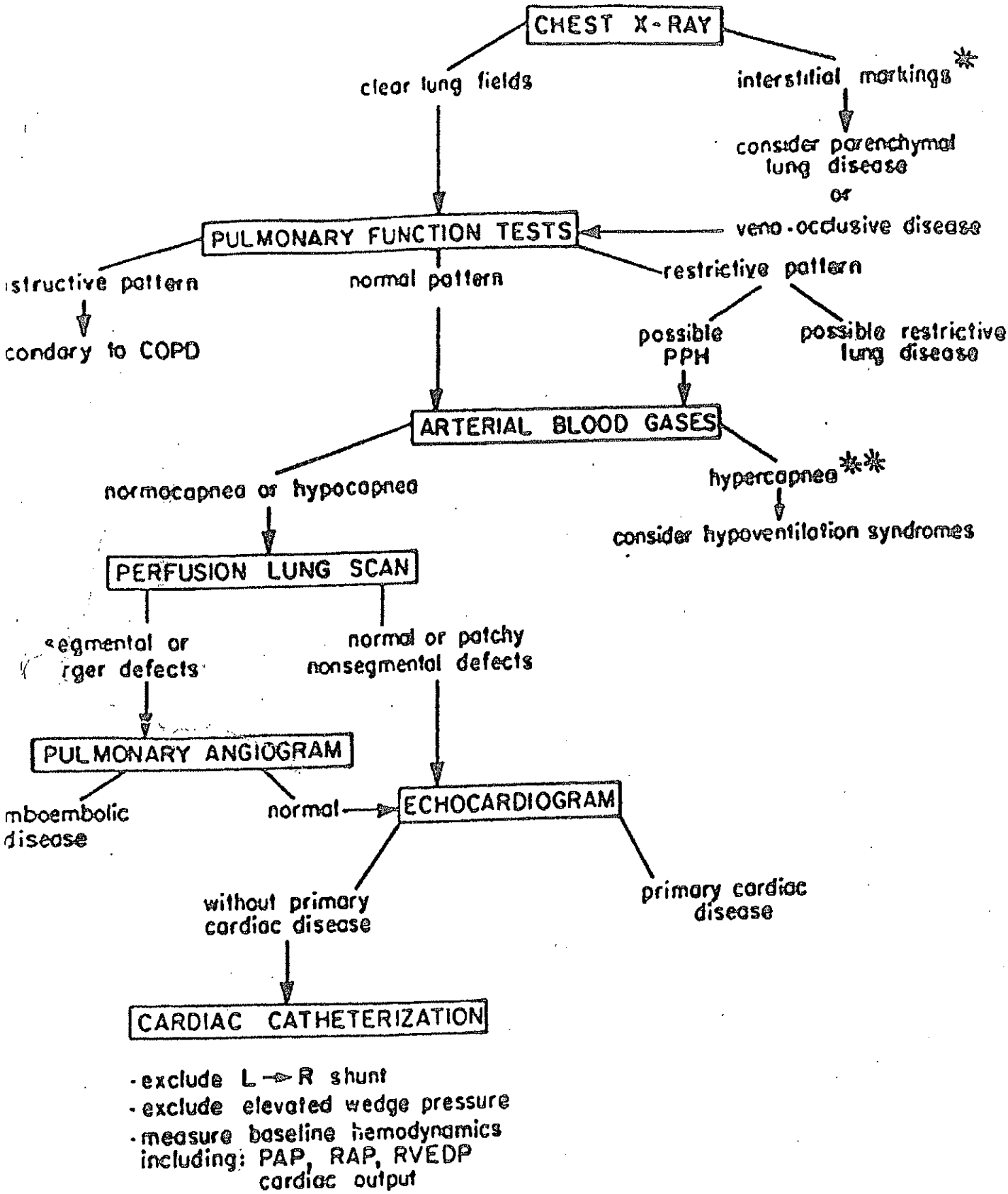
Algorithm for the diagnosis of PPH

From Rich (1988)

Appendix A

ALGORITHM FOR THE DIAGNOSIS OF PPH



* Consider HRCT

** Consider sleep studies

Note on Complementary examinations:

Whenever one "mandatory examination" was missing, the international review panel was asked to decide if the case should be dismissed or kept.

Note on Exclusion criteria:

The conditions were excluded only if it was felt that they could account for the elevated pulmonary pressure.

Draft Outline of Protocol
International Case Control Study of
Primary Pulmonary Hypertension
ICCSPPH

April, 1992

1.0 INTRODUCTION

A number of spontaneous reports referring the use of anorexigenic drugs, particularly the ones containing fenfluramine (F) and dexfenfluramine (DF) in France, Belgium and other european countries, among cases of Primary Pulmonary Hypertension (PPH) have been collected. The Servier Laboratory has been receiving reports of PPH during approximately thirty years of commercialization of those drugs. In Montreal, a statistical analysis of some of the Servier's Laboratories reports has been done. The National Committee of Pharmacovigilance of France (NCPF) has recommended lately a nationwide study of products containing F and DF (Besançon) while, over the years, the Servier Laboratories has introduced changes in the manufacture of those specific drugs.

PPH is a rare and not well known disease. There are no epidemiologic studies treating this subject. Its incidence is also not known. The risk factors associated with PPH were never investigated in a thorough epidemiologic fashion generating a variety of supposed opinions and ideas concerning the "primary" concept of this disorder.

The data available rest mostly over the report of case series. The U.S. case report however, analyzed in a systematic manner the presence of certain factors. In 5% of the patients studied for instance, anorexigenic drugs were involved but the F and the DF drugs are not marketted in this country.

In France, the reports provided by a specialized center named Clamart indicate that the exposure to F and DF was noted in 6.9% of the subjects in the past, and a current exposure in a time frame of 4.5 years, was found to be 5.6%, summing up to a total of 12%. Taking into consideration the antecedents of aminorex, the plausibility that this product has some effect over this specific disease is elevated. The F and the DF are widely used in France. It is estimated that the number of patients treated each year with those drugs reaches around 280 thousand persons. That is approximately 5% of the women in the age group of 20 to 55 years. The point prevalence of exposure in the general population is thought to be low but, long term prevalence of exposure is possibly high.

A number of other risk factors have been suggested such as other anorexigenic, other drugs, oral contraceptives, pregnancy, genetic traits, etc. They will have to be listed and studied exhaustively, so that data about incidence of PPH; about the role of each risk factor, if each one of them is a starter or a contributor; about the eventual reversibility of the disorder; about the harzard function of PPH vis a vis each risk factor; about the effect of duration of exposure; about the risk to have PPH after a drug or a risk factor is discontinued and, so forth.

In that context, the Servier Laboratories have accepted to support this International

Epidemiological Study of PPH (IPPHS). In order to write the present protocol draft, a panel of independent experts was created. The members of this International Scientific Board (ISB) were identified by Professor Abenhaim, of the McGill University in Montreal, Canada. The Servier Laboratories were not consulted about the composition of this panel. The panel has been extended to include scientists from the U.K., the Netherlands and Switzerland. The members are listed in appendix A.

2.0 OBJECTIVES

2.1 GENERAL OBJECTIVES

1- To estimate the incidence of PPH.

2- To estimate quantitatively the association between different risks factors and the syndrome usually labelled as PPH.

3- To determine the causal or contributive role of each risk factor studied.

2.2 SPECIFIC OBJECTIVES

1- To compute the incidence rates of PPH for the regions of Bordeaux and Toulouse in France and possibly for Belgium.

2- To determine the odds ratio for each risk factor cited by the scientific literature and by the experts in field, including drugs, especially anorexigenic drugs and particularly the F and the DF drugs.

3- To determine quantitatively the interactions among risk factors studied.

3.0 METHODOLOGY

3.1 DESIGN

A prospective cohort type of study design would demand conditions and efforts not quite realistic given the rarity of the PPH disease. The use of existing data bases is also inadequate since the prevalence of exposure to certain products in North American countries, where such data bases exist, is inexistent. Furthermore, the diagnostic of PPH requires precise criteria that certainly would not be easily found on such data banks.

Therefore, we recommend a multicenter case control study. In order to gather the most possible number of cases, this study will be conducted in France, Switzerland, The Netherlands, Belgium and United Kingdom where cases have been notified in the past and where one of the risk factors to be studied, or the F and the DF drugs, are widely utilized.

3.2 CASE DEFINITION

3.2.1 INCLUSION CRITERIA (to be completed)

1- An algorithm for PPH case validation will later be produced having as reference Rich's scheme to reach a PPH diagnosis.

2- All PPH prevalent cases of less than one year and incident cases are going to be considered in the preliminary phase of the study. For the analytic study however, only the PPH cases diagnosed shortly after the start date of the study are going to be eligible.

3- Others to be defined.

3.2.2 EXCLUSION CRITERIA (to be completed)

1- Cases considered unclear according to the judgement of experts.

2- Cases, for the case-control study, that were not interviewed.

3- Others to be defined.

3.3 OPTIONS OF CONTROL GROUP (to be discussed and decided)

1- Patients of the cases's general practitioner.

2- Patients of a random sample of physicians of a pre-established list and thereafter matching of cases and controls of the same physician.

3- Next of kin controls.

4- Other population-based controls.

Annexe 1-48

Professeur Lucien Abenhaim
1-10, Summers St, flat #1
Londres EC1R 5BD
Royaume-Uni

Londres, le 4 janvier 2011

A l'attention de:
Mission IGAS sur le Médiator.
Ministère de la Santé
14, Avenue Duquesne
75007 Paris

Courrier envoyé par voies électroniques.

Madame, Messieurs,

Cette note vous a été adressée essentiellement en préparation de notre dernière rencontre. Je prendrai cette occasion pour résumer les conditions de déroulement de l'étude internationale "IPPHS" sur l'hypertension pulmonaire primitive (HTAP), ses conclusions et les suites qui y ont été données, par le sponsor principal (Servier) et les autorités de santé. Je dirai enfin ce qu'il en a été lors de l'exercice de mes fonctions de directeur général de la santé.

1) L'étude IPPHS

J'ai été contacté par les laboratoires Servier à l'automne 1991 alors que j'étais professeur de pharmaco-épidémiologie à l'université McGill au Canada (où j'ai passé 20 ans), pour commenter 7 cas d'HTAP exposés à l'une ou l'autre de leurs fenfluramines (Isoméride ou Pondéral). J'ai conclu à la plausibilité du lien, du fait notamment de l'antécédent de l'épidémie d'HTAP liée à l'aminorex dans les années 60. Après plusieurs réunions, dont certaines avec l'équipe de Clamart qui avait observé certains de ces cas, Servier, et des experts français et étrangers, ainsi qu'après des échanges avec des membres de la Commission de pharmacovigilance, nous avons convenu en 1992 de réaliser une étude dite 'cas-témoins', internationale (France, Royaume Uni, Belgique, Pays Bas), que je coordonnerais depuis le Canada avec l'appui de collègues américains et canadiens. Le comité scientifique comportait, outre des épidémiologistes et statisticiens, un nombre important de cliniciens de chacun des pays et d'Amérique du Nord. Menée avec une méthodologie qui a été jugée par le Medical Research Council du Canada -qui l'a évaluée de façon indépendante-, comme 'exceptionnelle', et par un responsable de l'agence française du médicament comme 'irréprochable', l'IPPHS a recherché des cas d'HTAP dans 220 centres cliniques en Europe, et des témoins auprès d'une centaine de médecins généralistes. Elle a mobilisé plus d'une quarantaine de personnes. Grâce à cet effort, elle a pu produire des résultats de la plus haute qualité sur une grande variété de facteurs associés ou non à l'HTAP (ce qui correspondait à son objectif général). Dès début 1994 un risque significativement élevé d'HTAP associé à la prise d'anorexigènes a été mis en évidence dans l'analyse

intermédiaire de la cinquantaine de premiers cas et de la centaine de premiers témoins, analyse remise aux autorités sanitaires des quatre pays et présentée à l'agence française du médicament. Ce rapport concluait à une augmentation "significative" du risque d'HTAP liée aux expositions passées aux anorexigènes et que "La différence entre ces produits n'est pas statistiquement significative". Nous ajoutions : "Ce résultat est cohérent avec l'hypothèse a priori de l'étude". L'agence nous a enjoint de mener l'étude à son terme. Nous avons présenté un second rapport dans les jours qui ont suivi la collecte du dernier cas, soit le 7 mars 1995 (plus de 400 HTAP possibles nous ont été rapportées, dont 95 rencontraient les critères d'inclusion ; nous les avons appariées à 355 témoins indemnes de la maladie). Dans cette analyse, aucune ambigüité n'était permise, elle montrait un risque significativement élevé d'HTAP lié aux anorexigènes, et augmentant nettement avec la durée de prise. Le lien était plus clair avec les fenfluramines (Isoméride, Pondéral) qu'avec les anorexigènes amphétaminiques étudiés - le clobenzorex (Dinintel), le mefenorex (Incital), le fenproporex (Fenproporex Deglaude), l'amfépramone (Tenuate Dospan, Prefamone, Anorex)-, mais du fait de la consommation conjointe fréquente, il était difficile de les distinguer en termes de risque. De plus, plusieurs cas (mais aucun témoin) avaient consommé des 'préparations magistrales' pour perdre du poids dont le contenu nous était alors inconnu mais dont la comptabilisation avec les anorexigènes dans une analyse faisait grimper significativement le risque évalué (d'un facteur 4 à 7). Ce rapport concluait à propos de l'HTAP:
"L'ampleur de l'association avec les anorexigènes, la temporalité de l'association, la relation avec la durée d'utilisation et la cohérence des résultats avec les observations précédentes confirment l'hypothèse d'un lien de causalité".

Le rapport a été présenté par nous au Comité technique de pharmacovigilance (CTV) le 26 avril 1995 et à la Commission nationale de pharmacovigilance (CNPV) le 28 avril 1995, en même temps que les résultats d'une enquête nationale de pharmacovigilance sur les mêmes produits anorexigènes confiée au Centre régional de pharmacovigilance (CRPV) de Besançon. Il est important de noter que, comme le stipulait une convention signée par nous avec le président de la CNPV en 1993 (document fourni), nous avions signalé tous nos cas d'HTAP exposés aux coupe-faim à la pharmacovigilance de Servier, qui les avait fait partager dans cette enquête nationale. Inversement, nous avions pu vérifier que l'IPPHS n'avait pas manqué un nombre significatif de cas rapportés en PV (par des centres ne participant pas à l'IPPHS).

En s'appuyant sur ces éléments, rapportés le 28 avril 1995, la CNPV a recommandé la restriction drastique de la prescription des coupe-faim, en la limitant par une prescription initiale hospitalière aux personnes souffrant d'une obésité morbide, se qui se traduisait par une chute vertigineuse des expositions – but souhaité.

Nous avons présenté ces résultats, toujours avec le soutien financier de Servier (cf. 4 ci-après), qui s'en est d'ailleurs acquitté sans difficulté, dans plusieurs congrès et avons organisé deux symposiums internationaux (dont l'un en plénière d'un congrès international à Montréal), sur le sujet.

Servier nous a fourni en mai 1995 un financement de continuité (portant jusqu'à septembre 1996), que nous avons d'abord employé à compléter la documentation des préparations magistrales auprès des cas et des témoins, par visites directes chez leurs pharmaciens : celles retrouvées se sont presque toutes avérées contenir de la fenfluramine, et il est apparu que leur consommation s'effectuait toujours sur le long terme. Ce qui a fait grimper de 4 à 6 le risque relatif associé aux anorexigènes et de 10 à 23 le risque relatif pour les prises de plus de 3 mois.

Nous avons aussi, grâce à ce financement, analysé plus à fond les données pour la publication. Celle-ci a eu lieu en août 1996, dans le New England Journal of Medicine. Nous concluions sans ambigüité au rôle causal des anorexigènes, principalement des fenfluramines, dans l'HTAP. Grâce à la disponibilité du contenu des préparations magistrales, ce qui augmentait aussi la puissance de l'étude pour certaines expositions, il apparaissait en effet que le risque se concentrait sur les fenfluramines, celui associé aux autres coupe-faim amphétaminiques n'étant pas statistiquement significatif (mais ne pouvant être exclu)[1]. Cette conclusion à la causalité était un fait sans précédent pour les fenfluramines – les autres anorexigènes pouvant s'appuyer à cet effet sur l'antécédant de l'aminorex- et assez rare en épidémiologie pour être noté.

2) J'en viens maintenant à la question du Médiator au regard de notre étude.

Afin d'éviter le fameux 'biais de mémoire' souvent reproché aux études basées sur des interrogatoires de patients[2], nous interrogions les patients sur 21 grandes catégories d'indications de traitement, en leur présentant à chaque fois une liste des 5 médicaments les plus vendus pour ces pathologies, soit 105 médicaments en tout. La perte de poids représentait une de ces indications, avec 5 anorexigènes identifiés (Isoméride, Pondéral, et 3 amphétaminiques). Le Médiator était identifié parmi les médicaments du traitement des troubles des lipides sanguins, sans doute du fait de son indication comme adjuvant dans le traitement des hypertriglycéridémies. Nous n'avons pas analysé séparément les 105 médicaments listés, ni les milliers rapportés spontanément par les patients, pour que l'étude n'encoure pas la critique classique du 'tripatouillage à l'aveuglette des données' (data dredging), qui aurait fait perdre toute crédibilité, voire significativité statistique, à nos résultats[3]. Nous n'avons donc pas

[1] Les odds ratios bruts étaient similaires pour les fenfluramines vs. les autres amphétaminiques, mais les premières avaient des effectifs plus élevés et accaparaient la 'force' des estimations dans les modèles.

[2] C' est un biais très important à éviter en épidémiologie et d'ailleurs, cette question a été soulevée dans l'éditorial critique du New England Journal of Medicine en Août 1996 rédigé par des consultants de la firme, ainsi que par de nombreux autres intervenants que le laboratoire Servier a mobilisés pour évaluer nos résultats sur cette question (voir entre autres, Lane, D. and Kramer, M., Journal of Clinical Epidemiology , 1999 Dec;52(12):1279-87)

[3] Cette critique a été formulée récemment, par exemple, par l'Afssaps et par l'OMS à l'encontre d'une étude française sur le vaccin hépatite B et la sclérose en plaques, où on a reproché aux auteurs d'avoir testé trop de produits sans hypothèse a priori, et décidé de ne pas retenir le risque que cette analyse avait fait ressortir pour un produit (voir entre autres, WHO Global Advisory Committee on Vaccine Safety: response to the paper (in press) by Y. Mikaeloff and

spécifiquement examiné le Médiator dans l'étude, car on ne nous a ni signalé qu'il était utilisé comme anorexigène, ni sa parenté chimique avec les fenfluramines. Ceci est d'autant plus étonnant que, selon ce que j'ai appris il y a quelques jours, une enquête nationale de pharmacovigilance avait été lancée aussi sur le Médiator, du fait de sa parenté chimique avec les coupe faim, enquête dont le résultat a été rapporté en juillet 1995 par le même centre régional de pharmacovigilance de Besançon quelques semaines seulement après celle d'avril 1995 faite sur les anorexigènes. L'enquête du CRPV sur le Médiator a semble-t-il observé que tous les cas d'HTAP rapportés étaient aussi exposés à un anorexigène. Ni Servier, ni aucun de nos autres interlocuteurs ne nous en a fait part. L'examen actuel de notre rapport de 1995 montre que seuls 2 cas d'HTAP (2%) et 18 témoins indemnes de cette maladie (5%) avaient rapporté un traitement pour une hyperlipidémie : je ne sais pas si l'un des 2 cas prenait du Médiator, mais même si c'était le cas pour les deux, une simulation statistique (faite aujourd'hui) montre que nous n'aurions pu conclure au risque de ce produit en 1995 dans notre étude. Donc, même si on nous avait signalé ce soupçon, nous n'aurions pas pu conclure à un risque dans notre analyse de 1995. Mais j'en aurais été au courant, ce qui ne fut à aucun moment le cas.

3) J'en viens maintenant à ce qui s'est passé en Amérique du Nord.

Nous avons eu la surprise d'apprendre, au cours de l'été 1995, qu'une demande d'autorisation de mise sur le marché pour la version américaine de l'Isoméride (Redux) était déposée. Malgré notre témoignage à la FDA, le produit a été autorisé fin novembre 1995 pour une utilisation au long cours dans le traitement de l'obésité, et avec autorisation de publicité directe au consommateur. Nous avions pourtant indiqué lors de notre audition publique à la FDA que, si on prenait en compte les préparations magistrales, le risque d'HTAP au long terme était multiplié par 23. Mais les Etats-Unis faisaient face à une épidémie d'obésité morbide et ils ont jugé que le jeu en valait la chandelle. Je dois dire que j'ai été très choqué par la possibilité de prescription incontrôlée et massive que cette décision signifiait car les données d'efficacité (essentiellement une étude française du Pr Guygrand) ne présentaient aucune mesure d'efficacité convaincante en termes de morbidité cardiovasculaire ou autre. Le pire était que, dès l'annonce de la décision de la FDA (en novembre 1995), la prescription de Pondimin (équivalent américain du Pondéral) et de phentermine (un amphétaminique anorexigène) a explosé (notamment sous la forme de la combinaison dite 'fen-phen' pour fenfluramine-phentermine). Ces molécules et leur génériques étaient sur le marché depuis longtemps, mais assez peu utilisées.

Nous avons donc entrepris, avec les cliniciens nord-américains qui nous avaient aidés dans l'IPPHS, et notamment le Professeur Stuart Rich de Chicago, une campagne de sensibilisation aux risques du produit. Devant l'absence d'étude - étude que nous réclamions-, j'ai décidé d'utiliser les sommes disponibles de la

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colleagues in Neurology entitled "Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood", October 2008).

subvention de continuité de l'IPPHS pour financer une étude de surveillance, dite 'Surveillance of North American Pulmonary Hypertension' (SNAP) dans plusieurs grands centres américains. A compter de cette date, nos relations avec Servier, jusque là sans aucun problème, se sont nettement dégradées, notamment avec la filiale nord-américaine de la firme (et non avec l'Institut de recherche international Servier, basé en France). C'est ce qui transparaît dans une lettre découverte beaucoup plus tard par les avocats des victimes, lors d'une perquisition au siège de Wyeth-Ayerst, où la présidente de Servier Amérique déclare à son homologue américain qu'il faut trouver des moyens de nous 'neutraliser'. Après le temps nécessaire au développement du protocole, le recrutement des centres et l'obtention des accords des comités d'éthique, SNAP a recruté des cas d'HTAP et des témoins à compter de septembre 1996, jusqu'en décembre 1997. SNAP conclura : "L'ampleur de l'association avec l'HTAP , l'augmentation de l'association avec la durée d'utilisation et la spécificité de la fenfluramine sont cohérents avec les études précédentes indiquant que les fenfluramines ont un lien de causalité à l'HTAP". Aux Etats-Unis, l'essentiel des expositions aux anorexigènes étaient le fait de fenfluramines et/ou phentermine.

Notre publication dans le NEJM a connu une grande publicité, aidée en cela par le fait que les éditorialistes choisis par la revue et qui la critiquaient étaient des consultants réguliers de la firme, ce que j'ai révélé à la presse (ils avaient d'ailleurs témoigné en faveur du produit lors de l'audition à la FDA). Ces démarches ont pour le moins agacé Servier Amérique. Divers types de pressions se sont exercées, dont une campagne très vive contre l'évolution de nos résultats entre 1995 et 1996, occultant le fait que nous avions bien indiqué dès 1995 dans le rapport et à la FDA que la prise en compte des préparations magistrales faisait grimper l'évaluation du risque. D'autres pressions se sont déroulées en 1997.

La découverte des valvulopathies par l'équipe de la Mayo Clinic (dont un membre, Michael McGoon, avait participé activement à notre équipe de l'IPPHS) fut le coup de grâce aux produits, retirés du marché mondialement par les firmes pharmaceutiques à partir de septembre 1997.

A noter que nous avons favorisé l'émergence de l'étude SOPHIA (Study Of Pulmonary Hypertension In America) qui a pris le relais de SNAP, c'est à dire à compter de la fin 1997. Le retrait des produits et la publicité sur leurs risque rendait le contrôle du biais de notoriété quasi impossible. SOPHIA conclut néanmoins qu'en l'absence d'une épidémie observable :
" L'association (observée) entre les dérivés de la fenfluramine et l'HTAP est chérente avec les élévations du risque observées précédemment"

4) Aux fins de transparence, il me semble important d'exposer les financements des études.

Le budget de l'étude IPPHS a été défini globalement avec les laboratoires Servier et un observateur (clinicien ayant observé des cas). Initialement fixé à 2 millions

de dollars, il a atteint environ 2,5 millions[4], soit une moyenne, sur 3 ans, et en tenant compte de l'équipe nord-américaine, d'environ 150 000 dollars par an et par pays (fourchette de 50 à 300 000 environ). Le financement se faisait au Centre d'épidémiologie clinique du Jewish General Hospital (JGH) de l'Université McGill (où j'enseignais) et au Centre de recherche sur les risques Inc (CRR), société que je dirigeais, en accord avec le JGH, pour faciliter les dépenses de terrain, notamment hors Canada. Un accord de reversement des sommes non dépensées par le CRR au JGH a été signé et les comptes vérifiés (équivalent de rapport de commissaire aux comptes) du CRR déposés auprès du JGH. Le dernier financement de l'IPPHS et de toutes ses suites a eu lieu en 1996.

Les derniers honoraires versés par Servier pour l'IPPHS (interprétation des cas et des résultats, présentations de l'étude auprès des autorités et divers intervenants) remontent également à 1996.

Par ailleurs, j'ai mené deux autres études financées par Servier dans ma carrière:

a) Une analyse d'une base de données anglaise sur les hypoglycémiants, dont le rapport complet a été déposé auprès du Conseil de pharmacologie du Québec en 1994. L'ensemble du financement (très limité) s'est terminé à cette date. Les jeunes chercheurs qui y avaient contribué ont publié deux articles, l'un méthodologique en 1994, l'autre de résultat en 1997, avec une simple relecture de ma part dans ce dernier cas.

b) Une étude sur l'insuffisance veineuse. Cette étude devait comporter, par contrat, une *'Composante A'* (épidémiologie clinique et développement d'instruments de mesure) et une *'Composante B'* (essai pharmaco-économique d'un des produits de Servier). La Composante B a été annulée du fait de la dégradation des rapports avec Servier suite à l'IPPHS. La collecte des données de la partie A par nos équipes s'est déroulée jusqu'à son terme en 1997, mais le dernier financement reçu de Servier est antérieur. Les chercheurs ont publié sur ces données de la composante A pendant plusieurs années (jusqu'en 2006), en mettant mon nom dans certaines des publications au titre du rôle initial que j'y avais joué.

5) J'en viens maintenant à mon activité à la direction générale de la santé.

J'ai pris mes fonctions en août 1999 et les ai quittées en août 2003. A ma connaissance, aucun produit avec l'indication d'anorexigène n'était sur le marché pendant cette période. On ne m'a à aucun moment indiqué que le Médiator avait fait l'objet de questions sur son utilisation détournée à cette fin, ni d'une enquête pour sa parenté chimique avec les fenfluramines. J'ai la faiblesse de penser que, si cela avait été le cas, j'aurais agi comme je l'avais fait auparavant vis à vis de ces

[4] Par comparaison, l'étude SOPHIA (Study Of Pulmonary Hypertension In America), menée par Harvard pour confirmer nos résultats aux Etats-Unis, financée par Wyeth-Ayerst, a eu, selon mes informations, un budget de 6 millions de dollars. Elle a recruté plus de patients que l'IPPHS mais dans seulement 12 centres. Bien que confirmant les résultats de l'IPPHS, la méthodologie de SOPHIA a été jugée moins valide par les revues scientifiques du fait notamment du biais de notoriété après le retrait des fenfluramines et a connu beaucoup de difficultés de publication.

produits, et fait prendre, s'il le fallait, les mesures nécessaires. Le fait est que je n'en ai jamais été saisi.

J'ai pu récupérer les archives pour l'ensemble des points abordés dans cette note et les tiens à votre disposition.

Je vous prie de recevoir, Monsieur l'Inspecteur général, mes salutations distinguées.

Professeur Lucien Abenhaim

PJ :

1. Accord IPPHS-CNPV (remis avec autre courrier)
2. Publication IPPHS, NEJM, août 1996 (remise lors de l'audition)
3. Etude SNAP (Chest, 2000)
4. Etude SOPHIA (American Heart J, 2006)

Annexe 1-49

COMPTE RENDU

Nous nous sommes réunis à Strasbourg, le 5 mai 1993, pour décrire les rapports entre l'IPPHS et le Réseau français de Pharmacovigilance.

Deux impératifs s'imposent :

a) éviter d'introduire un biais dans le recrutement des cas d'hypertension artérielle pulmonaire par un a priori sur le rôle des médicaments;

b) respecter le fonctionnement du réseau français de Pharmacovigilance qui implique la déclaration obligatoire des effets indésirables des médicaments au centres régionaux.

L'IPPHS conserve des liens étroits avec le réseau de Pharmacovigilance selon les points suivants :

1. Lorsque des cas d'HTAP sont signalés aux chercheurs de l'IPPHS, avec une référence explicite à la responsabilité possible d'un produit pharmaceutique (quel qu'il soit), il est du devoir des chercheurs d'enjoindre les cliniciens à rapporter ces cas aux centres régionaux de Pharmacovigilance concernés.

2. Les chercheurs ne seront cependant pas "proactifs" à ce niveau, c'est-à-dire qu'ils ne procèderont pas à la déclaration eux-mêmes, puisque le principe d'une étude cas-témoins est, au plan méthodologique, de recruter les cas et les témoins sans égard a priori à leur exposition.

3. En cas de demande exprès de la Commission de Pharmacovigilance, si celle-ci y était amenée par un impératif quelconque - nous nous engageons à ouvrir les dossiers de recherche collectés et à lui fournir les données dont nous disposerons.

4. Le Professeur B. BEGAUD, membre du Conseil scientifique de l'IPPHS, peut agir comme relais (informel) avec le Professeur P. BECHTEL, Directeur du Centre régional de Pharmacovigilance de Besancon, chargé de l'enquête officielle de Pharmacovigilance sur la dexfenfluramine.

Pr. Lucien ABENHAIM
International Scientific Board
International Primary Pulmonary Hypertension Study (IPPHS)

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Président de la Commission Nationale de Pharmacovigilance

UNIVERSITE LOUIS PASTEUR
Faculté de Médecine
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STRASBOURG

Annexe 1-50

REPUBLIQUE FRANCAISE

AGENCE DU MEDICAMENT

Saint Denis le, 04 FEV. 1994

DIRECTION DE L'EVALUATION DU MEDICAMENT

UNITE DE PHARMACOVIGILANCE

Suivi : P. GIL
tél : 48.13.22.85
cx3101.dex

REUNION D'INFORMATION
Dexfenfluramine, fenfluramine et Hypertension Artérielle Pulmonaire
du 31 Janvier 1994

Assistaient à la réunion :

L.	ABENHAÏM	(McGill, Montréal, IPPHS)
P.	BECHTEL	(C.R.P.V. Besançon)
B.	BEGAUD	(C.R.P.V. Bordeaux, IPPHS)
F.	BRENOT	(Hôpital A. Béclère)
A.	CASTOT	(Unité de Pharmacovigilance, Agence du Médicament)
M.	DAVID	(C.R.P.V. Besançon)
N.	DAVID	(Enregistrement, Agence du Médicament)
P.	DUROUX	(Hôpital A. Béclère)
J.L.	IMBS	(Président de la Commission Nationale)
P.	GIL	(Unité de Pharmacovigilance, Agence du Médicament)
C.	KREFT-JAIS	(C.R.P.V. Paris-Broussais)
G.	LAGIER	(Conseiller Scientifique, Agence du Médicament)
S.	LEGER	(Unité de Pharmacovigilance, Agence du Médicament)
Y.	MORIDE	(IPPHS)
G.	SIMONNEAU	(Hôpital A. Béclère)

Annexe 1-50

I - OBJECTIFS DE LA REUNION

Cette réunion avait pour objectifs :

- d'échanger des informations entre différents intervenants dans l'évaluation du dossier,
- de contribuer à juger de l'évolution de la situation,
- de faire le point sur les données disponibles à ce jour.

II - MISE A JOUR DE L'ENQUETE OFFICIELLE

1) Le nombre de cas

• Madame M. DAVID (C.R.P.V. de Besançon) présente un point évolutif des données recueillies au cours de l'enquête officielle de pharmacovigilance.

• L'enquête officielle, présentée devant la Commission Nationale de Pharmacovigilance le 17 Juin 1993, avait permis de recueillir jusqu'au 1er Décembre 1992 :

- 28 observations concernant la dexfenfluramine et,
- 11 observations concernant la fenfluramine.

A ce jour :

- 10 nouvelles observations concernent la dexfenfluramine et,
- 5 concernent la fenfluramine,

Cependant, ces nouveaux cas n'ont pu être encore expertisés par M. le Pr WEITZENBLUM.

5 dossiers recueillis par les C.R.PV mais transmis à l'I.P.P.H.S. n'entrent pas dans cette analyse.

La répartition de ces cas selon les critères établis par M. le Pr WEITZENBLUM se fait comme suit :

ISOMERIDE

ENQUETE (jusqu'au 01/12/92) / (Nouveaux cas)
28 (10)

	TOTAL	C.R.P.V.	A. BECLERE	LABO (non CRPV, non A.Béclère)
H.T.P.	14+(5)	4+(1)	5+(1)	5+(3)
H.T.P. (dossiers incomplets)	4+(3)		2+(2)	2+(1)
H.T.P. Post capillaire	3+(1)	1		2+(1)
H.T.P. Modérée	2+(1)			2+(1)
C.I.A.	2		1	1
DIVERS	3			3
TOTAL	28+(10)	5+(1)	8+(3)	15+(6)

PONDERAL

ENQUETE (jusqu'au 01/12/92) / (Nouveaux cas)
11 (5)

	TOTAL	C.R.P.V.	A. BECLERE	LABO (non CRPV, non A.Béclère)
H.T.P.	3+(2)		1+(1)	2+(1)
H.T.P. (dossiers incomplets)	3+(1)	1	1+(1)	1
H.T.P. Post capillaire	1+(1)			1+(1)
H.T.P. Modérée	4+(1)	1		3+(1)
TOTAL	11+(5)	2	2+(2)	7+(3)

2) Les évolutions

En matière d'évolution de la maladie chez ces patients atteints d'hypertension artérielle pulmonaire, on relève :

- parmi les 38 cas (10)* où l'ISOMERIDE® est cité :

  - 7 améliorations (1),
  - 16 stables (5),
  - 5 transplantations pulmonaires (1), dont 2 décédés (0),
  - 6 patients en attente d'une transplantation pulmonaire (2) dont 4 décédés (2),
  - 1 patient décédé d'une décompensation rapide (1),
  - 3 évolutions inconnues (0),

- parmi les 16 cas où le PONDERAL® est cité :

  - 3 améliorations (1),
  - 4 stables (1),
  - 3 patients en attente d'une transplantation pulmonaire (0) dont 2 décédés (0),
  - 2 évolutions inconnues (1),
  - 1 patient décédé accidentellement.

Au total, concernant les évolutions défavorables, 7 patients sont décédés (dont 4 étaient en attente d'une transplantation pulmonaire), 2 sont en attente d'une transplantation pulmonaire et 5 ont été transplantés (dont 2 sont décédés).

3) Les facteurs de risque

La revue des différentes observations met en évidence la présence de nombreux facteurs de risque connus de l'hypertension artérielle pulmonaire tels que l'hypertension artérielle, l'obésité, les contraceptifs oraux, la préexistence d'une dyspnée, un traitement prolongée ainsi que le syndrome de Raynaud et la migraine.

Mr SIMONNEAU réfute cependant les contraceptifs oraux comme un facteur de risque et rappelle par ailleurs que ces traitements sont habituellement poursuivis chez les femmes présentant une hypertension artérielle pulmonaire primitive.

M. BECHTEL précise que ces hypertensions artérielles pulmonaires semblent apparaître pour des posologies élevées ou des traitements prolongés, ce qui pourrait être lié à un problème de métabolisme dû au polymorphisme métabolique de la fenfluramine.
On ne possède d'ailleurs pas d'étude de corrélation dose/concentration pour cette molécule. M. BECHTEL va collaborer avec le service de M. DUROUX pour étudier ce polymorphisme.

La multiplicité de ces facteurs associés souligne les difficultés rencontrées lors d'une approche classique de pharmacovigilance et la nécessité de disposer d'une étude épidémiologique.

()* : cas notifiés depuis le 01/12/92

III - L'I.P.P.H.S.

- M. ABENHAÏM rappelle quelques caractéristiques de l'étude I.P.P.H.S.
Cette étude doit permettre le recrutement de :
  - 100 cas incidents (diagnostic fait après le 01/09/92),
  - 400 témoins appariés selon l'âge et le sexe,

ainsi que des cas prévalents (diagnostic fait entre le 01/01/92 et le 31/08/92) afin de disposer d'une base de comparaison.

Les effectifs sont calculés pour mettre en évidence un risque supérieur à 4.

- En France, le recrutement a effectivement débuté après le 30 septembre 1992 et dans les autres pays concernés (Royaume-Uni, Pays-Bas, Belgique, Suisse) à compter du 1er mars 1993. Au total, 150 centres participent à cette étude.

- A ce jour, environ 150 cas d'H.T.A.P. ont été recueillis, dont 66 ou 67 cas incidents correspondant à l'ensemble des critères déterminés.
Pour l'analyse intermédiaire, 49 cas ont été interviewés, tous revus par le Comité Scientifique International, ainsi que 129 témoins.

La répartition, selon les pays, se fait comme suit :

France	31
Royaume-Uni	8
Belgique	7
Pays-Bas	3
Total	49

Le codage et l'informatisation de ces dossiers est en cours de réalisation.
Au rythme actuel, la fin des inclusions pourrait avoir lieu courant l'été 94. L'analyse intermédiaire ne pourra être disponible qu'au cours de la seconde semaine de Mars 1994.

Le problème du recrutement des témoins est soulevé, notamment le problème de l'appariement sur le poids.

Le recrutement de témoins et l'interview de l'ensemble des patients sont longs. Il est indispensable pour chacun d'eux d'établir l'histoire de vie du patient afin de retrouver la période d'apparition d'une première dyspnée (date index) à partir de dates signifiantes dans la vie d'un individu.

Deux types de validation ne pourront être réalisées avant l'analyse intermédiaire.
Il s'agit de :

- l'étude du biais de déclaration des cas,
- la validation de l'information collectée.

IV - CONCLUSIONS

Cette absence de validation est susceptible d'affecter considérablement la fiabilité des décisions éventuellement engendrées par les résultats de l'analyse intermédiaire, ce d'autant que le nombre de témoins paraît insuffisant.

Ces résultats doivent donc être analysés avec circonspection. Dans ces conditions, l'utilité même de disposer d'une telle analyse intermédiaire, y compris vis à vis de l'avenir de l'étude, peut être remise en cause.

Cependant, cette analyse intermédiaire dont la possibilité est prévue dans le protocole initial a déjà été officiellement demandée au Comité Scientifique International de l'I.P.P.H.S. par les autorités françaises car, le nombre de cas d'H.T.A.P. survenant en France pose un réel problème de Santé Publique.

Compte tenu de l'absence de résultats de l'analyse intermédiaire et de faits nouveaux, la Commission Nationale de Pharmacovigilance ne semble pas devoir être immédiatement saisie de ce dossier.

Annexe 1-51

Confidential

Do not circulate

INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY

REPORT OF THE

INTERMEDIATE ANALYSIS

Copie Remise à :
Prof. J. L. Imbs

L. Abenhaim and the IPPHS Study Group

April 5, 1994

EDIATE ANALYSIS OF THE
NARY HYPERTENSION STUDY
IIS TUESDAY, APRIL 5, 1994

AUBIER, M.
Member, IPPHS Int'l Scientific Board

BENICHOU, J.
Member, IPPHS Int'l Scientific Board

DEMEDTS, M.
Member, IPPHS Int'l Scientific Board

NAEIJE, R.
Member, Scientific Advisor

RICH, S.
Member, IPPHS Int'l Scientific Board

STRICKER, B.
Member, Scientific Advisor

WOUTERS, E.
Member, IPPHS Int'l Scientific Board

WARNING

The recruitment of patients in the IPPHS is not yet terminated. Thus, the findings reported in the present document only involve half the number of patients originally planned in the protocol and less than one third of the needed control group.

Hence, the results presented here should be interpreted with extreme caution, even if some of these results reach the conventional levels of so-called "statistical significance".

A final report will be released at the end of the study with analyses made on the entire study population. Considering the work already done in the implementation of the study and the analysis, and at the present pace of recruitment, we are confident that the recruitment of cases will be completed during the summer of this year, that is exactly on schedule.

This report is endorsed by all the members and scientific advisors of the IPPHS. It will be released, at his request, to Professor Jean-Louis IMBS, President of the French Pharmacovigilance Commission (letter dated January 24, 1994) and to Dr Laurent Perret, President of the Institut de Recherche Internationales Servier (IRIS). Results should remain strictly confidential and the present document is not to be circulated under any circumstances, nor cited.

We wish to thank the Institut de Recherches Internationale Servier who has sponsored this study and has allowed us to work in total independence.

1. INTRODUCTION

The following report summarizes the findings obtained in an intermediate analysis of data so far collected in the International Primary Pulmonary Hypertension Study (IPPHS), a large scale epidemiologic case-control study conducted in 5 European countries (France, United Kingdom, Belgium, The Netherlands and Switzerland). The complete protocol may be found in Appendix.

Two major factors prompted the conduct and the release of an intermediate analysis of the IPPHS data. First, this analysis was planned in the original protocol where it was stated that it should be done upon the recruitment of 50 cases. Not doing it would be considered as a breech of the protocol. Second, it was formally requested by the French Pharmacovigilance Commission.

While an intermediate analysis is almost considered as standard procedure in clinical trial settings, such an analysis is rarely officially released in the context of observational studies where retrospective data are collected. The conduct of the study has in itself no impact on the risk factors studied since the exposures occured several months or years before the outcome at end.

The objectives of the intermediate analysis were:

1. To identify potential problems with the ongoing study in order to eventually reappraise the study methods. This includes potential biases, logistics problems and inconsistencies in the type and formats of the variables collected

2. To conduct a preliminary assessment of the effect of risk factors selected a priori on the occurrence of PPH.

2. METHODS

2.1 Feasibility study

A feasibility study was conducted in may 1992 in France. Four approaches were taken:

1. One hundred and ten (110) Divisions of Pneumology and/or Cardiology of University Hospitals in France have received a letter asking them to participate in the study (two mailings). Seventy-eight of them (78%) have responded and 1 has refused. The remainder have not responded. All the major centres have actually consented to participate, including the referring centres and transplantation centres. Of the respondents, 22 had seen no cases in the past year, 28 had seen 1 to 2 cases per year, and 9 had seen more than 2 cases per year. Nineteen (19) did not report the number of cases that they had seen. Nine other centers later on accepted to participate.

2. A field feasibility study has been conducted during the month of May 1992 (4 weeks) in the Aquitaine region of France (around Bordeaux). This region represents a catchment population of approximately 4.2 million inhabitants. The heads of the divisions of Pneumology (3), Cardiology (8), Internal Medicine (6), Chest Surgery (2) and Intensive Care units (4) of the five University and Military Hospitals have been contacted in the region. Three (3) large private clinics were also surveyed. Finally, 32 local hospitals were contacted. They were all visited whenever they declared that they had diagnosed a PPH case in the preceding 16 months. Seventeen (17) cases were found. After applying an algorithm for case-ascertainment, 7 cases were considered meeting the inclusion criteria for the study. Extrapolating these results, when applied to the whole of France, this figure would lead to 72 potential "validated" cases per year in this country.

3. Forty-two (42) private cardiologists and 18 pneumologists were randomly selected among the list of cardiologists practicing in the Aquitaine region. They were contacted by telephone. The objectives of this survey were: (i) to validate the patterns of referral of PPH cases seen by private cardiologists; (ii) to possibly identify more cases of PPH that would have been missed in the hospital centres. Forty-one declared that they would refer a case of PPH for treatment and/or confirmation of diagnosis to a University Hospital, 9 to a private clinic and 10 to local hospitals. It was confirmed that most of these cases would however end up in a University Centre. These centres were among the 23 surveyed. Two potential cases of PPH had been seen by the private cardiologists in the 16 months preceding the interview. These 2 cases were among the 17 found in the survey of the University Centres.

4. Mortality data from France (INSERM) and The Netherlands indicate that approximately 20 individuals per 10 million inhabitants die each year with a primary or secondary diagnosis of PPH.

From these results, we concluded that the incidence of PPH in a country like France was in the order of 2 per million inhabitants and per year.

The five countries involved in the study altogether have 150 million inhabitants, with a maximum expected number of 300 incident cases per year. It was estimated that 50% of the cases would meet the inclusion criteriae for the study and that 50% of them could be recruited, i.e: a maximum of 75 per year. To allow for the uncertainty in the incidence, it was planned that 100 cases could be recruited over 2 years.

2.2 Main study

Centres

The IPPHS has been launched in september 1992. Its objectives are to identify risk factors for primary pulmonary hypertension (PPH). All suspected risk factors are considered. A large series of other variables are explored in the absence of epidemiologic data on the disease.

In the 5 countries, all centres susceptible to see PPH cases were contacted in order to sollicitate their participation.

Centres were asked to report their cases by sending a pre-addressed post-card to the local research team (LRT) established in each country (Switzerland was managed by the same LRT as France). All the Centres were contacted regularly (every three months) by telephone in order to verify that all their cases were reported. They also received regular reminders by mail. In France, a special series of conferences was organized in 7 cities where the main referal centres for PPH are located (Paris, Strasbourg, Lyon, Marseille, Nice, Bordeaux and Nantes). More than 40 clinicians from the participating Centres in the five countries attended a special one day symposium at the Conference of the American College of Chest Physicians in Chicago where the rationale and methods of the study were presented.

Cases

Inclusion criteria: The required tests are detailed in the protocol attached in appendix.

Only cases who were diagnosed as PPH after september 1st, 1992, were considered as "incident cases" and thus eligible for this study. The date retained for the diagnosis was the date of the catheterization. Cases diagnosed before but reported to the study teams were considered as "prevalent cases" and were not used for this study. However, clinical data were collected for a number of those cases, in particular those diagnosed between January 1st, 1992 and August 31, 1992. For the analytical part of this intermediate analysis (case-control analysis), the study population was restricted to only those 50 cases who were incident, alive, interviewed and who had matched controls.

Screening: A screening of cases reported is made over the phone or on site by a physician who verifies that the inclusion criteriae for the study are met.

Extraction of medical data: Whenever a case is considered as admissible for the study, a pulmonary physician or a cardiologist, appointed by the LRT in each country, goes on site to review the medical chart and extract the data for the study.

Case validation: All of these cases have been reviewed by the International Review Committee (experts from the United States and Canada) and only those who were considered as very likely or

likely PPH cases were retained. Results of all tests (including catheterization) were considered, and copies of X-Rays, CT-Scans and other imaging techniques were obtained for the majority of cases. When these images were not available to the review committee, cases were given a lower rank of appropriateness for the study.

Controls

Up to four controls per cases are recruited. As stated in the protocol, controls are patients who consult the same general practitioner (GP) as the case. If not possible, another GP practicing in the case's neighborhood was selected. However, due to logistics reasons, all matched controls have not been interviewed at the time of this intermediate analysis. Hence, other individuals who met the matching criteria for these cases were found elsewhere: controls of cases who died before the interview or who were rejected after the interview, controls of prevalent cases (not considered in this intermediate analysis), controls of other cases included in the analysis who have several controls.

Interviews

Interviews were conducted by specially trained interviewers who were blinded on the objectives of the study. They had no medical background. Drug use was elicited through a five step procedure (see below).

Index date

The index date corresponds to the date of onset of symptoms of the case (mainly dyspnea). This date was used as the index date for the matched controls. All exposure were considered only if they had started before this index date.

General Variables

The following variables were included in the analyses:

1. *Demographic characteristics:* age, gender, race (not reported).
2. *Clinical profile:* catheterisation data, chest x-ray, lung perfusion scan, angiogram, symptoms, pulmonary function tests, blood chemistry, blood gases, anti-nuclear antibodies.
3. *Other disease characteristics:* family history of PPH.
4. *Medical history:* due to the large number of disease types, past diseases and co-morbidity were classified, for this analysis, into ICD-9 broad classes, with the exception of cardiovascular and respiratory diseases which were more detailed.
5. *Medical family history:* classified into ICD-9 broad classes
6. *Blood group:* A, B, O and Rhesus.
7. *Pregnancies:* pregnancies before the index date.

8. *Obesity:* Obesity before the index date was assessed by the body mass index (weight divided by height squared). The highest weight in the past was used as a marker for obesity before the index date. The cut-off to define obesity was databased and defined as the upper 25th percentile of the distribution of body mass indices among controls (BMI=30).
9. *Habits:* smoking, coffee, tea, herbal tea, alcohol, food habits (cheese, chocolate, paté, smoked meat, game meat, yeast extracts) were considered before the index date and after.
10. *Behaviour:* conducive to weight loss or preoccupation with figure: use of artificial sweeteners, natural foods, past episode of anorexia, dieting, weight loss before index date, plastic surgery before index date, sports.
11. *Low or high pressures:* Altitude, plane trips, scuba diving

Drugs

Analyses of drug exposure was conducted in two different perspectives:

1. Testing of hypotheses: the association between drugs selected a priori and the occurrence of PPH was assessed with the following: anorexigens (amphetamine-like drugs, fenfluramine, dexfenfluramine), oral contraceptives, thyroid extracts.

2. Generating hypotheses: some associations were discovered during the bivariate analyses and are reported.

For the adjustment of models, co-medications were classified into broad classes according to the Anatomical Therapeutical and Chemistry Classification (1993).

Ascertainment: only drug use as reported in the face to face interview were considered for this intermediate analysis. The information appearing in the cases medical charts were not used in order to maintain comparability of data between cases and controls. However, in a later stage, these informations will be used to validate the questionnaire data and also to estimate potential information biases in the study. Five methods were used to obtain this information: 1) history of life events drug use; 2) medical history/drug use; 3) drug spontaneously reported; 4) eliciting of drug use by presentation of drug listings; 5) presentation of a visual display with selected packages.

Parameters: The following parameters were used to study past exposure to drugs:

- *time window:* in the absence of an accepted model for the physiopathologic process of the disease, it was decided that any exposure that acts on the vasoreactivity would be considered as a potential risk factor for the disease process and that this effect could be immediate or delayed. Exposure was considered for all times before the index date. A

specific analysis was done for exposure that occured between August 1989 and the index date, because of the better accuracy of data available for this period. Exposure after the index date was documented but not considered in risk analysis models. (Note: persons who had exposure in more than one of these time periods were considered as exposed provided that they had exposure before the index date).

. *duration of exposure:* the duration of exposure during the risk period was measured in number of days of treatment before the index date. Occasional and intermittent use were recorded as a categorical variable. Because of the small numbers involved, this results are not reported with the intermediate analysis.

Anorexigens: Anorexigens where more indepthly studied tahn other drugs. Their use was expressed in the following categories:

1) Use of fenfluramine or dexfenfluramine (F/DF) only;
2) Use of amphetamine-like drugs only (including Amfepramone, Mazindol, Clobenzonese, Fenproporex),
3) Multiple use of anorexigens, at least one product being F DF;
4) Multiple use of anorexigens, at least one product being amphetamine-like;
5) Use of both F/DF and amphetamine-like drugs;
6) Use of at least one anorexigen.

Statistical analysis

Descriptive analyses: categorical data are reported as frequency distributions and continuous data are reported by the mean, standard deviation, median, minimum and maximum values. When necessary, heterogeneity between countries or genders were assessed by the chi-square statistics (for categorical data) and the Z statistics (for continuous data).

Bivariate analyses: In these analyses, data from cases were compared to those from controls. Hence, only the information available on both groups was used. Differences between cases and controls were assessed by the chi-square test for categorical variables and the Z score statistics for continuous variables.

Adjusted odds ratios: The magnitude of the effect of selected risk factors on the occurrence of PPH was assessed by the odds ratio, an estimate of the relative risk. In order to control for possible confounders, multivariate analyses were conducted. The main variables in the models were exposure to the drugs of interest (see above). In addition, the following variables were included in the models: marker of obesity (see above), systemic hypertension, pregnancies, behaviour conducive to weight loss (other than drug use) (see above). The odds ratios presented are also controlled for a series of variables which were statistically different between cases and controls. All these analyses were matched.

The uncertainty associated with odds ratio estimates was assessed by the 95% bilateral confidence interval. All statistical analyses were conducted using the Statistical Analysis System (SAS), version 6.0. Multivariate analyses were conducted using the Egret Statistical package.

Country effect: The characteristics of patients reported to the study may differ in the countries included in the study. The influence of drug use on the reporting may vary as the publicity made on the study and possible associations differ. This would also allow to identify possible differences associated with the varying prevalence of some exposures from country to country.

Effect of the reporting centre: some centres may be specialized in treating PPH with defined characteristics. One centre having reported more than half of the cases recruited in France, those cases were compared to the cases from other centres on a number of variables.

3. RESULTS

3.1 Study population

Three hundred and six (306) centres were contacted in the five countries, of which 223 (72.9%) have accepted to participate in the study. The distribution of centres by country are presented in Table 1.

Two hundred and fifteen (215) cases of PPH were identified altogether (Table 2). After a first creening, 105 of them did not meet the inclusion criteria for the study (in Belgium and the Netherlands, the screening was mainly done on site and the number of cases not admissible was not recorded). Reasons for exclusion were based on the date of diagnosis, the availability of catheterization data, age and other criteria listed in the protocol. A total of 110 incident cases of PPH (diagnosed after September 1st, 1992) were considered admissible after the first screening. The detailed description of the study population recruited so far is presented with Table 3.

Sixteen (16) patients died after reporting or were actually dead at the time of reporting.

The Review Committee has assessed 89 cases, of which 68 were accepted for the study, 15 were rejected, 6 have not been categorized yet. Among the 83 categorized, the success rate was 81.9%.

Three (3) cases could not be interviewed for various reasons (refusal, unable to be contacted, unable to be interviewed, leaved the country). For 16 patients, medical data were not extracted by the time of the intermediate analysis and 9 others had not been

interviewed.

It is worth noting that there are several elligible cases in process of data collection. If the same rate of success applied to this set of subjects as for the cases so far, we would have approximately 20 more cases available in the next few weeks.

One hundred and twenty three (123) matched controls could be used for the intermediate analysis, that is an average of 2.46 controls per case.

The distribution of cases and controls per country available for the intermediate analysis is presented in Table 4.

3.2 Clinical presentation of cases

All the available incident cases were used to describe the clinical profile of PPH cases. Table 5 presents the data for the main clinical parameters. The clinical characteristics of the case patients in our study are extremely similar to the patients included in the NIH registry. One can consider the cases as corresponding truly to primary pulmonary hypertension as defined by internationally recognized standards.

3.3 Comparison of cases and controls

- General risk factors

1. *Habits:* As shown in the table 6.1, cases and controls before the onset of symptoms of PPH were very comparable in their smoking and drinking behaviours as well as in their eating habits. As expected, cases changed their habits after the onset of symptoms (results not shown).

2. *Behaviour conducive to weight loss or preoccupation with figure:* According to the markers used in the study, cases and controls were as likely to be conscious of their weight or figure, with the exception of laxative and anti-obesity preparation use before the onset of symptoms where a greater proportion of cases were using these products (table 6.2).

3. *Obesity:* Cases had a greater body mass index (BMI) than controls (median 28.30 versus 25.50).

4. *Pregnancy:* There was no significant difference between cases and controls in pregnancies before the onset of symptoms of PPH, 36 cases (76.6%) and 91 controls (85.1%)(p=.204) having had at least one pregnancy.

5. *Blood group:* No statistically significant differences (Table 6.3).

6. *Sexual partners:* The majority of interviewees answered they only had 1 sexual partner in the last 10 years. 24.0% of cases and 21.5% of controls have had 2 or more. The difference between cases and controls was non significant (p=.614).

7. *Other suspected risk factors:* there was no difference between cases and controls in their exposure to altitude, utilization of planes and the practice of scuba diving (Table 6.4).

Co-morbidity and family history

Cases reported less comorbid conditions before the index date than controls. This was particularly the case for heart disease and musculo-skeletal complaints, where the adjusted odds ratios were borderline to significance (OR = 0.5 and 0.3 respectively, with p=0.06 in both instances).

For most conditions, cases and controls were fairly homogeneous with respect to family history. However, significantly more controls than cases had a family history of heart disease disease (63.6% versus 46.0%, p=.033) and of arthritis (29.8% versus 12.2%, p=.017) (Table 6.5).

These statistical differences between cases and controls was controlled for in the multivariate analyses (all presented adjusted odds ratio). As stated in the discussion further below the differences in co-morbid conditions and familial history are not likely to have confounded the results presented here.

All classes of drugs

Table 7 presents the results of the bivariate analyses for the exposure to all drugs studied, presented by ATC sub-classes. Of the 68 comparisons made, only two appeared significant, that is the use of laxatives and of anti-obesity preparations.

Exposure to anorexigens

Tables 8.1 to 8.5 and 9.1 to 9.5 show the distribution of exposure to anorexigens in cases and controls of the four countries were incident cases were available for the case-control analysis (France, the United Kingdom, Belgium and The Netherlands).
Four categories for individual drug consumption were first considered:

1) use of at least fenfluramine or dexfenfluramine (F/DF)
2) use of at least one amphetamine-like anorexigen
3) use of F/DF and of an amphetamine-like anorexigen
4) use of at least one anorexigen.

Table 8.1 shows that 6.5% of controls had used at least one of these drugs in the past (all exposures). The exposure varied greatly between countries (Tables 8.2 to 8.5), France and Belgium

having approximately the same level of exposure in controls (10.5% and 9% respectively), while none of the controls in the U.K. and Netherlands were exposed. This absence of exposure in the later country is likely to be due to the very small numbers involved (50 controls altogether), but the differences observed reflect well the differences in the sales of these drugs in France and Belgium on the one hand vs UK and The Netherlands on the other hand.

When only the exposure between August 1989 and the index dates were considered (Tables 9.1 to 9.5), 3.3% of all controls had taken an anorexigen, the numbers being 5.3% and 4.5% in France and Belgium. The time window considered being in practice of about 2 years for most cases, these percentages of exposure appear to be very close to sales figures. The percentage of cases exposed were accordingly of 20.0% for all countries altogether. Thirty percent (30.0%) of cases had used an anorexigen.

The percentage of cases exposed at any time in the past varied also between countries, from 43.3% in France to no exposure in the Netherlands (Tables 8.2 to 8.5). The latter figure is however based on only 4 cases. In Belgium, one case who had been exposed to F/DF and to an amphetamine-like drug was reported as non exposed in Tables 8.4 and 9.4 apparently because of technical problems. We found out this only after all the analyses were done. If this case was counted, the percentage of cases exposed (corrected number: 28.6%) would become closer to that of France, in particular for the shorter time window.

The homogeneity of the reporting of cases was assessed by comparing the main reporting centre in France to all the other centres of that country (Table 10). In this analysis, the exposure to F/DF only, to amphetamines-like drugs only, to F/DF+amphetamines-like drugs and one anorexigen at least are reported. It appears that the percentage are very comparable, for both time-windows considered, and for all the categories of exposure, despite the relatively smaller numbers.

Tables 11.1 and 11.2 present the relative risks associated to anorexigens after adjustment for the risk factors which were selected a priori and for those who appeared significant in the bivariate analyses (hypertension, high BMI, pregnancy, oral contraceptives, laxatives). It appears that the use of at least one anorexigen was associated with a relative risk (estimated by the odds ratio) of 5.3 and 5.7 respectively for each time-window (best estimates). The best estimate of the relative risk was 5.5 and 6.2 for all past exposures to amphetamine-like drugs and fenfluramine derivatives. Although the confidence intervals are wide (and include 1 for amphetamine-like drugs), the results appear very stable across time windows and with differing combinations of exposure tested.

When exposure to only one of these compounds was considered, the best estimates of the relative risks were smaller (2.7 and 4.0),

and it was higher when exposure to both these categories of compounds had occured (8.7).

Table 12 presents the multivariate analysis with the effect of the main suspected risk factors, also controlled for co-morbidity. As expected, the best estimate of the relative risk for anorexigens remains of the same order of magnitude (5.8). None of the other factors appear significant, altough a tendency might be demonstrated for hypertension (best estimate of 2.3), oral contraceptives (1.8) and laxatives (3.3).

4. DISCUSSION

Recruitment

We have recruited 74 validated incident cases (including the dead) in France, 11 in Belgium and 11 in the Netherlands over 15 months. Considering that many cases could not been kept in the study because of our very strict inclusion criteria, these figures are not inconsistant with the number of cases expected each year (2 per million according to our feasibility study). It is likely that we have missed a number of incident cases, but we do not feel that this could be a very important phenomenon. Actually, we had estimated in our feasibility study that 72 admissible per year would occur annually. Our criteria for admissibility in the feasibility study were less strict than those actually applied in the main study. We have contacted very frequently all the centres involved. The local research teams have positively harassed the participating centres. In our systematic visit to the main centres of 7 French cities, (Paris, Strasbourg, Lyon, Marseille, Nice, Bordeaux, Nantes) we had no basis to consider that a large number of cases could have been missed.

The only country which clearly differs from the others as far as the recruitment of cases is concerned, is the UK were only 14 cases could be considered for the study so far. However, 66 cases had been identified (compared to 107 in France for instance). The ratio of identified cases to inclusion is greatly in disfavor of the UK. Among possible explanation are the smaller rate of catheterization and the delay for referal to specialized centres. Both these phenomenons would result in a lower rate of inclusion in the study. On the basis of this intermediate analysis, it appears urgent to analyze the reasons for this discrepancies.

Switzerland has joined the study only lately. Only francophones cases are considered because of the load involved in the traduction of the material in the 3 other official langages of that country. Thus, the catchment population for the study is about 1.5 million. With a rate of recruitment similar to the other countries, 0 to 2 cases were expected over the period of recruitment, while none were found.

A number of other incident cases are in the process of data collection. On the basis of the present rate of success in the validation of cases and conduct of the interviews, approximately 20 other cases should be available very soon.

The recruitment of controls is doing well. It is a little bit slower than the recruitment of cases, but this is to be expected in view of all the steps involved to obtain access to the controls to be interviewed.

Sample size

Another important weakness lies in the small number involved at this stage. Only a few cases more in one or another cell of the database would result in significant differences. Association that do not appear "statistically significant" now could very well be confirmed when more subjects are involved. The absence of exposure to anorexigens in some categories of controls, in some countries, is an exemple of the lack of accuracy of the estimates, since the drugs are marketed in all the countries considered. This weakness will be largely overcome by the end of the study, when three times as many control subjects will be available.

Validity of the results

Cases and controls were extremely comparable for all the risk factors studied. The only differences found were on comorbidity and familial history of heart and musculo-skeletal diseases, were controls were found to have more of these diseases than cases. It is difficult to know what this phenomenon means at this stage. The four hypotheses proposed are:

i) selection bias of physician-based controls (the visit to a GP being prompted by a complaint): this could in particular explain the difference in mild conditions such as muscult-skeletal disorders);

ii) selection bias of cases: cases with preexisting heart conditions were excluded because of the doubt on the primary nature of their PPH. They were not excluded from controls.

iii) underreporting of mild conditions by cases;

iv) chance alone.

All these hypotheses should be explored rigourously in the next phase of the study. It was originally planned to match the controls to the cases on the basis of the number of visits to physician per year. This appeared impossible to be done in practice. Doing it would have possibly controlled for this bias. We could explore further the possibility to a posteriori perform a matching of cases and controls on this variable. We could also consider heart disease as an exclusion criteria for controls. Underreporting of co-morbid conditions should also more indepthly be assessed in cases. Another possibility is to recruit the next controls through another source (e.g community controls).

In any case, it is unlikely that these biases, if they exist, may have confounded the results presented here. To be a confounder, a variable should be associated both with exposure and to the outcome. musculo-sketal disorders do not fit with this definition. Heart disease might be associated with the risk of PPH (actually here it would diminish the probability of being considered as a case). It is unlikely that it was associated with the other exposures, although it should be explored. Very reassuring are the facts that for almost all the risk factors studied, including smoking and other habits that might be associated with heart disease, we did not find any difference between cases and controls. Thus, it is very unlikely that this could have had an effect on the variables that are found significantly associated with PPH in the result section.

Reporting biases

The potential reporting biases could not be controlled for at this stage. There has been a wide publicity especially in France around the possible association between anorexigen, and in particular fenfluramine and dexfenfluramine, and PPH. That could have affected the reporting in both directions: some clinicians could have been more likely to report cases exposed, while other could consider anorexigen-exposed cases as "non primary". We have hints that both phenomenons have occured for a little number of cases. We do not know what the magnitude of these phenomenons are. We are in the process of validating the reporting.The participating centres will be audited in the next months: (i) all centres who reported cases will be visited in the next months to ensure that there was no biases in the reporting and (ii) a sample of non reporting centres will be visited as well. (iii) cases included in the study will be compared to non included ones. The fact that there is no difference in the percentage of cases exposed identified in the main reporting centre from France as compared to all other centres is reassuring. The delay of diagnosis in anorexigen exposed PPH patients could be shorter, which would result in a higher proportion of cases exposed in the study than is actually the case.

Questionnaires

The questionnaire has not been fully validated yet. In order to keep the interviewers blind to the objectives of the study, we have not been able to perform some checks. These will be done at the end of the study. In all studies using questionnaires, there is room for recall biases. An obvious possibility is that cases would be more likely to recall their exposure to anorexigens derivatives than controls. In France especially, there has been a wide publicity made towards cardiologists and pulmonary physicians regarding the possibility of the association between fenfluramine derivative use and PPH. Many of the cases interviewed had already been specifically asked by their physician about those drugs. This recall bias could have artificially increased the relative risk presented for those drugs. However, we have no indication that the the exposure of controls has been underestimated.

Consistency

Despite the limitations above-mentioned, it is worth noting that the results regarding anorexigens present a certain consistency. First, the exposure of controls closely paralels sales figure for these drugs in the different countries. The differences in exposures between France and Belgium on the one hand vs the UK and the Netherlands on the other hand is not surprising in view of the differences in sales figure. The analyses being matched, these difference were taken into account in the results reported here. The exposure of cases in France is the same when comparing the main reporting centre to all the other centres. The same magnitude of the odds ratio is found when examining different time-windows, different anorexigens (F/DF vs amphetamine-like drug) and controlling for possible confounders or other significant variables. It is also worth noting that the relative risk seems to increase when several exposures occured to different anorexigens as opposed to exposure to only one of them (i.e. from 4.0 for F/DF alone to 8.7 for F/DF+amphetamine-like drugs). It is difficult to know whether the apparently slightly higher odds ratios in the shorter time window (august 1989 to index date) corresponds to an actual exposure-disease phenomenon or if it is explained by the fewer numbers involved, when only 1 case more exposed would produce this apparent increase. Also, F/DF had a much larger part of the market in this time-window.

5. INTERPRETATION OF THE RESULTS

Relative risks (odds ratio): The results are presented in the form of odds ratios. An odds ratio of 1 signifies that the cases and the controls do not differ in terms of their exposure to a given risk factor. An odds ratio inferior to 1 indicates to what proportion cases are less exposed than controls. An odds ratio superior to 1 indicates to what extent cases are more exposed than controls (e.g.: an odds ratio of 5 indicates that cases are 5 times more frequently exposed than controls).

Whenever a study is unbiased, one can consider that a contemplated odds ratio is a valid estimate of the actual relative risk of having a disease in the patients presenting with the exposure at hand, For instance, in this study, if the results are unbiased, patients exposed to anorexigens would have about 5 times more frequently a primary pulmonary hypertension than comparable non exposed individuals.

Best estimates and Confidence intervals: The so-called best estimate presented for an odds ratio is the value that was observed with the available data. The 95% confidence intervals indicate that, given the available sample size, one is confident that the true odds ratio would 95% of the time fall between the boundaries of the confidence intervals. If one of the boundaries includes 1, it is conventionally considered that the best estimate is less reliable since in more than 5% of the time, with the given sample size, the true odds ratio could actually point in the inverse direction than the presented best estimate. The width of the confidence interval is only a function of the sample size at hand and should be interpreted in keeping in mind other informations available. For instance, The lower bound of the odds ratio for F/DF+amphetamine-like drugs is 0.7 while the lower bound for F/DF alone is 1.1: this reflects well that the boundaries of the confidence interval is mainly a function of the number of subjects available for the analysis.

Causality: In interpreting odds ratios or relative risk to infer that an exposure is a cause of a disease one should, especially when the relative risk is small: i) rule out possible confounders; ii) obtain an understanding of the potential mechanisms of action; iii) examine dose-response relationships. In this study, we have assessed a very wide number of potential confounders and verified to what extent they could bias the results presented, We have not been able to find any reason to believe that the results could be confounded. However, there are still some possibilities that unknown confounders or variables not

controlled for could exist. For instance, the fact that laxatives are asociated with a higher relative risk of PPH is intriguing. One can hardly see why such an exposure could induce the development of PPH. It is very much possible that this association occured by chance alone, in view of the small number involved. It is also possible that the use of laxatives is a marker of an underlying confounder that was not controlled for. If this was the case, the same explanation could possibly apply to anorexigens. In the latter instance, the number of cases and controls exposed is somewhat higher, and the role of chance in the observed results is accordingly much lower. But one cannot at this stage exclude that the use of these drugs is a marker of an underlying phenomenon, although one can hardly know which one. Finally, anorexigens could act as "triggers" in susceptible individuals rather than actually causing the disease. It should be possible to better analyse all these phenomenons when more cases and controls will be available, with the study of time-to-events and of the personal characteristics of cases exposed as compared to controls.

SUMMARY AND CONCLUSIONS

1. The International Primary Pulmonary Hypertension Study (IPPHS) was launched in september 1992. Five countries participate in the study (France, the United Kingdom, Belgium, The Netherlands and Switzerland). Two hundred and six (206) clinical centres participate in the study. Its objective are to identify risk factors for primary pulmonary hypertension (PPH), a rare but very serious disease, with an annual incidence estmated to be around 2 cases per million inhabitants per year.

2. 215 cases of PPH were identified so far from the 5 countries, of which 110 were incident cases, diagnosed after september 1st, 1992. 15 cases were rejected by the expert review committee, 16 had deceased before reporting, before the extraction of medical data or before interview, 3 were impossble to interview (numbers not mutually exclusive). 50 cases could be used for this intermediate analysis. 20 more cases are in the process of validation. The recruitment of cases in the IPPHS is going as expected. The number recruited so far meet the objective set in the protocol and the target number of 100 validated cases within 2 years after the launch of the study are very likely to be met. Also, the quality of the cases correspond to international standards and fully respect all the inclusion and exclusion oriteria for the study.

3. Up to four controls are recruited by case. They are identified through general practionners. The recruitment of controls is doing well. It is a slower than the recruitment of cases, but this is to be expected in view of all the steps involved to obtain access to the controls to be interviewed. 123 controls, matched to the 50 cases, could be used for this intermediate analysis. These controls are very much comparable to the cases on all the requiered variables. Exception to this are some variables associated with co-morbidity, which are not likely to have confounded the results presented here. This should be easily controlled for in the future and was actually controled for in the presented intermediate analysis.

4. Cases and controls are interviewed by specially trained interviewers with a material adapted to each country. The questionaire are in the process of validation. A very wide range of factors are studied. A priori hypotheses concerned anorexigens, oral contraceptives, use of thyroid extract, obesity, hypertension, pregnancy and familial history of the disease. Hypothesis generating is undergone on lifestyle habits (smoking, dietary habits, consumption of alcohol, cafeine, etc), morbid conditions, family history of diseases, exposure to all classes of drugs and other factors. Exposures considered are only those which occured before the beginning of symptoms of PPH (index

date).

5. Univariate, bivariate and multivariate anlyses, were conducted for this intermediate analysis. This analysis had been planned in the protocole of the study, when 50 cases would be available. Its objective are to identify potential areas for adaptation of the study protocol and logistics. The numbers available are small and thus limited the extent of the analysis to be performed.

6. The results of the intermediate analysis are provided to the head of the French Commission for Pharmacovigilance, afer its official request. They are also, accordingly, provided to the Institut de Recherches Internationales Servier, who sponsored the study, and to other regulatory authorities which submit a formal request to the chairman of the IPPHS. The report of the intermediate analysis has been approved by the international scientific board of the study and its scientific advisors, who have all work in complete independence.

7. The best estimate of the relative risk of PPH is 5.8 (1.7-20.1) for all past exposures to anorexigens. Exposure to fenfluramine or dexfenfluramine (F/DF) or to amphetamine-like drugs in isolation are associated with relative risks of 4.0 (1.1 -14.5) and 2.7 (0.2-38.1) respectively, the difference between these product being non statistically significant. The use of both F/DF and amphetamine-like drugs seems to increase the relative risk up to 8.7 (0.7-103.7). The very wide confidence intervals reflect the small sample size available. The results concerning anorexigens appear quite consistant when different time windows are studied, as well as when different combinations of exposure are considered. Despite the wide confidence intervals, it is felt that the best estimates presented here do reflect the order of magnitude of the actual odds ratio associated with these drugs. This result is consistent with the a priori hypothesis of the study.

8. An intriguing finding is the higher relative risk for the exposure before to laxatives [3.3 (0.4-31.5)]. This finding might be due to chance alone or indicate that patients using drugs to loose weight and who develop primary primary hypertension share an unknown risk factor for the disease. This will have to be explored further in the subsequent stages of the study.

9. The mechanisms underlying the observed association cannot be proposed at this stage. Factors explaining a potential individual susceptibility remain to be assessed.

10. There are some indications that two other highly prevalent risk factors which were listed among the a priori hypotheses for the study could be associated with PPH, although the associations are weak and may disappear or be confirmed at later stages of the recruitment. Oral contraceptive use is associated with an odds ratio of 1.8 (0.6-5.9) in this sample and essential hypertension with an odds ratio of 2.3 (0.4-12.6). This will have to be confirmed when the study will be completed. The interaction between all the risk factors for PPH will have to be studied.

11. None of the validation studies for the control of potential reporting and information biases has been completed so far. The study is going well and should be completed on schedule. Some adjustments to the protocol and in the logistics of the study have to be decided.

12. The International Scientific Board of the IPPHS strongly feels that the study should be completed in order to consolidate the data and to analyse the possible role of oral contraceptives, hypertension, laxatives and patterns of exposure to anorexigens, as well as other factors

Table 1: Participating Centres

Country	Centres (N) contacted	Centres (N) that agreed	Participation rate* (%)
France	138	86	62.3
United Kingdom	46	42	91.3
Belgium	71	67	94.4
The Netherlands	48	25	52.1
Switzerland	3	3	100.0
TOTAL	**306**	**223**	**72.9**

Table 2: Cases identified and screened admissible per country

	Cases identified	Admissible cases
France	107	74
United Kingdom	68	14
The Netherlands	11	11
Belgium	11	11
Switzerland	18	0
Total	215	110

Table 3: Recruitment of cases for case-control analysis

Incident cases admissible:	110
Excluded	
(numbers are not mutually exclusive)	
. Deceased	16
. Impossible to interview	3
. Rejected by Review Committee	15
Included, data collection in process	
(numbers are not mutually exclusive)	
. Medical data not extracted yet	16
. No decision taken by review committee:	6
. Interviews not done:	9
. No matched controls:	2
Number of cases alive, interviewed and with matched controls:	50

Table 4: Number of Cases and Controls Recruited per Country

Country	Cases (N) (% study popn)	Controls (N) (% study popn)
France	30 (60.0)	57 (46.3)
United Kingdom	9 (18.0)	28 (22.8)
Belgium	7 (14.0)	22 (17.9)
The Netherlands	4 (8.0)	16 (13.0)
Switzerland	0 (0.0)	0 (0.0)
TOTAL	50	123 (100.0)

Table 5: Characteristics of PPH patients included in the analysis

Characteristic	No.	% study popn
Sex		
Men	5	10.0
Women	45	90.0
	Mean	SD
Age at diagnosis	43.8	14.0
Delay between symptom onset and diag. (month)	19.8	17.0
Symptoms	No.	%
Dyspnea on exertion	46	92.0
Dyspnea at rest	5	10.0
Fatigue	10	20.0
Near syncope	11	22.0
Syncope	9	18.0
Angina pectoris	8	16.0
Palpitations	6	12.0
Raynaud's phenomenon	4	8.0
Oedema of lower limbs	19	38.0
NYHA Class		
No impairment	1	2.1
Mild	15	30.0
Marked	29	58.0
Impairment at rest	3	6.0
Do not know	2	4.0
Symptoms leading to first presentation		
None	2	4.0
Dyspnea on exertion	41	82.0
Syncope	3	6.0
Oedema of lower limbs	1	2.0
Other	1	2.0
Do not know	2	4.0
Incidental discovery		
ECG	1	2.0
Echocardiogram	1	2.0
Known family history of PPH		
Yes	1	2.0
No	44	88.0
Do not know	5	10.0

Table 5 (cont'd): Characteristics of PPH patients included in the analysis

Characteristic		SD
CBC		
Haemoglobin (g/l)	14.5	1.8
Leucocytes ($10^3/mm^3$)	8.7	6.2
Platelets ($10^3/mm^3$)	415.6	1318.8
Liver function tests		
Total bilirubin (umol/l)	18.8	11.2
ALT% predicted	92.6	---
AST % predicted	90.9	---
Gamma GT (mIU/ml)	74.1	80.3
Alkaline phosphatase (mIU/ml)	146.7	129.3
Prothrombin time	1.9	1.0
Arterial blood gases		
pH	7.5	0.05
$PACO_2$ (KPa)	4.6	3.3
PAO_2 (KPa)	18.3	22.1
SAO (%)	94.2	3.7
Pulmonary function tests		
Forced vital capacity (% predicted)	95.5	16.1
Total lung capacity (% predicted)	97.6	15.4
FEV (% predicted)	89.4	17.7
DLCO (% predicted)	76.8	26.1
Right catheterisation		
Pulmonary arterial pressure systolic (mmHg)	88.9	17.1
Pulmonary arterial pressure diastolic (mmHg)	39.9	15.0
Pulmonary arterial pressure mean (mmHg)	57.1	34.0
Mean pulmonary capillary wedge press.(mmHg)	11.3	7.7
Cardiac output	3.9	1.1
Cardiac index	2.1	0.6
Mean right atrial pressure (mmHg)	11.7	7.4
Min. right ventricular end-diastolic press. (mmHg)	15.0	19.6
Heart rate (bpm)	86.2	14.8
Syst. blood pressure systolic	135.2	19.5
Syst. blood pressure diastolic	84.0	12.6
Syst. blood pressure mean	101.2	14.1
SVO_2	60.4	13.6
PVO_2	5.5	1.5
Left ventricular end-diastolic pressure	7.7	2.3

Table 6: Bivariate Analysis of Risk Factors

6.1 Habits

	Cases (N) (%)	Controls (N) (%)	p value
Smoking	16 (36.0)	37 (30.6)	.490
Alcohol	31 (62.0)	75 (62.0)	.998
Coffee	37 (74.0)	100 (82.6)	.198
Tea	21 (42.0)	62 (51.2)	.271
Herbal tea	10 (20.0)	25 (20.7)	.922
Coke	20 (40.0)	35 (28.9)	.158
Cheese	47 (94.0)	109 (90.1)	.553
Chocolate	36 (72.0)	84 (69.4)	.679
Paté	21 (42.0)	70 (57.85)	.154
Smoked meat	21 (42.0)	58 (47.9)	.110
Game meat	5 (10.0)	13 (10.7)	.885
Yeast extract	24 (48.0)	58 (47.9)	.971

6.2 Behaviour conducive to weight loss or preoccupation with figure

	Cases (N) (%)	Controls (N) (%)	p value
Anorexia	6 (12.0)	16 (13.2)	.828
Shopping in health food stores	12 (22.0)	42 (34.7)	.387
Unstable weight	31 (62.0)	71 (58.7)	.687
Sports	24 (48.0)	73 (60.3)	.139
Cosmetic surgery	3 (6.0)	6 (5.0)	.781
Laxatives	4 (8.0)	2 (1.7)	.040

Table 6: Bivariate Analysis of Risk Factors (continued)

6.3 Blood group

	Cases (N) (%)	Controls (N) (%)	p value
Blood group			
A	19 (38.0)	39 (32.2)	.498
B	7 (14.0)	11 (9.1)	
AB	3 (6.0)	7 (5.8)	
O	15 (30.0)	36 (29.8)	
Do not know	6 (12.0)	28 (23.1)	
RH factor			
Positive	38 (76.0)	84 (69.4)	.298
Negative	5 (10.0)	8 (6.6)	
Do not know	7 (14.0)	29 (24.0)	

6.4 Other suspected risk factors

	Cases (N) (%)	Controls (N) (%)	p value
High altitude	14 (28.0)	44 (36.4)	.240
Plane	25 (50.0)	67 (55.4)	.738
Scuba diving	2 (4.0)	5 (4.1)	.968

6.5 Family history

	Cases (N) (%)	Controls (N) (%)	p value
Heart disease	23 (46.0)	77 (63.6)	.033
Lung disease	18 (36.0)	53 (43.8)	.346
Arthritis	6 (12.2)	36 (29.8)	.017
Alzheimer	4 (8.0)	4 (3.3)	.186
Blood disease	7 (14.0)	9 (7.4)	.180
Neurological dis.	4 (8.0)	7 (5.8)	.591
Psychological disease	10 (20.0)	23 (19.0)	.881
Cancer	22 (44.0)	54 (44.6)	.940
Early onset diabetes	0 (0.0)	7 (5.8)	.082
Maturity onset diabetes	11 (22.0)	29 (24.0)	.782
Early death of unknown cause	3 (6.0)	11 (9.1)	.352

Table 7: Exposure to other drugs (between August 1989 and index date)

ATC sub-classes	Cases (%)	Controls (%)	p value
Alimentary tract & metabolism			
Stomatological preparation	1 (2.00)	2 (1.65)	.875
Antacids & gastroprot. agents	4 (8.00)	18 (14.88)	.222
Antispasmodic & antichol.	0 (0.00)	5 (4.13)	.145
Antiemetics & antinauseants	1 (2.00)	0 (0.00)	.119
Laxatives	4 (8.00)	2 (1.65)	.040
Antidiarrheals, antiinfect.	0 (0.00)	3 (2.48)	.261
Antiobesity prep.,excl.diet products	11 (22.00)	4 (3.31)	.001
Digestives, incl. enzymes	0	0	---
Antidiabetic therapy	0 (0.00)	1 (0.83)	.519
Vitamins	1 (2.00)	12 (9.92)	.076
Mineral supplements	0 (0.00)	7 (5.79)	.082
Tonics	4 (8.00)	11 (9.09)	.819
Blood & blood-forming organs			
Antithrombotic agents	2 (4.00)	3 (2.48)	.591
Antihemorrhagic prep.	1 (2.00)	0 (0.00)	.119
Antianemic prep.	0 (0.00)	2 (1.65)	.360
Serum lipid reducing agents	1 (2.00)	7 (5.79)	.286
Plasma substitute and perf. soln.	0 (0.00)	1 (0.83)	.519
Cardiac therapy	1 (2.00)	7 (5.79)	.286
Antihypertensives	6 (12.00)	8 (6.61)	.242
Diuretics	7 (14.00)	7 (5.79)	.075
Peripheral vasodilators	0 (0.00)	1 (0.83)	.519
Vasoprotectives	8 (16.00)	15 (12.40)	.530
Beta blockers	3 (6.00)	7 (5.79)	.957
Dermatologicals			
Antifungals for dermato. use	0 (0.00)	1 (0.83)	.519
Prep. for treat. of wounds & ulcers	0	0	---
Antipruritics, incl. antihistamines	1 (2.00)	0 (0.00)	.119
Antipsoriatics	1 (2.00)	0 (0.00)	.119
Antibiotics & chemotherapy, dermato.	1 (2.00)	5 (4.13)	.491
Corticosteroids, dermato.	1 (2.00)	2 (1.65)	.875
Antiseptics & disinfectants	1 (2.00)	1 (0.83)	.516
Anti-acne prep.	0 (0.00)	2 (1.65)	.360
Genito-urinary & sex hormones			
Gyneco. & antiseptics	0 (0.00)	1 (0.83)	.519
Other gynecological products	0	0	---
Sex hormones & modulators	16 (32.00)	29 (23.97)	.347
Urologicals	0 (0.00)	1 (0.83)	.519

Table 7 (continued): Exposure to other drugs (between August 1989 and Index date)

Systemic hormonal prep., excl. sex hormones			
Corticosteroids for systemic use	0	0	---
Thyroid therapy	1 (2.00)	4 (3.31)	.645
Calcium homeostasis	0 (0.00)	2 (1.65)	.360
Antibacterials for systemic use	14 (28.00)	36 (29.75)	.819
Antimycotics for systemic use	0 (0.00)	1 (0,83)	.519
Antivirals for systemic use	0	0	---
Vaccines	0 (0.00)	1 (0.83)	.519
Cytostatic agents	0	0	---
Endocrine therapy	0	0	---
Immunosuppressive agents	0	0	---
Musculo-skeletal system			
Antiinflammatory & antirheumatic	6 (12.00)	31 (36.62)	.078
Topical prod. for joint & musc. pain	0 (0.00)	1 (0.83)	.519
Muscle relaxants	1 (2.00)	2 (1.65)	.875
Antigout preparations	1 (2.00)	2 (1.65)	.875
Other drugs for disorders of MSK syst.	0	0	---
Nervous system			
Anesthetics	0 (0.00)	1 (0.83)	.519
Analgesics	24 (48.00)	66 (54.55)	.436
Antiepileptics	1 (2.00)	0 (0.00)	.119
Psycholeptics	8 (16.00)	33 (27.27)	.116
Psychoanaleptics	2 (4.00)	12 (9.92)	.199
CNS drugs, incl. parasympathomime	0	0	---
Antiparasitic products			
Antiprotozoals*	0 (0.00)	1 (0.83)	.519
Ectoparasiticides, incl. scabicides	0	0	---
Respiratory			
Nasal preparations	1 (2.00)	3 (2.48)	.850
Throat preparations	0 (0.00)	1 (0.83)	.519
Anti-asthmatics	3 (6.00)	6 (4.96)	.781
Cough & cold preparations	3 (6.00)	5 (4.13)	.599
Antihistamines for systemic use	2 (4.00)	6 (4.96)	.787
Sensory organs			
Ophtalmologicals	0 (0.00)	3 (2.48)	.261
Diagnostic agents	0	0	---
General nutrients	1 (2.00)	2 (1.65)	.875
* Phytotherapy (non specified)	2 (4.00)	1 (0.83)	.150
Unknown drugs	6 (12.00)	19 (15.70)	.533

Table 8: All Past Exposure to Anorexigens Before Index Date

8.1 All countries	Cases (N) (%) (50)	Controls (N) (%) (123)
F/DF (at least)	13 (26.0)	7 (5.7)
Amphet.-like (at least)	5 (10.0)	2 (1.6)
F/DF + Amphet.	3 (6.0)	1 (0.8)
ANY ANOREXIGENS	15 (30.0)	8 (6.5)

8.2 France	Cases (N) (%) (30)	Controls (N) (%) (57)
F/DF (at least)	11 (37.7)	6 (10.5)
Amphet.-like (at least)	5 (16.7)	1 (1.8)
F/DF + Amphet.	3 (10.0)	1 (1.8)
ANY ANOREXIGENS	13 (43.3)	6 (10.5)

8.3 United Kingdom	Cases (N) (%) (9)	Controls (N) (%) (28)
F/DF (at least)	1 (11.1)	0 (0.0)
Amphet.-like (at least)	0 (0.0)	0 (0.0)
F/DF + Amphet.	0 (0.0)	0 (0.0)
ANY ANOREXIGENS	1 (11.1)	0 (0.0)

8.4 Belgium	Cases (N) (%) (7)	Controls (N) (%) (22)
F/DF (at least)	1 (14.3)(+1)	1 (4.5)
Amphet.-like (at least)	0 (0.0)(+1)	1 (4.5)
F/DF + Amphet.	0 (0.0)(+1)	0 (0.0)
ANY ANOREXIGENS	1 (14.3)(+1)	2 (9.0)

(+1): See explanations in the text.

8.5 The Netherlands	Cases (N) (%) (4)	Controls (N) (%) (16)
F/DF (at least)	0 (0.0)	0 (0.0)
Amphet.-like (at least)	0 (0.0)	0 (0.0)
F/DF + Amphet.	0 (0.0)	0 (0.0)
ANY ANOREXIGENS	0 (0.0)	0 (0.0)

Table 9: Exposure to Anorexigens Between August 1989 and the Index Date

9.1 All countries	Cases (N) (%) (50)	Controls (N) (%) (123)
F/DF (at least)	10 (20.0)	3 (2.4)
Amphet.-like (at least)	1 (2.0)	1 (0.8)
F/DF + Amphet.	1 (2.0)	0 (0.0)
ANY ANOREXIGENS	10 (20.0)	4 (3.3)

9.2 France	Cases (N) (%) (30)	Controls (N) (%) (57)
F/DF (at least)	8 (26.7)	3 (5.3)
Amphet.-like (at least)	1 (3.3)	0 (0.0)
F/DF + Amphet.	1 (3.3)	0 (0.0)
ANY ANOREXIGENS	8 (26.7)	3 (5.3)

9.3 United Kingdom	Cases (N) (%) (9)	Controls (N) (%) (28)
F/DF (at least)	1 (11.1)	0 (0.0)
Amphet.-like (at least)	0 (0.0)	0 (0.0)
F/DF (at least)+ others	0 (0.0)	0 (0.0)
ANY ANOREXIGENS	1 (11.1)	0 (0.0)

9.4 Belgium	Cases (N) (%) (7)	Controls (N) (%) (22)
F/DF (at least)	1 (14.3) (+1)	0 (0.0)
Amphet.-like (at least)	0 (0.0) (+1)	1 (4.5)
F/DF + Amphet.	1 (3.3) (+1)	0 (0.0)
ANY ANOREXIGENS	1 (14.3) (+1)	1 (4.5)

(+1): See explanations in the text.

9.5 The Netherlands	Cases (N) (%) (4)	Controls (N) (%) (16)
F/DF (at least)	0 (0.0)	0 (0.0)
Amphet.-like (at least)	0 (0.0)	0 (0.0)
F/DF (at least)+ others	0 (0.0)	0 (0.0)
ANY ANOREXIGENS	0 (0.0)	0 (0.0)

Table 9.6: Exposure to anorexigens after index date

Country	Cases (N) (% study popn)	Controls (N) (% study popn)
France	4 (13.3)	6 (10.5)
United Kingdom	0 (0.0)	0 (0.0)
Belgium	0 (0.0)	1 (4.5)
The Netherlands	0 (0.0)	1 (6.3)
TOTAL	4 (8.0)	8 (6.5)

Table 10: Homogeneity of Cases Reported in France

All Past Exposure Before Index Date

Main Reporting Centre	Cases (N) (%) (13)
F/DF (only)	3 (23.1)
Amphet.-like (only)	0 (0.0)
F/DF + Amphet.	3 (23.1)
ANY ANOREXIGENS	6 (46.2)

France without Main Reporting Centre	Cases (N) (%) (17)
F/DF (only)	5 (29.4)
Amphet.-like (only)	2 (11.8)
F/DF + Amphet.	0 (0.0)
ANY ANOREXIGENS	7 (41.2)

Exposure between August 1989 and index date:

Main Reporting Centre	Cases (N) (%) (13)
F/DF (only)	3 (23.1)
Amphet.-like (only)	0 (0.0)
F/DF + Amphet.	1 (7.7)
ANY ANOREXIGENS	4 (30.8)

France without Main Reporting Centre	Cases (N) (%) (17)
F/DF (only)	4 (23.5)
Amphet.-like (only)	0 (0.0)
F/DF + Amphet.	0 (0.0)
ANY ANOREXIGENS	4 (23.5)

Table 11: Matched Adjusted Odds Ratio for PPH associated with Anorexigens

11.1 All Past Exposure before Index Date

	MATCHED ADJUSTED OR	(95% CI)
Amphetamine-like drugs only	2.7	(0.2 - 38.1)
F/DF only	4.0	(1.1 - 14.5)
At least one Amphetamine-like	5.5	(0.9 - 36.1)
At least F/DF	6.2	(1.6 - 23.7)
F/DF + Amphet.	8.7	(0.7 - 103.7)
ANY ANOREXIGEN	5.3	(1.6 - 17.7)

11.2 Exposure Between August 1989 and Index Date

Amphetamine-like drugs only	NC	
F/DF only	6.6	(1.3 - 34.5)
At least one Amphetamine-like	3.4	(0.2 - 67.9)
At least F/DF	8.0	(1.6 - 40.4)
F/DF + Amphet.	NC	
ANY ANOREXIGEN	5.7	(1.4 - 23.5)

NC = mathematically not convergent due to a value = 0 in one of the cells

Table 12: Multivariate logistic regression model

All exposure before index date

Regression term	B value	p-value	Odds ratio	95% CI
Anorexigens	1.75	.006	5.8	1.7 - 20.1
Hypertension	0.81	.355	2.3	0.4 - 12.6
High BMI	.0.22	.674	1.2	0.4 - 3.5
Pregnancy	-0.004	.995	1.0	0.3 - 3.7
Oral contraceptives	0.59	.327	1.8	0.6 - 5.9
Laxatives	1.199	.297	3.3	0.4 - 31.5

Analysis adjusted for other variables (heart disease, muscular skeletal disorder, etc.)

AGENCE DU MEDICAMENT

Direction de l'Evaluation

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CONCLUSIONS DE LA REUNION

"STRATEGIE THERAPEUTIQUE DE L'OBESITE"

MARDI 31 MAI 1994

♦

Cette réunion a rassemblé des spécialistes en nutrition, endocrinologie, diabétologie, gynécologie, pédiatrie, pneumologie, médecine interne, pharmacologie, pharmacovigilance et des médecins généralistes. D'autre part, l'avis des spécialistes en hypertension et en cardiologie a été pris.
(La liste des participants est jointe en annexe).

La réunion est présidée par le Directeur de l'Evaluation.

OBJET DE LA REUNION

L'objet de la réunion est d'établir, dans le cadre d'une bonne approche thérapeutique de l'obésité, les indications et les conditions d'utilisation des anorexigènes et plus particulièrement de la dexfenfluramine (Isoméride®) et de la fenfluramine (Pondéral®). En effet :

- Il est bien connu par des études rétrospectives et prospectives que l'obésité est un facteur de surmorbidité et surmortalité cardio-vasculaire.
  L'obésité agit sur plusieurs facteurs de risque : hypertension artérielle, diabète, dyslipémie, et il est établi qu'une perte de poids est bénéfique sur ces pathologies.
  L'obésité est en outre un facteur de risque indépendant (développement de l'athérosclérose).

- Cependant, les résultats intermédiaires d'une étude épidémiologique internationale sur l'hypertension artérielle primitive (International Primary Pulmonary Hypertension Study ou I.P.P.H.S.) examinés le 10 Mai 1994 par la Commission Nationale de Pharmacovigilance, objectivent l'existence d'une association entre l'HTAP primitive et la prise de dexfenfluramine et de fenfluramine : le risque relatif est voisin de 5. Ce risque semble concerner également les autres médicaments anorexigènes ; les résultats définitifs de l'étude pourront le confirmer.
  La durée du traitement pourrait influer sur la survenue de l'HTAP primitive. Il n'existe pas d'observation validée d'HTAP associée à une exposition de dexfenfluramine et fenfluramine de moins de 3 mois.

Par ailleurs la prévalence de l'HTAP primitive est en France de l'ordre de 2 cas par million d'habitants par an. La gravité de cette pathologie est majeure ; en effet l'équipe du Prof. Duroux (Antoine Béclère, centre de référence de l'HTAP) rapporte que sur 31 patients, 1/3 sont décédés, et 17 sont sur liste d'attente de transplantation pulmonaire ou cardio-pulmonaire et sont actuellement traités par perfusion continue de prostacycline (traitement contraignant et particulièrement onéreux).

Le nombre de personnes (essentiellement des femmes) actuellement traitées en France par dexfenfluramine et fenfluramine est d'environ 750.000 par an. Le nombre de personnes traitées globalement par anorexigènes est de l'ordre de 1,1 million par an, ce qui rapporté à la population féminine adulte, représente environ 10 % par an.

Ces traitements non remboursés, sont prescrits à la demande, et semblent actuellement le plus souvent utilisés dans des situations non justifiées (traitement cosmétique de surpoids modeste).

Compte tenu, d'une part des bénéfices potentiels sur les facteurs cardio-vasculaires et d'autre part des risques en particulier celui de l'HTAP, quelle est la place des anorexigènes, et plus particulièrement de la dexfenfluramine ?

DISCUSSION

1) **De l'avis des spécialistes en nutrition du groupe**, la dexfenfluramine et la fenfluramine sont des médicaments efficaces, et utiles. Ils les prescrivent en moyenne chez moins de 10 % de leurs patients.

   Des études cliniques ont montré que l'efficacité du produit était spécifiquement supérieure au placebo, sur des durées de traitement de 3 mois et 1 an, en traitement adjuvant au régime. Le taux de répondeurs au traitement est de l'ordre de 33 % à 1 an de traitement (perte supérieure à 10 % du poids initial).

   L'obésité tend à être reconnue comme un état chronique, justiciable d'une pharmacothérapie adaptée à long terme.

   L'effet thérapeutique du traitement se traduit par :

   - une amélioration de l'adhérence des patients au traitement diétique,
   - une induction d'une perte de poids lorsqu'un traitement diététique adapté s'est avéré improductif,
   - une augmentation de la fréquence de stabilisation du poids à long terme (en évitant les rechutes),
   - une stabilisation du poids chez les sujets en phase dynamique ascendante.

Les indications de ce traitement pourraient être :

- l'obésité patente, avec un indice de masse corporelle (*) supérieure à 30,
- dans les cas d'indice de masse corporelle entre 27 et 30 :
  - une obésité androïde, plus particulièrement chez les sujets de sexe masculin,
  - une obésite associée à un facteur de risque secondaire poids-dépendant : hypertension artérielle, diabète non insulino-dépendant, hypertiglycéridémie et hypolipoprotéinémie de haute densité.
- les indications d'un traitement de durée plus brève, peuvent-être :
  - une prise de poids à l'arrêt du tabac,
  - un surpoids dû à un contexte socio-psychologique temporaire.

L'usage intermittent de ce type de traitement est nocif, la variance du poids étant un risque propre, indépendant du poids initial.

2) **L'avis des autres spécialistes du groupe diffère.**

Ils estiment l'efficacité de ce traitement comme mineure, voire marginale, ou même inexistante.
A long terme, ce traitement est jugé comme ayant un taux constant d'échec sur l'obésité.
Au plus, il est considéré par certains, comme une aide psychologique à l'adhésion au traitement diététique.

On ne dispose pas de données montrant que les anorexigènes permettent effectivement de réduire la mortalité et la morbidité cardio-vasculaire liées à l'obésité.

En cardiologie, l'excès de poids constitue un facteur de risque coronarien et sa prise en charge est un des éléments du traitement global du patient.
Les patients obèses sont pris en charge sur le plan nutritionnel et les anorexigènes n'ont pas de place dans la pratique habituelle des cardiologues.
Une réduction de poids est toujours difficile à obtenir chez des patients hypertendus.
Dans le cas de pathologie coronarienne au premier plan, une perte de poids modérée est souvent obtenue chez des patients motivés, soit après un premier accident cardiaque, soit en pré-opératoire avec maintien de la réduction pondérale après l'intervention.

L'intérêt des produits anorexigènes dans le diabète non-insulino-dépendant mérite d'être mieux documenté et des études sont en cours de publication.
Certains diabétologues ne prescrivent pas d'anorexigènes, les considérant inefficaces à long terme, et cherchant à éviter que, chez ces patients peu observants, leur prise se fasse au dépend du traitement anti-diabétique oral.
D'autres diabétologues les prescrivent comme adjuvant au traitement antidiabétique, en 2ème intention après échec d'un traitement diététique, dans le cas d'obésité sévère.

De même, la dexfenfluramine n'est pas prescrite dans les obésites prises en charge en gynécologie, ni dans les obésités communes en pédiatrie où l'induction de modifications comportementales donnent des résultats satisfaisants à long terme.
Les seules indications en pédiatrie pouvant revendiquer ce traitement sont des situations particulières telles que le syndrome de Willie-Prader et apparentés, les séquelles de neurochirurgie ou du traitement des tumeurs cérébrales.

CONCLUSIONS

1) Il est conclu, de façon unanime, pour la dexfenfluramine et la fenfluramine , que :

- l'indication doit être restreinte au "traitement de 2ème intention, après échec d'un traitement diététique adapté, d'obésité patente ayant un indice de masse corporelle (*) supérieur à 30". (Ce type de patients représente environ 6 % de la population française),

- Par ailleurs :

  . la durée du traitement ne doit pas dépasser 3 mois,

  . le traitement est contre-indiqué chez l'enfant,

  (NB : cependant, dans de rares cas, des traitements plus prolongés peuvent être conduits par des spécialistes hospitaliers en nutrition et en pédiatrie, sous couvert d'un suivi attentif.)

2) L'information devra être modifiée pour les anorexigènes autres que la dexfenfluramine et la fenfluramine.
Cependant, la révision de l'ensemble des anorexigènes ne pourra être arrêtée qu'après obtention des résultats définitifs de l'étude I.P.P.H.S., et confirmation d'une association significative entre ces substances et la survenue d'une HTAP.

3) Une information sur l'obésité et les approches stratégiques médicamenteuses sera adressée par l'Agence aux praticiens. Cette information définira des règles de bonnes pratiques médicales de prise en charge globale de l'obésité et précisera la place de la pharmacothérapie.
Une première rédaction doit être proposée par les spécialistes en nutrition du groupe.

4) D'autre part, il paraît nécessaire de réaliser une enquête pour définir les profils de patients actuellement traités par anorexigènes. L'intérêt évident de cette enquête est de mieux connaître les sous-populations traitées (objectif uniquement esthétique, surpoids modéré, obésité patente, pathologies associées).
Une enquête identique, renouvelée après un délai de 1 à 2 ans, permettra de suivre les modifications du comportement des prescriptions apportées par la diffusion des bonnes pratiques de prise en charge de l'obésité, et par les changements des indications et des conditions d'utilisation des anorexigènes.

5) De la même façon, l'évolution et la fréquence de HTAP primitive sera suivi en fonction du temps, en France, par la Pharmacovigilance.

(*) L'indice de masse corporelle est égal au poids (en kg) divisé par la taille au carré (en m^2).

Participants

Mme D'ACREMONT	Gynécologie–Endocrinologie	NECKER
M. ALTMANN	Diabétologie – Endocrinologie	LAENNEC
M. APFELBAUM	Nutrition	BICHAT
M. BERLIN	Pharmacologie – Endocrinologie	LA PITIE
M. CARLIER	Pharmacovigilance	
M. DOUMITH	Diabétologie – Endocrinologie	LA PITIE
M. DUROUX	Pneumologie	A N T O I N E BECLERE
Mme FRELUT	Pédiatrie	ROBERT DEBRE
Mme GOMPEL	Gynécologie – Endocrinologie	HOTEL–DIEU
M. GUY–GRAND	Nutrition	HOTEL–DIEU
M. HUGUES	Pharmacovigilance	
M. JACOTOT	Médecine interne	HENRI MONDOR
M. LAGIER	Pharmacovigilance	
M. LEBLANC	Diabétologie – Endocrinologie	SAINT LOUIS
M. LUBETSKY	Diabétologie – Endocrinologie	LARIBOISIERE
M. REVEILLAUD	Médecine générale	VERRIERES–LE–BUISSON
M. WILMANN	Médecine générale	SAINTES
M. ZIEGLER	Diabétologie – Endocrinologie	NANCY

Avis de

M. CASTAIGNE	Cardiologie	HENRI MONDOR
M. LE HEUZEY	Cardiologie	BROUSSAIS
M. MENARD	Cardiologie – Hypertension	BROUSSAIS

REPUBLIQUE FRANCAISE

Annexe 1-53

AGENCE DU MEDICAMENT

Saint Denis le 1 MAI 1994

DIRECTION DE L'EVALUATION DU MEDICAMENT

UNITE DE PHARMACOVIGILANCE

237
suivi : S. LEGER
tél : 48.13.22.84

*(cnpv105.con)

COMPTE RENDU DE LA COMMISSION NATIONALE DE PHARMACOVIGILANCE DU 10 MAI 1994

Etaient présents :

M. IMBS, Président, M. HUGUES, Vice-Président,
M. ANKRI, M. BEGAUD, M. CARON, M. CHAST,
Mme CHICHMANIAN, M. CARLIER (suppléant de M. DE LA SELLE), B. DUPUIS
M. EVREUX, Mme LEPECHEUR-LEMARCHAND (suppléant de M. GISLAIN),
M. JUILLIERE (suppléant de M. GUIZE), Mme JOUAN-FLAHAULT, M. JOUGLARD,
M. LABOURE, M. LARREY, M. GORIN (suppléant de M. LECOMPTE),
, M. MERLE, M. MOULIN, M. MUNERA, M. MURAT, M. NETTER,
M. PAUL, M. ROUJEAU, Mme SOUBRIE, Mme BARON (représentant Monsieur le Directeur Général de la Santé), Mme GOUJARD(représentant M. le Directeur Général de l'INSERM), M.ALEXANDRE représentant M. le Directeur Général l'Agence du Médicament

Conseiller Scientifique : M. LAGIER

Experts: M.ABENHAIM, M. APFELBAUM, M. AUBIER, , M. DUROUX,
M. FOURNIER, M.GUY-GRAND, Mme KREFT-JAIS, M. LELOUCH, Mme MORIDE,
M. NICOLAS, M. WEITZENBLUM.

Rapporteurs à la commission: M.BECHTEL, Mme DAVID.

Représentants des laboratoires: M.HALIMI, M.LERIDANT, Mme NATHAN, M.PERET, M.WAGNIARD.

Assistaient à la réunion : N. DAVID, F. MANCEL, M. REIDIBOYM, M. BERDAI, Mme SAINT SALVI.

Unité de Pharmacovigilance : Mme CASTOT, M. GIL, Mme LEGER,

Etaient excusés: M. BAUMELOU, M. DE LA SELLE, M. GISLAIN, M. GUIZE,
M. LECOMPTE, M.LENOIR, M. LEVERGE, M.NETTER.

La Commission Nationale de Pharmacovigilance a pris connaissance des données de pharmacovigilance relatives à la dexfenfluramine et à la fenfluramine, des résultats de l'analyse intermédiaire de l'étude épidémiologique cas-témoin internationale sur l'hypertension artérielle pulmonaire primitive menée par l'I.P.P.H.S. Study Group et coordonnée par le Pr Lucien ABENHAIM (Université McGill, Montréal), des avis d'experts pneumologues et nutritionnistes et de ceux des représentants des laboratoires titulaires d'AMM des produits concernés (Groupe SERVIER).

Elle a estimé qu'il existe une association entre l'hypertension artérielle pulmonaire primitive et la prise de fenfluramine ou de dexfenfluramine.

Ce risque est faible mais porte sur une pathologie grave. Il semble aussi concerner les autres médicaments anorexigènes, les résultats intermédiaires de l'étude épidémiologique indiquant une augmentation, mais non significative du risque relatif.

En conséquence, la Commission Nationale de Pharmacovigilance souhaite :

1) – promouvoir une meilleure utilisation du médicament :

– en encadrant les conditions de prescription : réévaluation des indications dans l'optique du seul traitement de l'obésité vraie avec morbidité associée et respect strict d'indications, de la posologie et de la durée de traitement limitée à 3 mois pour la dexfenfluramine.

– en mentionnant au niveau de la rubrique "Mise en Garde", le risque d'hypertension artérielle pulmonaire primitive et l'arrêt de traitement en cas de dyspnée.

– en informant les prescripteurs de ces dispositions.

2) – qu'une attention particulière soit portée à l'identification de la durée de traitement comme facteur de risque possible de survenue d'une hypertension artérielle pulmonaire primitive, dans le cadre de l'enquête officielle de pharmacovigilance.

3) – la poursuite de l'étude épidémiologique internationale jusqu'à son terme.

Par ailleurs, la Commission Nationale de Pharmacovigilance souhaite la mise en place d'un groupe de travail associant les divers spécialistes impliqués dans le traitement de l'obésité. Ce groupe sera chargé de la réévaluation des conditions d'utilisation des anorexigènes, en tenant compte du rapport bénéfice/risque. Il est notamment attendu une définition de la durée optimale du traitement.

Enfin, la Commission Nationale de Pharmacovigilance souhaite que l'enquête officielle de pharmacovigilance soit étendue à l'ensemble des classes des anorexigènes.

Annexe 1-53

REPUBLIQUE FRANCAISE

AGENCE DU MEDICAMENT

Saint Denis le, 13/5/1994

DIRECTION DE L'EVALUATION DU MEDICAMENT

UNITE DE PHARMACOVIGILANCE

CONFIDENTIEL

CONCLUSIONS DE LA COMMISSION NATIONALE DE PHARMACOVIGILANCE DU 10 MAI 1994

La Commission Nationale de Pharmacovigilance a pris connaissance des données de pharmacovigilance relatives à la dexfenfluramine et à la fenfluramine, des résultats de l'analyse intermédiaire de l'étude épidémiologique internationale sur l'hypertension artérielle pulmonaire primitive menée par l'I.P.P.H.S. Study Group et coordonnée par le Pr Lucien ABENHAÏM (Université McGill, Montréal), des avis d'experts pneumologues et nutritionnistes et de ceux des représentants des laboratoires titulaires d'AMM des produits concernés (Groupe SERVIER).

Elle a estimé qu'il existe une association entre l'hypertension artérielle pulmonaire primitive et la prise de fenfluramine ou de dexfenfluramine.
Ce risque est extrêmement faible mais porte sur une pathologie grave. Il semble aussi concerner les autres médicaments anorexigènes.

En conséquence, la Commission Nationale souhaite :

1 - la gestion du risque de cette association en :
- encadrant les conditions de prescription : respect strict des indications, de la posologie et de la durée de traitement limitée à 3 mois pour la dexfenfluramine ; réévaluation des indications dans l'optique du traitement de l'obésité avec morbidité associée (en particulier diabète, hypertension, dyslipidémie),
- en mentionnant au niveau de la rubrique Mise en Garde le risque d'hypertension artérielle pulmonaire primitive.
- en informant les prescripteurs de ces dispositions.

2 - qu'une attention particulière soit portée à l'identification de la durée de traitement comme facteur de risque possible de survenue d'une hypertension artérielle pulmonaire primitive, dans le cadre de l'enquête officielle de pharmacovigilance

3 - la poursuite de l'étude épidémiologique internationale jusqu'à son terme.

Par ailleurs, la Commission Nationale de Pharmacovigilance souhaite la mise en place d'un groupe de travail associant les divers spécialistes impliqués dans le traitement de l'obésité.
Ce groupe sera chargé de la réévaluation des conditions d'utilisation de ces produits, en tenant compte du rapport bénéfice/risque et en définissant notamment la durée optimale du traitement.

Enfin, la Commission Nationale de Pharmacovigilance souhaite que l'enquête officielle de pharmacovigilance soit étendue à l'ensemble des classes des anorexigènes.

Annexe 1-53

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT

Saint Denis le, 13 MAI 1994

DIRECTION DE L'EVALUATION DU MEDICAMENT

UNITE DE PHARMACOVIGILANCE

AVIS AUX PRESCRIPTEURS

La Commission Nationale de Pharmacovigilance réunie le 10 mai 1994 a pris connaissance des données de pharmacovigilance relative à la dexfenfluramine et à la fenfluramine, et des résultats de l'analyse intermédiaire de l'étude épidémiologique internationale sur l'hypertension artérielle pulmonaire primitive menée par l'I.P.P.H.S. Study Group et coordonnée par le Pr Lucien ABENHAÏM (Université McGill, Montréal).

Elle a estimé qu'il existe une association entre l'hypertension artérielle pulmonaire primitive et la prise de fenfluramine ou de dexfenfluramine. Le risque en est extrêmement faible, mais il porte sur une pathologie grave. Il peut, de plus, concerner les médicaments anorexigènes dérivés des amphétamines.

En conséquence, l'Agence du Médicament porte à l'attention des prescripteurs l'avis de la Commission Nationale qui a estimé nécessaire de :

- rappeler la nécessité de respecter strictement les indications, la posologie et la limitation de la durée du traitement à 3 mois pour la dexfenfluramine,
- mentionner au niveau de la rubrique Mise en Garde le risque d'hypertension artérielle pulmonaire, figurant déjà dans la rubrique Effets Indésirables de la monographie des médicaments contenant de la fenfluramine et de la dexfenfluramine

L'Agence du Médicament, sur proposition de la Commission Nationale de Pharmacovigilance, met en place un groupe de travail associant les divers spécialistes impliqués dans le traitement de l'obésité, afin de réévaluer dans les meilleurs délais les conditions d'utilisation des médicaments anorexigènes.

143-145, boulevard Anatole France - 93200 SAINT-DENIS - tél : 48.13.20.00 - fax : 48.13.22.83

Annexe 1-54

INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY
- IPPHS
International Coordinating Centre

Centre for Clinical Epidemiology and Community Studies
Sir Mortimer B. Davis – Jewish General Hospital
3755 Côte Ste-Catherine Road
Montreal, Quebec CANADA H3T 1E2
Tel.: (514) 340-7563 Fax: (514) 340-7564

McGill

THE INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY (IPPHS)

SUMMARY REPORT No. 1

1. Overview of sociodemographic, clinical and general characteristics of the study population.

2. Global analysis of suspected risk factors.

3. Detailed analysis of anorexigens.

March 7, 1995

Annexe 1-54

DO NOT CITE OR QUOTE

FOREWORD

This is a summary report of the International Primary Pulmonary Hypertension study. This large scale international study was conducted in five countries, with the aim of producing an epidemiological understanding of this rare but very serious disease.

This report is far from complete. It summarizes the results obtained for the most general risk factors for the disease. The analysis presented here has been structured to mainly produce detailed estimates of the odds ratios associated with anorexigen use and related factors. This was justified by our commitment vis-à-vis the regulatory authorities of France, the United Kingdom, The Netherlands, Belgium and Switzerland to provide them with results on this issue as soon as possible. In fact we issued an interim report one year ago which was used for interim regulatory decisions.

Many more in-depth analyses would be of interest, whether on the clinical aspects of the disease, the general risk factors, or even suspected risk factors which were only broadly addressed here. The database we have developed should allow us to explore some of the relations more fully and, possibly, to qualify associations which were not examined in detail here.

THE IPPHS GROUP:

The International Coordination Centre: Prof. Lucien Abenhaim, Dr. Yola Moride, Mr. Thierry Ducruet, Dr. Jacques Benichou.

The International Scientific Board & Scientific Advisors: Prof. Lucien Abenhaim (chair), Prof. M. Aubier, Prof. Bernard Begaud, Dr. Jacques Benichou, Prof. William Dab, Prof. Maurits Demedts, Prof. Tim Higenbottam, Dr. David Langleben, Prof. Robert Naeije, Prof. Celia Oakley, Prof. Stuart Rich, Prof. Gérald Simonneau, Dr. Bruno Stricker, Prof. C.A. Wagenvoort, Prof. Emmanuel Weitzenblum, Prof. E.F.M. Wouters.

The Local Research Teams: Dr. François Brenot, Dr. Aniceï Chaslerie, Dr. Claudine Peiffer, Dr. Marion Delcroix, Dr. Xavier Kurz, Dr. Denise Walckiers, Dr. Ellen Pouw, Ms. Miriam Sturkenboom, Dr. Hans Petri, Dr. David Dutka, Dr. Mark Ryan, Dr. Neal Uren.

The Expert Review Panel: Prof. Stuart Rich (Chair), Dr. David Langleben, Dr. Michael McGoon, Dr. Lewis Rubin.

Participating Centres: The list of centres who participated in the study can be found in Appendix A4.

This report will be forwarded to the authorities of several countries, under the scientific responsibility of the undersigned members of the IPPHS Group. However, the authors of the study are all the members of the IPPHS Group which are listed above.

DO NOT CITE OR QUOTE

This final report of the International Primary Pulmonary Hypertension Study (IPPHS) has been read and accepted this Monday, March 6, 1995 by the following members of the International Scientific Board and Scientific Advisors.

ABENHAIM, L. (chair)

AUBIER, M.

BEGAUD, B.

BENICHOU, J.

DAB, W.

DEMEDTS, M.

HIGENBOTTAM, T.

KANG LEBEN, D.

NAEIJE, R.

OAKLEY, C.

RICH, S.

SIMONNEAU, G.

STRICKER, B.

WAGENVOORT, C.A.

VEITZENBLUM, E.

WOUTERS, E.F.M.

4) For the amphetamin-like anorexigens (ALA of non-fenfluramine like drugs) the statistical power of the study is far to low to conclude that a significant association between exposure and PPH exists. For instance, the 95 % two-side confidence interval for the ALA odds ratio ranges from 0.7 to 56.2. Moreover, for some drugs like mefenorex the number of exposed cases is null.

Answers to questions raised by the representants of the producers of amphetamin-like anorexigens at the Commission of Pharmacovigilance of June 19, 1995 and in the comments commissioned by DIAMANT Laboratories.

Prepared by : Lucien ABENHAIM, MD, ScD
Department of Epidemiology and Biostatistics
McGill University (Canada)

1 - Selection of cases

The critic indicates that 40 % of the included cases were exposed to anorexigens vs 10 % of the controls. (figures of 34,8 % and 10,1 % respectively are provided in the note summarizing the discussion at the Commission de Pharmacovigilance). It sees room for selection bias in these differences.

However, the numbers used are not appropriate. More elements are provided below, although most of them can be retrieved from the report.

Actual numbers and proper comparisons

Firstly, Point 4.1.1.4 of the report could have been misinterpreted. It should be understood as : "(Among those) of the 109 non-included cases which have been interviewed, 11 were exposed to a definite anorexigen and 2 to an unclassified product". This corresponds to one term of a sensitivity analysis which was not fully reproduced in the report. Actually, 59 of the 109 non-included cases were not interviewed.

Secondly, if one counts all products in the one hand (the number of "40 %" exposed included cases accounts for, I guess, the 20 definite exposures, the 11 unclassified and the 6 after the index date), one should also count them on the other hand (11, 2 and 2 respectively for non-included cases). The cited percentage of 10,1 % of exposure for the non-included cases incorporates all non-interviewed cases and does not take into account the 4 unclassified exposures or exposures after the index date. Reported on the 50 interviewed, the exposure of non-included cases is 15/50 (30 %), as compared to exactly 38,9 % for included cases. The 50 non-included cases comprise incident, but also prevalent and rejected cases, the latter having by definition a lower expected exposure than included cases.

Thirdly, very few of the 109 non-included cases met the inclusion criteria for the study. In all fairness, the exposure of included cases should be compared to non-included cases meeting all the inclusion criteria. Defined as above, four (4) of the twelve (12) interviewed non-included cases meeting all the inclusion criteria for the study (except validation by the Expert Committee) were exposed. Their exposure (33,3 %) is similar to those included (the small difference is due to the slightly higher proportion of UK cases reported after the end of the study).

DO NOT CITE OR QUOTE

(iv)

Expert Review Panel

We have reviewed the section of this report corresponding to the validation of cases of primary pulmonary hypertension and declare it conform.

IICH, S. (CHAIR)

ANGLEBEN, D.

McGOON, M.

ACKNOWLEDGEMENTS

This study would not have been possible without the contribution of researchers from the International Coordination Centre, the Local Research Teams in France, Belgium, The Netherlands and the U.K. and the other members of the IPPHS group. They are all full co-authors of this study.

Dr. Yola Moride was the cornerstone of the organization of the study. She contributed greatly to the development of the study protocol, the coordination of the study in the field, the interim analysis and the creation of the database.

There is not enough space to describe the patient expertise displayed by Dr. Anicet Chaslerie in the coordination of the study in France, both for epidemiological aspects and the logistics; the accurateness of the investigations of Dr. Claudine Peiffer into the medical charts and hospital departments, and the multiple collaborations of Dr. François Brenot. They recruited and validated two-third of the cases included here, screening hundreds of reports in the process. Dr Patrick Blin completed the feasibility study.

The team from Belgium, coordinated by Dr. Xavier Kurz and animated by M. Delcroix and D. Walkiers, recruited the highest number of included cases per million inhabitants in the study and also provided us with an incidence study for Belgium which is a very valuable scientific contribution per se.

The Dutch team of Miriam Stuifkenboom and Dr. Ellen Pouw, in addition to the recruiting of cases and controls in the Netherlands, have added to the study the validation of the questionnaire (not reported here) and an ever-challenging perspective. Dr. Hans Petri launched the study in his country, giving it its important initial impetus.

No European initiative today would be complete without the United Kingdom. Drs. Neil Uren, Mark Ryan and David Dutka were our "relay team" in the U.K. They recruited a fair amount of cases and controls and obtained an excellent collaboration from GPs. The U.K. also contributed greatly to the validation studies (not reported here).

General practitioners in all countries helped us identify potential controls, obtained consent from them and helped us contact them. The Institut de Recherches en Médecine Générale (IRMG) and the Société de Formation à la Thérapeutique des Généralistes (SFTG), through the efforts of Drs. Liard and Falcoff, were extremely helpful in recruiting the general practitioners.

Interviewers were responsible for the actual collection of information. This required travelling to remote parts of each country, by train, car, and sometimes more awkward means. Medical archivists of the JGH skillfully coded hundreds of questionnaires and thousands of drugs, even when under the pressure of time constraints.

Such a study could not be reported adequately without a Thierry Ducruet. Thierry positively spent nights and days on the statistical analysis and one can be sure that whatever is shown here is really present in the data. This is of inestimable value. Dr. Jacques Benichou came to help us in Montreal in the summer, the fall and winter, but he saw more computers, print-outs and tables here than lakes, leaves and snow. Prof. Alexander Walker accepted to review our final data presentation and made very useful suggestions.

I am extremely grateful to Linda Carfagnini, a name that everybody now knows in the academic centres, local research teams, board members offices and almost all the participating centres, as the "sesame" by which so much happened. All my acknowledgements to Liza Bouchard and to the staff of the Centre for Clinical Epidemiology and Community Studies from the McGill Jewish General Hospital, who provided the administrative support to this study.

The Medical Research Council of Canada peer-reviewed this project and approved its funding under the "MRC-Industry" Program (grant #9404UO-27203-UI-A). The Ministry of Public Health and Environment of Belgium also supported the study in that country.

I would like to sincerely thank the Institut de Recherches Internationales Servier (IRIS), who supported this study. It is worth noting that, despite the important funds involved and the issues at stake, the independence of the study was completely respected from the start to the end. Worth noting also is that the IRIS helped us disseminate the results of the interim analysis to the regulatory authorities, the scientific community and the media and has committed itself to supporting the communication of the results from this report through a special symposium to be held in Montreal on May 5, 1995.

Last but not least, I would like to thank the more than 600 individuals who agreed to participate in this study. Some of them, the so-called "controls", were patients referred from general practitioners, who voluntarily contributed their time to this study with no compensation. Extremely few of the potential "controls" approached refused to participate, which is an indication that, when asked to contribute to an important endeavour, one can count on more people than one might expect.

The most important contributors to this study were those who suffered from this very serious, stressful disease known as "primary pulmonary hypertension". They are referred to in this report as "cases", a dry technical term which should not be misinterpreted as a lack of care on our part. As epidemiologists, our hope is that this work will contribute to the knowledge of this disease, from which they suffer or suffered. We know that their participation was motivated by this consideration and not by any individual interest. I hope that the attention paid to this disease has helped some of them in some way.

Lucien Abenhaim
Chair, IPPHS

exportation
vente alcools
cocaine. drogue IV
extrait thyroïdien
HTA systémique
Lupus érythémateux
Cirrhose primitive biliaire

Incidence : 2 per million
417
Age Median 40 ans
F tr /

Annexe 1-54

)O NOT CITE OR QUOTE

EXECUTIVE SUMMARY

. The International Primary Pulmonary Hypertension Study (IPPHS) was launched in ctober 1992. The study was coordinated in Montreal and five countries participated rance, The United Kingdom, Belgium, The Netherlands and Switzerland).

. The general objective of the study was to develop an epidemiological understanding f primary pulmonary hypertension and of the risk factors potentially contributing to s occurence. The specific objectives of the study were: (A) to investigate the role f several suspected risk factors: (i) anorexigens (all classes); (ii) obesity; (iii) systemic ypertension; (iv) recent pregnancies; (v) oral contraceptives; (vi) thyroid extracts; (vii) xposure to high altitude. (B) to generate hypotheses on the potential role of a number f other factors: (i) familial history of morbidity; (ii) personal medical and surgical istory; (iii) blood groups; (iv) smoking; (v) dietary habits; (vi) weight loss behaviour; vii) all other classes of drugs.

. The IPPHS was a case-control study. Incident cases diagnosed after September 1, 992, were identified from more than 100 centres who actively participated in the tudy, of which 35 provided at least one retained case. Cases were all screened by cardiologist or a pulmonary physician and verified by an Expert Review Panel in lorth America, which obtained the data from medical extraction forms, and when vailable, copies of X-Rays, perfusion lung scans and pulmonary angiograms. Controls vere identified within lists of consecutive patients seen by the case's GP or an lternate GP. Controls were matched to the case on age (+/- 5 years), gender, ountry and number of visits to the physician per year.

4. Two hundred and ninety eight (298) cases of PPH were identified between October 1992 and September 1994 (included), among which a number did not meet the nclusion criteria (49 prevalent cases diagnosed before September 1992, 33 found to e secondary pulmonary hypertension, 26 were dead or died before interview, 15 were younger than 18 y.o. or older than 70 y.o., 17 were reported after September 1994 or could not be evaluated on time by the Expert Review Panel, 16 could not be nterviewed, refused, were not resident of the country or were lost to follow-up, 9 did ot have a catheterization, 3 suffered from an excluded disease and 1 chart was not ound; number are not mutually exclusive). Eleven (11) cases had AIDS and could not e used for the case control analysis and 23 more cases were rejected by the nternational review panel.

5. Ninety five (95) cases could finally be used for the case-control analysis, with 355 matched controls. They were very similar on all parameters used for comparison (age, gender, occupation, familial history of disease, personal preexisting morbidity except those under scrutiny, use of all subclasses of drugs except suspected drugs).

- Cumpreheusin epidemio by F de Rivera
- Objectifs : anorexigens - obesité = vendies mais Conclusion

6. Cases responded to the classical definition of primary pulmonary hypertension, and are in particular very similar to the cases included in the NIH registry, the French and the British series. They were 44.7 years old in average (SD = 12.3), and there were 2.3 women for 1 man. Dyspnea was the initial symptom in 91% of the cases, with a severity of grade III of the New York Heart Association classification, at the time of first admission. The median delay between the onset of symtoms and the diagnosis (catheterization) was 16 months. The mean pulmonary arterial pressure was 57.3 (+/- 12.8). All other tests were typical of primary pulmonary hypertension. Controls had an identical age and gender distribution.

7. Cases and controls were interviewed by specially trained interviewers who were kept blind on the specific objectives of the study (they had no medical background). Univariate, bivariate and multivariate analyses were conducted. In the later, only suspected risk factors were investigated, with also a number of factor retained on the basis of the bivariate analysis. This Summary Report No. 1 only presents an overview of the general, sociodemographic and clinical characteristics of the patients, and a global analysis of suspected risk factors. It presents a detailed analysis of the anorexigens.

8. No significant differences were found between cases and controls on their familial history of disease, preexisting morbidity, dietary habits, lifestyle characteristics (weight loss behaviour), exposure to almost all ATC sub-classes of drugs, stays in high altitude, recent and total number of pregnancies, surgical history, use of oral contraceptives, thyroid extracts, hashish and marijuana.

9. Small differences were observed in the distribution of blood groups (B being slightly over represented in cases), familial history of cancer, consumption of game meat, use of analgesics and haematological drugs. Those differences were not further explored in this report.

10. Smoking and having tried to lose weight by several means (excluding anorexigens), were significantly more frequent in cases than in controls. They were controled for in the multivariate analysis.

11. Four cases had experienced cirrhosis. Three cases were HIV positive. 11 more cases of AIDS cases were excluded. The analyses were controlled for these variables, either directly or indirectly.

12. A lifetime prevalence of body mass index greater or equal to 30 was associated with an adjusted odds ratio of 2.4 (1.3-4.7). The same relationship with PPH was maintained whatever the subgroup analyses.

13. The prevalence of treated systemic hypertension before the onset of symptoms was higher in cases than in controls, but the confidence interval of the odds ratio was included one [OR = 2.5 (0.8-7.2)]. Similar estimates were found in other models.

14. 6.5% of the controls had used an anorexigen at least once in the past. The percentage was 3% for the last year before the index date (5% in France), thus very closely paralleling expectations based on sales figures. The proportion of controls exposed was also consistent with sales figures across countries. Cases had used an anorexigen much more frequently: 21.1% for all past exposures and 18.5% for the one-year time-window (all countries combined). Dexfenfluramine had been used by 16 cases and 19 controls, fenfluramine by 3 cases and 3 controls and amphetamine-like anorexigens by 6 cases and 6 controls. In the UK and in The Netherlands, the prevalence of exposure to anorexigens was extremely low and did not allow an estimate of exposure-related risk.

15. The adjusted odds ratio for the exposure to at least one anorexigen was 3.8 (1.6-8.7) if all past exposures were considered, and 5.3 (1.9-14.4) for the one year-time-window. There was no apparent difference in the point estimates of the odds ratios between the type of anorexigens studied. In the one year time-window, exposure to dexfenfluramine fenfluramine and/or only was associated with an odds ratio of 5.8 (1.6-16.2), while amphetamine-like anorexigens only had a odds ratio of 6.4 (.7-56.2).

16. Duration of use of anorexigens was correlated with the observed odds ratios, which were of 1.9 (0.5-6.9) for short durations of use (3 months or less) and 9.1 (2.6-31.5) for longer durations.

17. The validation studies and sensitivity analyses performed demonstrated a good robustness of the observations.

18. The study confirmed that the incidence of the diagnosed disease in the general adult population in Belgium and France is in the order of 2 cases per million inhabitants per year.

19. The absolute risk of PPH in anorexigen users with the highest prevalence of risk factors (longer duration of use and a BMI greater or equal to 30) could be estimated to be less than 1 in 10.000 or less in groups. In all other groups the risk would be substantially lower.

CONCLUSIONS

1. The study demonstrated that the use of anorexigens and a BMI greater or equal to 30 are independent risk factors. In addition, it is suggested that systemic hypertension is an independent risk factor for the disease although it did not maintain significance in the multivariate analysis.

2. The magnitude of the association ~~association~~ with anorexigen use, the temporality of the association, the relation with the duration of use as well as the consistency of the results with previous observations support the hypothesis of a causal relationship. The exact role of the anorexigens in the risk of PPH cannot however be definitively established due to the lack of knowledge of the pathogenic mechanisms, the lack of specificity of the effect within the class of anorexigens, the non-exclusion of all potential confounders and the low absolute risk. From this study, the factors of individual susceptibility could not be identified.

3. The study confirms the role of cirrhosis as a risk factor for PPH. The roles of obesity and systemic hypertension are important new observations which merit further investigation. In a substantial number of PPH cases, no risk factor was indentified.

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able 20 Anorexigen use by cases and controls (all exposure in the past)
able 21 Exposure of case and controls to individual anorexigens (all past exposures)
able 22 Exposure of case and controls to individual anorexigens (one-year time-window before index date)

23 Distribution and crude odds ratios for exposure to any anorexigen in cases and controls, according to the presence of other risk factors (all past exposure)

24 Odds ratios of exposure to retained risk factors in PPH cases and controls: global and stratified by status of exposure to anorexigens (matched)

25 Adjusted odds ratios from multivariate conditional logistic regression of main risk factors on PPH (all past exposures before index date)

26 Adjusted odds ratios for subclasses of anorexigens (all past exposures and one year before index date)

e 27 Adjusted odds ratios for exposure to anorexigens before and after a one-year time-window preceding the index date

e 28 Distribution of use and adjusted odds ratios for duration of use of anorexigens (all past exposure before index date)

le 30 Variation in the exposure of cases and controls

le 31 Exposure of controls vs. estimations based on sales figures

le 32 Sensitivity Analysis: Variations of the odds ratio according to several definitions of exposure to anorexigens

APPENDIX A

1: International Coordinating Centre
International Scientific Board
2: Local Research Teams
3: Expert Review Panel
4: List of participating centres
5: Results of feasibility study (attached)
6: Report from Expert Review Panel
7: Reasons for the exclusion of cases in France
8: Reasons for the exclusion of cases in Belgium
9: Reasons for the exclusion of cases in the U.K.
10: Reasons for the exclusion of cases in the Netherlands
11: Reasons for the exclusion of cases in Switzerland
12: Models used for the analysis of exposure to sub-classes of anorexigens
13: Age distribution of cases by country
14: Female to male ratios of cases per country (potential cases & included cases)
15: Median delays for diagnosis by country
16: Distribution of sub-classes of drugs in cases and controls

APPENDIX B
(can be consulted upon request)

B1: Protocol, December 1, 1992
B2: Medical Extraction Form
B3: Rationale for selection of controls: Article in Chest
B4: Questionnaire "A"
B5: Calendar questionnaire on life events, morbidity and drug use
B6: Visual Display - selected packages of drugs
B7: Sealed questionnaire: Illicit drugs and sexual habits
B8: Control selection form: GPs' consecutive patient list

I. INTRODUCTION

1 Background[1]

imary Pulmonary hypertension is a term used to define a subcategory of pulmonary ypertension which occurs mainly in females in the third to fourth decade of life. It a very rare disease usually associated with a poor prognosis.

lthough the name of the disease stems from its distinction from pulmonary ypertension secondary to known cardiac or pulmonary causes, PPH should not be onsidered as only pulmonary hypertension for which no cause is found. The clinical resentation, the usual age of onset, the progression of the disease and the autopsy eatures make PPH a clear separate clinical entity and distinguish it from secondary ulmonary hypertension, even if its diagnosis requires the careful exclusion of econdary causes. The terminology used to define the pathologic changes is, owever, heterogenous. The World Health Organization first classified PPH into lexogenic pulmonary arteriopathy, thrombotic pulmonary arteriopathy and pulmonary eno-occlusive disease. A recent consensus panel from the American College of Chest hysicians included pulmonary capillary hemoangiomatosis.

The epidemiologic knowledge on the disease is very scant. The largest case-series, such as the NIH registry, the French case-series and the British case-series, have confirmed the female predominance (2:1) and that the age mode is in the late fourth and early fifth decade. Indices commonly used to quantify the occurrence of a disease, such as incidence, prevalence and mortality, are not available in the literature. From the feasibility study which preceded this study, we had estimated that the annual incidence (number of new cases per year) could be 2 cases per million per year or less in a country like France. Different numbers have been proposed by others.

Case reports and an epidemics have suggested the role of numerous risk factors for the disease but very few of them have been confirmed.

Several cases of familial primary pulmonary hypertension point to the existence of a genetic factor. Abnormalities of the pulmonary vascular bed which may cause a predisposition to the disease have also been suggested.

Pregnancy is often cited as a risk factor, as sporadic cases of the co-existence of primary pulmonary hypertension and pregnancy have been reported. One of the

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1 *The list of references used can be found in the bibliography. Individual references are not indicated in the text.*

or methamphetamine inhalation. Also, crack cocaine and intravenous drug use (IVDU) were reported in PPH cases, including newborns who had been exposed in utero.

Several drugs have been reported to be associated with PPH. Oral contraceptives and thyroid extracts are frequently mentioned. Non steroidal anti-inflammatory drugs (AINS) have also been implicated. Prolonged indornethacin use in mothers was found to be associated with PPH in newborns, but confounding by indication was not completely ruled out. There is, however, some evidence of biological plausibility. Similar observations were made in newborns whose mothers had a history of exposure to naproxen.

Veno-occlusive disease was found in patients treated by chemotherapy-related drugs (mitomycin-C, nitrosourea, cyclophosphamide). Two cases of pulmonary hypertension believed to be associated with a treatment by phenformin have been reported.

Reports have been published of amphetamine-associated primary pulmonary hypertension. Amphetamine-like drugs are used as anorexigens. The most common reports of drug-exposed PPH cases involve anorectic agents (anorexigens). Concerns were raised following the dramatic increase in the number of PPH cases diagnosed in a Swiss medical clinic in the 1960s. Half of the patients were somewhat overweight and females predominated. Later, 582 cases of PPH were identified in Germany, Switzerland and Austria, among which 68% had claimed they had used the drug Aminorex alone or in combination with other anorectic agents. From this, and another study, the incidence in patients who used Aminorex was estimated to be about 0.5-3%, corresponding to a relative risk of 1000. However, the investigation was not epidemiologic stricto sensu.

Since then, other anorectic agents have been reported to be associated with primary pulmonary hypertension. Sporadic PPH cases and one case-series were published which implicated fenfluramine derivatives. It was the latter which prompted the conduct of this study, although its goals are much broader.

1.2 Objectives of the Study

General Objectives:

To develop an epidemiologic understanding of primary pulmonary hypertension and of the risk factors potentially contributing to its occurrence.

hypotheses is that pregnancy and labour increase the demand on the heart-pulmonary system. Another frequently cited hypothesis is trophoblastic embolism. It is also suggested that pulmonary hypertension secondary to pulmonary thromboembolic disease and Eisenmeger's syndrome could be misdiagnosed as PPH.

The role of autoimmune connective tissue disease in primary pulmonary hypertension has been debated. Several series have confirmed that antinuclear antibodies titers were elevated in PPH patients. Some authors think that pulmonary hypertension in this case should be considered as secondary rather than primary.

Reports have repeatedly associated portal hypertension with primary pulmonary hypertension. The prevalence of PPH in cirrhotic patients was reported to be higher than expected in several cirrhosis case-series and, conversely, portal hypertension is sometimes noted in PPH patients. The issue commonly discussed is whether portal hypertension preceded primary pulmonary hypertension or if both were part of a common disease process.

Several cases, and even case-series, of HIV infected or AIDS patients with PPH have been reported worldwide. The mechanism of occurrence is not known and potential confounders have not all been ruled out.

It has been suggested that several environmental risk factors might play a role. Altitude is one of them, because of the common observation of elevated pulmonary pressures in subjects living in very high altitude.

Dietary factors have also been suggested. The occurrence of pulmonary hypertension originating from pulmonary venous occlusion after digestion of bush tea has been suggested. L-tryptophan, a food supplement used for ailments such as insomnia, depression, premenstrual syndrome, has been recently linked to the newly recognized Eosinophilia-Myalgia Syndrome (EMS), among which a few cases had pulmonary hypertension. However, despite the similarity to PPH this syndrome should be considered as a separate entity.

In the early 1980s an epidemic of atypical pneumonia with a high prevalence of pulmonary hypertension occurred in Spain. It was referred to as the "Toxic Oil Syndrome". It was found to be associated with the consumption of rapeseed oil, which was suspected to be contaminated by chemicals. This syndrome is not always recognized as typical PPH.

Substance abuse has been reported to be a risk factor for primary pulmonary hypertension. Cases of PPH have been reported associated with chronic glue (toluene)

Specific Objectives:

1) To investigate the role of several suspected risk factors: (i) anorexigens (all classes); (ii) obesity; (iii) systemic hypertension; (iv) recent pregnancies; (v) oral contraceptives; (vi) thyroid extracts; (vii) cocaine use; (viii) exposure to high altitude.

2) To generate hypotheses on the potential role of a number of other factors: (i) familial history of morbidity; (ii) personal medical and surgical history; (iii) blood group; (iv) smoking; (v) dietary habits; (vi) weight loss behaviour; (vii) all other classes of drugs.

This report produces data pertaining to all these general and specific objectives. It addresses the role of the suggested risk factors and in particular anorexigens, (specific objective #1) in a more detailed fashion.

1.3 Organization of the study and ethical issues

The study was peer-reviewed by the Medical Research Council of Canada, who approved it for MRC-Industry funding grant # 9404-00-27203-UI-A. The funds were provided by the Institut de Recherches Internationales Servier under a sponsorship agreement which ensured complete independence of the investigators and freedom of publication. The Ministry of Public Health and Environment of Belgium also supported the study in that country. It was launched under the auspices of the International Primary Pulmonary Hypertension Study Group which consists of an International Coordinating Centre, an independent International Scientific Board, Local Research Teams in each country, an Expert Review Panel and a large number of participating centres (Appendices A1 to A4). The board includes members who sit on national or European regulatory boards, but who participated in their own names.

The IPPHS was launched in October 1992 in France and in January 1993 in the other countries. An interim report, which included the analysis of 50 cases and 123 controls, was released to the regulatory authorities of the five countries participating in the study. The interim results were also shared with the main participating centres in each country who were invited to a special workshop in Paris in June 1994, as well as with the international scientific community at a Symposium on Pulmonary Circulation held in Prague in July 1994.

II. METHODS

2.1 Overview of the Study:

The IPPHS was a case-control study launched in October 1992. The complete protocol can be found in Appendix B1 and the results of the feasibility study can be found in Appendix A5. Health centres were contacted in France, the United Kingdom, Belgium, The Netherlands, and Switzerland (see Table 1). Of the 306 centres contacted, 223 agreed to participate. Table 1 displays the actual participation of centres. Incident cases of primary pulmonary hypertension were sought in each of the five countries. For each case, 4 controls were sought and matched on age (+/- 5 years), gender and number of visits to physician per year. Controls were physician-based. The goal was to recruit 100 cases and 400 matched controls.

2.1.1 Inclusion Criteria

Included were subjects of both genders, between 18 and 70 years old inclusively, resident in the reporting country for more than 6 months, who were able to, and accepted to, participate in the interview and who did not suffer from an active chronic disease (Table 2).

2.1.2 Cases

2.1.2.1 Definition: Only incident cases diagnosed after September 1st, 1992 were considered. The date of diagnosis was defined as the date of the first right heart catheterization. The diagnosis of primary pulmonary hypertension required the documentation of pulmonary hypertension and the ascertainment of the absence of secondary causes for the disease. The list of secondary conditions and tests required to validate the diagnosis is presented in Tables 3 and 4. For comparison purposes, a number of other cases were also evaluated (but not used in the case-control analysis).

2.1.2.2 Identification: Efforts were made to obtain an exhaustive recruitment of cases diagnosed in all the participating centres. The Centres were contacted or visited at least every three (3) months by telephone in order to identify cases which may not have been reported. The Centres had the opportunity to declare new cases to Local Research Teams in each country by sending pre-addressed postcards and they also received mailed reminders on several occasions.

2.1.2.3 Ascertainment: This process was approached in two stages. First, a cardiologist or pulmonary physician appointed by the Local Research Team verified that the inclusion criteria were met and that all the required information was available

for each case. They completed the Medical Extraction Form presented in Appendix B2. In a second step, the forms were sent to the Expert Review Panel together with copies of X-rays, perfusion lung scan and echocardiogram. This Panel, blind on exposure, classified cases into three groups: "A", "B" and "C" (see Expert Review Panel report in Appendix A6 for details). Only "A" and "B" cases were retained for the case-control analysis. They represented 80.5% of incident live cases evaluated.

2.1.2.4 Cases included: Two hundred and ninety-eight (298) cases were reported or identified for the study. Of those, 95 could be retained for the case-control analysis. Table 5 summarizes the reasons for exclusion (detailed reasons are displayed in Appendix A7 to A11 by country).

2.1.3 Controls

2.1.3.1 Definition and rationale: The aim was to recruit four physician-based controls per case. A detailed description of the rationale for the choice of this type of controls can be found in a previous publication (Appendix B3).

In summary, we did not opt for hospital controls because many cases were diagnosed (and subsequently reported) by highly specialized centres with nation-wide recruitment of patients. Consequently, the definition of the "catchment population" of the respective centres from which cases originated was not straightforward. Due to the large number of risk factors investigated, it was also difficult to identify hospitalized conditions which would be free of biases.

Physician-based controls were preferred to community controls mainly on the basis of feasibility and for purposes of validation. Firstly, the interviews were very long and required a significant commitment from subjects, which was obtained thanks to the intervention of their GP. Secondly, the intention was to validate the exposure to drugs (as well as medical history) from the GP's notes and/or medical files. Another issue was the insidious onset of the disease, lasting for several months or even years. This may have led to numerous contacts between the cases and the physicians before the diagnosis was made. This was a concern at the launch of the study considering the uncertainty around the index date for the disease (see below). It was felt that physician-based controls would better represent the source population from which the cases originated, especially in terms of the degree of accessibility to the health care system.

2.1.3.2 Selection of controls: Cases were asked to identify their general practitioner, who was then contacted by the hospital physician of the case and/or the local research team coordinator. In case of refusal to participate from the GP, or in the absence or lack of an appropriate control for a given case, controls were chosen among the patients of another GP practising in the same area. In some instances, it was necessary to use controls from more than one GP.

GPs were asked to provide a list of 100 consecutive patients to the Local Research Team for selection of controls (see Appendix B8). Sets of properly matched controls were identified by an independent epidemiologist for each country. Usually 4 controls were interviewed for each case, but in a few instances, a greater number of controls were available while in others, less or no controls could be found. In the latter case, GPs were asked to submit another list of consecutive patients. In some instances, it was necessary to select controls from another GP from the same country.

Four hundred and ninety-two (492) controls were interviewed. Of these, 355 were included in the case-control analysis. A significant number of other controls (137) could not be used either because their matched case had died before being interviewed, was subsequently found unsuitable for the study, was not evaluated by the Expert Review Committee or was a prevalent case. In addition, a number of interviews were forwarded to us too late to be included in this database (Table 6). Those controls were used for validation studies reported later in this report.

2.1.4 Interviews

2.1.4.1 Methods of Interview: An in-depth interview of each subject was conducted using questionnaires and visual aids (see Appendix B4 and B7). For each country, a specific questionnaire was developed in order to account for differences in drug tradenames, but the structure remained identical across countries.

The interviews were conducted by specially trained interviewers who had no medical background and who were blind as to the specific objectives of the study. A general questionnaire (Appendix B4) was first administered on sociodemographic and individual characteristics, medical, surgical, obstetrical history, habits, exposure to high pressure and high altitude, familial medical history and other general variables. In order to elicit drug use in a more specific way, a multi-step procedure was applied.

Subjects were questioned in detail on their personal life events since August 1, 1989 for cases interviewed before December 31, 1993 and since August 1, 1990 for subjects interviewed after that date. They were then asked about all sickness events

(mild to severe) for the same period. These two preliminary steps were intended to establish "landmarks" in the memory of the recent past back to 3 years. Each of these events was recorded on a calendar (Appendix B5). During the detailed interview, efforts were made to precisely draw the period of exposures on a calendar-like diagram available for each risk factor.

A calendar of drug use was established by three (3) different methods: (i) spontaneous reporting of drugs which were used at the time of the landmarks; (ii) presentation of lists of approximately 80 different brand names, chosen from amongst the most prescribed drugs in each therapeutic class, for each country (Appendix B5); (iii) presentation of a visual display with selected packages and/or tablets (Appendix B6). Exposure to anorexigens was treated in the same way as exposure to any of the other products investigated.

Subjects could also report their exposures before the time covered by the detailed interview, but exact dates were not systematically sought. Finally, a sealed questionnaire assessing the use of illicit drugs and sexual habits was given to the patient (Appendix B7).

2.1.4.2 Summary of Factors Investigated: The categorization of the factors assessed during the interview is summarized below. The order of presentation is from the more general to the more specific.

A) General characteristics

Sociodemographics: age, gender, occupation (10 classes), ethnicity.

Clinical characteristics: initial symptoms (for cases only); blood, pulmonary and cardiac tests.

Blood groups: ABO, Rhesus factor.

Morbidity

. Familial medical history: classified according to the ICD-9 broad classes.
. Personal medical history: detailed and later classified into broad classes (presence/absence before the index date).
. Personal surgical history (number of minor and major surgeries before index date) classified according to the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures.

Habits & Lifestyle:

. Smoking: current and 4 years before interview (Y/N)
. Alcohol: current use, use 4 years before interview and frequency.
. Selected dietary habits: coffee, tea, herb tea, colas, chocolate, cheese, paté, smoked meat, game meat, yeast extracts (before index date and after): current use and use 4 years before interview as well as frequency.
. Weight loss behaviour: This variable was constructed a priori by combining information obtained on unstable weight, use of laxatives, phytotherapy (when used for weight loss), isolated use of diuretics (except when systemic hypertension and/or use of a non-diuretic antihypertensive was mentioned). Presence of weight loss behaviour was defined as the presence of at least one of these factors reported before the index date.
. Number of sexual partners, before the index date.

B) All drugs (except those suspected a priori)

All classes were investigated, with approximately 80 specific products in each country (Appendix B5). Any use before the index date was considered.

C) Suspected risk factors

High altitude or high pressure

. Exposure to high altitude or high pressure: living in high altitudes for more than 6 months (in total), scuba diving, taking planes frequently.

Suspected health-related risk factors

. HIV: was recorded only in cases (when present in the medical charts).
. Cirrhosis: was defined as reported by the case, with a review of liver function tests and other clinical information, by a physician. "Alcoholic" or "post-hepatitic cirrhosis" was defined on basis of interviews.
. Systemic Hypertension: use of non-diuretic anti-hypertensive drugs in non-cardiac patients and for hypertension reported during an interview and confirmed by the use of at least one anti-hypertensive medication, including diuretics (before the index date). Excludes portal hypertension.
. High Body Mass Index: highest and lowest body-mass index (weight divided by squared height) in life-time. A BMI equal or greater than 30 was chosen as the cutoff to define obesity.
. Obstetrical history: total number of pregnancies and presence/absence of a recent pregnancy (less than 1 year before index date)

Suspected drugs (except anorexigens)

. Oral contraceptives
. Thyroid extracts
. Illicit drugs: marijuana, hashish, cocaine. Any use reported before the index date was considered.

D) Anorexigens

A detailed assessment is reported in the text.

2.1.5 Timing of events and exposures

2.1.5.1 Index date: The index date for the study of risk factors corresponds to the date of onset of symptoms of the case (dyspnea mainly). The same index date was applied to controls. Exposure was considered only if it had started before this index date. Because of the uncertainty in timing, uses of drugs which had occurred in the same month as the first symptoms were considered as "undetermined" in the main analyses and were addressed in the sensitivity analysis.

2.1.5.2 Time windows: In the absence of an accepted model for the pathophysiological process of the disease, all past exposures before the index date were considered for all risk factors except anorexigens. For anorexigens, it was

decided a priori to also use a one-year time-window before the index date. Any exposure which started or ended during these time-windows was considered as exposure for the relevant time-window.

2.2 Statistical analysis

The analysis includes three parts:

1. Description of the sociodemographic and clinical characteristics of the study population.
2. Bivariate analysis for general and suspected risk factors.
3. Multivariate analysis of retained risk factors.

These analyses were performed using SAS, statistical package version 6.13 (UNIX) and EGRET version 026.6.

2.2.1 Descriptive statistics

The sociodemographic characteristics of the cases and controls and the clinical features of the cases are described. Categorical variables are reported as frequency distributions and continuous data are reported by the mean, standard deviation, median, minimum and maximum values. When necessary, heterogeneity between countries, genders and other strata was assessed by the chi-square statistics (for categorical data). The significance level was set at .05.

2.2.2 Bivariate analysis

Cases and controls were compared on the frequency of exposure to the risk factors listed under section 2.1.4.2 (general potential risk factors and suspected drugs (except anorexigens) risk factors). Again, the presentation goes from the general to the specific.

Only the information available on both groups was used. In these analyses all past exposures before the index date were considered (time window not specified). Differences between cases and controls were assessed by the chi-square test for categorical variables and the Fisher exact test when one cell had less than ten (10) subjects.

The magnitude of the bivariate association between exposure to each of the potential risk factors and PPH was estimated by the use of matched odds ratios for the main suspected risk factors which had a significantly ($p < .05$) different prevalence in cases and controls in the bivariate analysis. Matched odds ratios of exposure between different strata of potential confounders were also calculated. All odds ratios are presented with their 95% bilateral confidence intervals. The body mass index (BMI) was dichotomized into BMI ≥ 30 and BMI < 30. Hypertension and smoking were dichotomized into yes/no categories.

For anorexigens, subjects were classified into 4 categories: (I) exposed to a defined product before the index date; (II) unclassified exposure (use of an unknown drug to lose weight or exposure at an unspecified date); (III) exposed after the index date; (IV) unexposed. Category (I) was considered as exposure and categories (III) and (IV) as unexposure. Two sets of analyses were conducted: one on all past exposure and one on exposure within the one-year time window.

2.2.3 Multivariate analysis

The magnitude of the effect of the selected risk factors on the occurrence of PPH was assessed by the adjusted odds ratio, an estimate of the relative risk. In order to control for potential confounding, multivariate analyses were conducted (conditional logistic regression).

2.2.3.1 Main model

The main variables in the models were exposure to the drugs of interest (anorexigens). Exposure to anorexigens was defined as exposure to any of the individual products during the relevant time-window. The main models used category "I" as exposure to anorexigens and "III" + "IV" as non-exposure. Models were controlled for unclassified exposure "II". In the sensitivity analysis, "II" was also considered as exposure. In addition, the following variables were included in the model: marker of obesity, systemic hypertension and smoking. Cases with IVD use or cirrhosis were withdrawn from the main models. The models are also controlled for weight loss behaviour, unclassified weight loss drug used. Interactions were further tested in the models: between anorexigens and BMI, anorexigens and hypertension. None was significant. The odds ratios presented are also controlled for a series of variables which were statistically different between cases and controls in the bivariate analysis. The uncertainty associated with odds ratio estimates was assessed by the 95% bilateral confidence interval.

2.2.3.2 Type of anorexigens: For the study of individual anorexigens, it was a priori decided to group fenfluramine and dexfenfluramine (F/DF) on the one hand and all amphetamine-like anorexigens (ALA) on the other hand. ALA included the amphetamine-like drugs specifically addressed in the questionnaire and those spontaneously reported by the interviewees (amfepramone, clobenzorex, fenosolone, fenproporex, mazindol, preludine).

The study of different profiles of use was planned as follows: (i) Use of F/DF only; (ii) Use of ALA only; (iii) Use of F/DF at least (with or without use of ALA); (iv) Use of ALA at least (with or without F/DF); (v) Use of both F/DF and ALA.

For these analyses, all exposures in the past were considered (before the index date), whether they had occurred concurrently or at different dates. Adjusted odds ratios were calculated for each profile by using several dummy variables (statistical models can be found in Appendix A12). Exposures of cases and controls to individual fenfluramine derivatives and amphetamine-like anorexigens are reported but no adjusted odds ratios were calculated for individual drugs.

2.2.3.3 Duration of use of anorexigens: The duration of exposure during the risk period (all exposures in the past) was measured as the sum of the number of days of treatment before the index date. Duration was categorized as: a) less or equal to 3 months (90 days); b) more than 3 months or undetermined duration which consists of responses such as occasional or episodic use.

2.2.3.4 Timing of event: Subjects were classified as a) exposed in the year before the index date (whatever previous exposure); b) exposed more than one year before the index date and not exposed in the year before the index date; c) not exposed at all in the past. Only "I" exposures (defined in section 2.2.2) were considered as exposure; categories III and IV were the reference and models were controlled for unclassified exposure (category II).

2.3 Validation studies

Studies were conducted in order to assess potential selection biases and for the validation of the questionnaires. They were conducted on all past exposures to anorexigens (category "I") before the index date.

2.3.1 Identification and reporting biases

2.3.1.1 Delay for diagnosis and severity of symptoms: These factors are compared between exposed and unexposed cases.

2.3.1.2 Main Reporting Centre effect: In each country, the exposure of the cases stemming from the main reporting centre was compared to the exposure of other cases. Results are reported for France, where one centre contributed half of the cases considered.

2.3.1.3 Included vs non-included cases: Exposure was compared between the cases included in the case-control analysis ("A" & "B" cases) and the exposure of excluded, rejected, prevalent and other reported cases which were not retained for the study.

2.3.1.4 Field studies: At the end of the study, all participating centres were contacted in order to review the cases that they reported and to potentially identify new cases which might not have been identified during the previous encounters. With a sample of these participating centres, stratified by the number of cases reported, an in-depth review of the process was conducted. Twenty-five centres were contacted or visited.

In addition, a sample of centres who had not reported any cases but had originally agreed to participate was contacted for an in-depth review. Fifteen centres were contacted for this purpose.

2.3.2 Bias in the selection of controls

2.3.2.1 Non-Included controls: Out of the 137 controls who were not included in the case-control analysis, 114 have been coded and entered in the database. The exposure of the controls, which were not used for the case-control analysis (see further above), was evaluated for anorexigens.

2.3.2.2 Exposure of controls vs sales figures The exposure of the controls included in the analysis was compared to the expected percentage of exposure to anorexigens according to sales figures in various countries.

2.3.3 Exposure misclassification

A number of analyses and studies were conducted in order to assess potential sources of information bias and their potential impact on the main results of the study.

2.3.3.1 Index date and protopathic bias: The index date was defined as the date of first symptoms, i.e. mainly dyspnea. It was felt that a certain amount of uncertainty could exist around this date. The odds ratio for anorexigen use before and after the index date (see also "protopathic bias" further below) were estimated. This comparison of the exposure of cases after the index date to the exposure of controls (for the same period) also provided some insight on the potential protopathic bias.

2.3.3.2 Unclassified exposures: Subjects who had reported the use of drugs to lose weight without being able to identify them or to precisely identify the date vis-à-vis the index date (category "II") were considered unexposed to any anorexigens in the main analysis. They were reclassified as exposed in the sensitivity analysis and the odds ratios were calculated.

2.3.3.4 Validation of questionnaires

In The Netherlands and the U.K., a validation study in which the data from the questionnaires are compared to the GPs' notes. Computerized pharmacy data is currently underway in The Netherlands. These validation studies could not be completed before this final report.

2.3.4 Country effect

Adjusted odds ratios for exposures to anorexigens were calculated for France alone.

Table 1 Participating centres

	Number of Centres :			
	Contacted in 1992	Agreed to participate	Actively* participated	Included at least one case**
France	138	86	61	18
UK	46	42	6	6
Belgium	71	67	30	7
The Netherlands	48	25	6	4
Switzerland	3	3	3	--

* Reported cases (retained or not) and/or participated in validation studies, regularly contributed.

** In the case-control analysis.

N/A: not available.

Annexe 1-54

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Table 2 Inclusion criteria for cases and controls

Age 18-70 (included)
Both genders
Resident for more than 6 months in the country
Interview possible
Consented to participate
Not suffering from active chronic diseases (cancer, systemic diseases, others)

Already married at the time of interview, or less 4

Table 3 List of secondary causes of pulmonary hypertension excluded

- congenital abnormalities of the lungs, thorax and diaphragm
- congenital or acquired valvular or myocardial disease
- pulmonary thromboembolism
- obstructive lung disease
- interstitial lung disease
- pulmonary artery or pulmonary valve stenosis
- pulmonary venous hypertension
- central hypoventilation with hypoxemia and hypercapnia
- parasitic disease affecting the lungs
- sickle cell anemia
- AIDS
- collagen vascular disease

Table 4 Tests requested for the confirmation of the diagnosis of primary pulmonary hypertension

MANDATORY PROCEDURES
- chest roentgenogram
- pulmonary function tests
- perfusion lung scan/pulmonary angiogram.*
- echocardiogram
- cardiac catheterization
REQUESTED PROCEDURES
- liver function tests
- HIV serology
- Antinuclear antibodies

* Mandatory if perfusion lung scan was suggestive of pulmonary embolism

Table 5 Reasons for the non-inclusion of cases (all countries)

TOTAL REPORTED		298
Did not meet inclusion criteria:		137
. <18 or >70 y.o	15	
. diagnosed before September 1, 1992	49	
. No date of catheterization	9	
. Secondary PH	33	
. Connective tissue disease	1	
. Other diseases	2	
. Non-resident	6	
. Reported after September 1994	10	
. Chart not found	1	
. AIDS	1	11
Dead or died before interview		26
Not retained by Expert Review Panel ("C" cases)		23
Not interviewed by end of recruitment		6
Lost to follow-up		2
Patient refused		2
Not evaluated by December 12, 1994		1
TOTAL INCLUDED		95

Table 6 Additional interviewed controls not included in the case-control analysis, by reason for non-inclusion

Reason for non-inclusion of controls	Number
Prevalent cases	54
Deceased cases	21
Rejected cases	48
Cases lost to follow-up	6
Cases not evaluated by Expert Review Panel	8
Total	137

* 4 duplicates + 2 incomplete

III. RESULTS

Ninety-five cases (95) and three hundred fifty-five (355) controls were included in the case-control analysis. The results presented below correspond to these subjects. The results of the validation studies, which included other non-included cases and controls, are reported in section 4.

3.1 Description of the study population

Table 7 displays the number of cases and controls included per country. Most of them came from France, followed by Belgium. This is to be expected as more recruitment efforts were made in these countries. The mean number of controls per case is 3.7.

3.1.1 Sociodemographics

The mean age of cases was 44.7 y.o. (SD = 12.3), and the median was 45 (min: 21; max:70). They were almost identical in controls (Table 8). There were no notable differences between countries (Appendix A13).

The overall female to male ratio was 2.3:1. This ratio was similar in the different countries (Appendix A14).

The distribution of occupations between cases and controls was very similar (Table 9). Most cases and controls were of European ethnic origin (95.6% and 96.9%, respectively).

3.1.2 Clinical parameters

3.1.2.1 Onset of symptoms and time to diagnosis: The main symptom which led to the discovery of the disease was dyspnea. Others included syncope, angina pectoris, family history of PPH and miscellaneous incidental discoveries (Table 10). In most cases, the severity of the dyspnea at time of diagnosis was classified as Class III of the New York Heart Association Classification (Table 10).

The mean delay between onset and symptoms and right heart catheterization was 16.7 months (SD:19.3). The median delay was 16 months (range: 1-104 months). Table 10 presents the distribution of delays. Appendix A15 displays the median delays for the diagnosis by country.

3.1.2.2 Tests: Table 11 presents the results of the pulmonary function tests, right heart catheterization parameters and arterial blood gases.

3.1.2.3 Blood groups: There were slightly more cases with blood group B than controls (14.7 vs 7.8% respectively) and group AB (4.2% vs 2.8%), but the number of subjects who did not know their blood group (12.6% and 15.5% respectively) rendered the interpretation of these results difficult. There was no difference in Rhesus groups (Table 12).

3.2. Bivariate analysis

3.2.1 General characteristics (morbidity, habits, lifestyle)

3.2.1.1 Familial history of disease: Except for the 2 cases with a familial history of primary pulmonary hypertension, cases and controls did not generally differ in regards to their familial history of morbidity (Table 13). There was significantly less cancer reported in the family of cases than controls, which was not further explored here.

3.2.1.2 Personal history of morbidity and surgery: Cases and controls were very similar in their personal history of morbidity before the index date (Table 14). There was no difference in the percentage of cases and controls who had undergone surgery, either minor or major ones (results not shown).

3.2.1.3 Habits and lifestyle

Smoking: Cases were significantly more often smokers than controls, 4 years before the interview (Table 15).

Dietary habits: The drinking of alcohol, coffee, tea, herbal tea, colas, was not different. The consumption of chocolate, cheese, yeast extracts, smoked meat, did not differ between cases and controls. Game meat was used significantly more often by cases than controls in the bivariate analysis (Table 15).

Weight loss behaviour: Cases differed somewhat from controls as to their behaviour regarding weight control although the p value did not reach conventional significance ($p = 0.06$) (Table 15).

Number of partners: There was no difference in the sexual activity of cases and controls, whether measured by the number of partners (Table 15) or by the history of sexually transmitted diseases (Table 14).

3.2.2 All subclasses of drugs (except anorexigens)

Table 16 displays the exposure of cases and controls to all classes of drugs except anti-obesity preparations and drugs used to lose weight. No significant difference was found for most classes of drugs. Differences appeared for anti-asthmatic drugs (more used by cases), analgesics (less used by cases), haematological and anti-hypertensive drugs (more used by cases). Except for the latter, those differences are not further explored in this report. Appendix A16 displays the results for the individual sub-classes of drugs.

3.2.3 Stays in high altitudes and exposure to high pressure

Long stays in high altitudes were not differently reported by cases and controls (Table 17). No differences were found for scuba diving or frequent flying either (results not shown).

3.2.4 Suspected health-related factors

Results are presented in Table 18.

3.2.4.1 HIV Infection: Three cases had documented HIV infection (two of them reported IVD use). 11 more cases were not retained because they had AIDS. HIV infection could not be tested in controls.

3.2.4.2 Cirrhosis: Two cases had an alcoholic cirrhosis before the index date, 1 case had definite post-hepatitic cirrhosis, and 1 case had a possible post-hepatitic cirrhosis. No controls reported cirrhosis (Table 18). No difference had been observed in the prevalence of hepatitis (Table 14).

3.2.4.3 Hypertension: The prevalence of treated systemic hypertension was greater for cases than controls ($p = 0.08$).

3.2.4.4 Body Mass Index (BMI): Cases had more often experienced a body mass index equal or greater to 30 at least once in their life than controls had ($p < 0.001$).

3.2.4.5 Pregnancies: There were no differences in the total number of pregnancies experienced by female cases and controls. The experience of a recent pregnancy was also similar.

3.2.5 Suspected drugs

3.2.5.1 Oral contraceptives: No difference was observed between cases and controls (Table 19).

3.2.5.2 Thyroid extracts: No difference was observed (Table 19).

3.2.5.3 Illicit drugs: The use of marijuana and hashish was not reported differently by cases and controls. IVD use was more frequent in case than in controls (4 cases vs 1 control). Two (2) out of the four (4) IVD users were HIV positive, rendering these results difficult to interpret. All IVD users were cocaine users too, whether case or controls. No case and three (3) controls had used cocaine and not IVDs. Since it is disputable to consider all cases with IVD use as "PPH" cases, and because of the potential confounding by HIV infection, it was decided to withdraw all IV drug users from the main multivariate model. We do not further report on these variables in this summary report.

3.2.5.4 Anorexigens: Exposure to any anorexigen (category "I") was significantly more frequent in cases than in controls (all past exposures, Table 20). Table 21 presents the distribution of individual anorexigen use in cases and controls (all past exposure). The subclasses of fenfluramine/dexfenfluramine (F/DF) on the one hand and amphetamine-like anorexigen (ALA) on the other hand, were differently distributed between cases and controls. Table 22 presents the same information for the one-year time-window before the event.

3.2.6 Odds ratios for retained potential risk factors (crude and matched)

3.2.6.1 Anorexigens:

Table 23 presents the matched odds ratios (crude) for primary pulmonary hypertension associated with the past exposure to anorexigens, contrasting categories "I" of exposure to no exposure ("III" + "IV"). It appears that any exposure to an anorexigen in the past (all times) is associated with PPH [matched odds ratio of 4.4 (2.2-9.1)].

Table 23 also presents the odds ratios for exposure to anorexigens stratified by level of potential confounder (BMI, hypertension, smoking) for all past exposures. Small variations were observed.

3.2.6.2 Body Mass Index (BMI): In this crude matched analysis, a BMI greater or equal

to 30 (lifetime prevalence) was associated with a higher odds ratio vis-à-vis PPH [OR=3.0 (1.7-5.1)] (Table 24). The effect of a high BMI was not significantly modified when stratified by level of exposure to anorexigen (matched odds ratios were calculated), but displayed some indication for confounding between BMI and anorexigen use (Table 24). Subjects who have had a BMI of 30 or greater at least once in their life were more likely to be exposed to anorexigens (ECOR= 2.7). The odds ratios for the exposure to anorexigens for subjects who had experienced a BMI ≥30 once in their life was 5.0 (1.5-16.2) while the odds ratios for the exposure to anorexigens for subjects who had not experienced a BMI ≥30 once in their life was 2.9 (1.1-7.4).

3.2.6.3 Systemic Hypertension: PPH cases reported treated systemic hypertension more often than controls [OR=2.8 (1.1-7.0)] (Table 24). The odds ratio for hypertension was not significantly modified according to the status of exposure to anorexigens (Table 24). The effect of anorexigens was not very different in hypertensive vs normotensive patients.

3.2.6.4 Smoking: The matched odds ratio for smoking and primary pulmonary hypertension was slightly elevated [OR = 1.6 (1.0-2.6)]. The odds ratios varied between anorexigen users [OR = 0.7 (0.3-1.4)] and non-users [OR = 1.7 (1.0-3.0)].

3.2.6.5 Cirrhosis: The odds ratio was not estimated due to the small numbers in each category of cirrhosis.

3.2.6.6 HIV: The odds ratio was not estimated due to the absence of information on the status of controls.

3.2.6.7 Other factors: The odds ratio for game meat consumption and the odds ratio for cancer history in the family were 2.2 (1.1-4.2) and 0.6 (0.4-0.9) respectively. These last factors were not further explored in this analysis. Although not strictly significant in the bivariate analysis, we kept weight loss-behaviour in the multivariate analysis.

3.3. Multivariate analysis

3.3.1 Main model

Table 25 presents the results of the main model using anorexigens, hypertension, high BMI, smoking and controlling for a number of other factors such as unclassified exposure. Cases with cirrhosis or IVD use are withdrawn from the model. The odds ratio for the exposure to any anorexigens in the past remains elevated when controlled for other factors [4.1 (1.8-9.7)]. Having experienced a high BMI remained significantly associated

with the risk of disease [OR=2.6 (1.3-5.0)] while systemic hypertension was not significantly associated with the risk of disease. There was no important difference observed when the one year time-window was used, except that the association appeared slightly stronger for anorexigens [OR= 5.9 (2.1-16.5)]. No other factors showed a significant association.

3.3.2 Individual anorexigens

Table 26 shows the results of the adjusted models for subclasses of anorexigens (all exposure in the past and one-year time-window). The effect of the exposure to only F/DF was estimated by an adjusted odds ratio of 3.8 (1.7-10.0). Exposure to at least an F/DF (with or without the use of an ALA) was estimated with an adjusted odds ratios of 4.1 (1.7-10.0) for all past exposure. The odds ratio was slightly more elevated for the one-year time-window [OR 5.8 (1.6-16.2)]. Amphetamine-like agents (ALA) displayed similar profiles of risk, although the numbers were small and the estimates consequently unstable. Several users had been exposed to both subclasses of drugs in the past, resulting in an odds ratio for primary pulmonary hypertension of 5.8 (1.0-33.1).

3.3.3 Recent vs. non-recent exposure to anorexigens

When exposure to anorexigens had been terminated for more than one year before the index date, the adjusted odds ratio was of 2.4 (0.6-8.8) as opposed to 5.9 (2.1-16.9) for more recent exposure (within one year) (Table 27). However, the effect of recent exposure was different according to previous experience with the drug: The odds ratio was 4.9 (1.0-23.7) for recent users who had not used the drug in the year before, but it was smaller [2.3 (0.5-10.9)] for those with previous exposure.

3.3.4 Duration of exposure to anorexigens

Table 28 presents the distribution and the adjusted odds ratios for durations of use of anorexigens of 3 months and less (92 days), more than 3 months and undetermined durations. It appears that the risk increased notably with longer duration of use [OR = 10.6 (2.8-39.5)] and was much smaller in short term use [OR =1.9 (0.5-7.3)]. The odds ratio for BMI remained unchanged since the three durations of use tested are mutually exclusive subcategories of exposure to all anorexigens in the past. When only recent exposures were considered (within one-year preceding the index date), the odds ratios for short duration and long duration of use were not significantly different: 2.3 (0.4-12.4) and 10.6 (3.7-28.8) respectively (Total duration).

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Table 7 Distribution of the cases and controls included in the case-control analysis, per country

Country	Cases (%)	Controls (%)
France	64 (67.4)	232 (65.4)
United Kingdom	11 (11.6)	36 (10.1)
Belgium	13 (13.7)	59 (16.6)
The Netherlands	7 (7.4)	28 (7.9)
TOTAL	95 (100)	355 (100)

1,7
1,8
1,8
1,8

excluding Clamart (35)

Témoins 149
95 PMS
89
184

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42 ne fument: 1 Témoin

Table 8 Sociodemographic characteristics of included cases (all countries)

	Cases		Controls	
Mean age (standard deviation)	44.7 y.o.	(12.3)	45.1 y.o.	(12.6)
Median age (25th perc., 75th perc.)	45 y.o.	(35-55)	44 y.o.	(36-56)

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Table 9 Distribution of occupations of included cases and controls

Occupation	Cases (%) (N = 95)	Controls (%) (N = 355)
Blue Collar	10.5	8.2
White Collar*	12.6	12.4
Secretary	6.3	3.9
Professional	3.2	4.5
Shopkeeper	7.4	7.0
Housewife	16.8	14.1
Student	0.0	2.5
Unemployed	12.6	7.3
Retired	9.5	14.1
Other	21.1	25.9
Total	100 %	100 %

* Does not include secretaries

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Table 10 Clinical presentation and diagnosis in cases

	Cases n	(%) Cases
Initial symptoms		
Dyspnea	86	(91)
Syncope	13	(14)
Angina pectoris	15	(16)
Oedema of lower limbs	9	(9)
Incidental test* discovery	5	(6)
Severity of dyspnea +		
NYHA I	2	(2.1)
II	30	(31.6)
III	58	(61.1)
IV	5	(5.3)
Delay between symptoms and catherization		
≤ 12 months:	35	
12-23 months:	22	
24-35 months:	15	
36 + months:	19	
DNK months	4	

date Index: 1er symptôme

* Chest X-ray, ECG, echocardiogram, other

+ At date of first admission

DNK : Do not know

Table 11 Arterial blood parameters, pulmonary function tests and right cardiac catheterization tests in included cases (N = 95)

	Mean (SD)
Arterial blood gases*	
pH	7.45 ± 0.04
PaCO2	30.8 ± 4.5
PaO2	75.8 ± 19.5
SaO2 (%)	93.9 ± 3.5
Pulmonary function tests (% predicted)	
Forced vital capacity	97.5% ± 14.9
Total lung capacity	97.3 ± 12.7
FEV	91.4 ± 16.3
DLCO	79.7 ± 22.2
Right catheterization*	
Pulmonary arterial pressure	
systolic	87.9 ± 20.9
diastolic	36.5 ± 10.4
mean	57.3 ± 12.8
Mean pulmonary capillary wedge pressure	9.1 ± 3.2
Cardiac output	4.1 ± 1.5
Cardiac index	2.3 ± 0.7
Mean right atrial pressure	10.9 ± 6.3
Min. right ventricular end-diastolic pressure	11.7 ± 6.3
Left ventricular end-diastolic pressure	8.5 ± 3.5
SVO2	60.8 ± 11.6
PVO2	37.5 ± 10.5
Systemic blood pressure*	
systolic	129.1 ± 19.7
diastolic	79.2 ± 13.2
mean	97.4 ± 14.4
Heart rate (bpm)	83.8 ± 12.7

* All pressures are in mmHg

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Table 12 Distribution of Blood ABO & Rhesus Groups in cases and controls

	Cases % (N = 95)	Controls % (N = 355)
A	35.8	35.2
B	14.7	7.8
AB	4.2	2.8
O	32.6	39.2
Unknown ABO	12.6	15.5
Rhesus +	76.8	67.6
Rhesus -	9.5	14.1
Unknown (Rh.)	13.7	18.3

Table 13 Familial history of disease in cases and controls

Disease	% Cases (N = 95)	% Controls (N = 355)	p value**
Familial PPH*	2.1	0	--
Cardiovascular	53.8	55.2	.73
Lung	33.3	41.4	.13
Rheumatologic	20.7	24.0	.40
Alzheimer	8.6	8.2	.86
Blood	9.7	10.2	.31
Neurologic	11.8	8.0	.22
Psych. disorders	19.3	16.8	.73
Cancer	38.7	52.5	.01
Diabetes	19.0	22.8	.58
Others	31.6	32.1	.77

* 2 cases had a familial history of PPH

** Matched

Table 14 Pre-existing morbidity* in included cases and controls (before the index date)

Disease	% Cases	% Controls	p value **
Cardiovascular	6.3	8.7	.45
Pulmonary disorders			
. Asthma	4.2	6.2	.46
. Bronchitis (Chr.)	11.6	7.0	.15
. Mult. Resp. Infections	12.6	7.9	.15
. Repet. Flu	12.6	19.2	.14
Endocrinologic. Dis.			
. Diabetes Juv.	2.1	0.9	.30
. Diabetes Mat.	2.1	2.8	.70
. Thyroid Dis.	5.3	7.3	.48
. Others	2.1	1.2	.79
Rheumatologic Dis.			
. Osteo-Arthritis	18.4	13.8	.16
. Arthritis	2.1	2.3	.93
. Bone deformities	1.1	4.8	.10
Urol. Kidney Gyn.	23.2	23.2	.92
Sexual. transmitted Dis.	6.5	7.3	.79
Digestive Dis.	22.1	25.9	.61
Dermatological	31.6	29.9	.75
Skin Allergies	9.5	10.7	.73
ENT	41.1	48.9	.61
Hay fever	10.5	11.8	.72
Venous dis.	41.1	41.1	.99
Phlebitis	3.1	5.2	.11
Neurologic. & Psychiat.	1.1	1.2	.80
Cancer Tumors	3.2	2.8	.19
Others	4.2	4.8	.81

* Excluding suspected morbidity (systemic hypertension, High BMI, liver disease, HIV infection).

** Unmatched.

Table 15 Distribution of habits and lifestyle characteristics in included cases and controls

	% Cases (N = 95)	% Controls (N = 355)	p value**
Smoking	44.2	31.6	.05
Dietary habits			
. Coffee#	80.0	84.2	.31
. Tea#	37.9	47.0	.16
. Herb Tea#	24.2	28.4	.35
. Cheese =	72.6	77.8	.23
. Chocolate =	27.4	34.7	.27
. Pate +	59.0	60.0	.75
. Smoked meat +	45.3	47.6	.72
. Game meat +	16.8	8.5	.02
. Yeast extracts +	36.8	31.3	.22
. Colas ~	40.0	32.4	.17
. Alcohol ~	72.6	63.9	.13
Lifestyle characteristics			
. Weight loss behaviour*	60.0	50.1	.06
. Number of sexual partners@	32.5	27.3	.31

\# Yes or No
= Once per week or more
\+ Once per month or more
~ Sometimes or frequently vs never
@ Three or more sexual partners in 10 years
* See text for description
** Matched

Table 16 Exposure to drugs (all subclasses except anti-obesity preparations and drugs used to lose weight) before index date

Groups of ATC sub-classes	Cases (%) N = 95	Controls (%) N = 355	p value **
1. Alimentary tract & Metabolism	31.6	31.6	.96
2. ENT	10.5	15.5	.17
3. Antiasthmatics	9.5	4.2	.05
4. Musculo-skeletal & anti-inflamatory	21.5	28.2	.14
5. Analgesics	50.5	58.9	.02
6. Neural. Psych.	27.4	25.9	.65
7. Hormonal prep.	3.2	5.6	.35
8. Anti-infectious & antimycotic.	29.5	30.7	.95
9. Dermatologic.	8.4	6.5	.58
10. Haemotological	8.4	3.7	.03
11. Cardiovascular	19.0	22.4	.64
12. Antihypertens & diuretics	22.1	9.0	.00
13. Sex hormones *	40.9	32.6	.18

* In females only, including oral contraceptives.
** Matched

Table 17 Exposure of cases and controls to high altitudes

Risk factor	Cases (%)	Controls (%)	p value **
Stays in high altitude*	15.8	16.5	.67

* More than 6 months total duration.
** Matched

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Table 18 Suspected health-related factors in cases and controls

	% Cases	% Controls	p value **
HIV infection@	3.2	--	--
Cirrhosis	4.2	0.0	--
Systemic Hypertension#	11.6	5.9	.03
Body mass index ≥30	35.8	18.2	.00
Recent pregnancy+	7.6	5.3	.48

N. cases = 95; N. controls = 355

@ 3 cases were HIV infected, of which 2 reported IVD use. 11 cases with AIDS had been excluded.

* One definite and one possible case.

\# Treated hypertension as defined in the text.

\+ Pregnancies that occurred within 12 months before the index date; percentages calculated on female cases (N=66) and controls (N=265) only.

** Matched

Table 19 Suspected drugs (except anorexigens) used by cases and controls (all exposures in the past, before the index date)

	% Cases	% Controls	p value **
Oral contraceptives*	28.8	34.3	.31
Thyroid extracts +	2.1	3.1	.75
Hashish, marijuana +	11.6	7.6	.43

* Percentages in females only (cases = 66; controls = 265)

\+ N.cases = 95; N.controls = 355

** Matched

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Table 20 Anorexigen use by cases and controls (all exposure in the past)

		Cases (%) n		Controls(%) n		p value **
I)	**Definite exposure**					
	Use of a defined individual product before index date	20	(21.1)	23	(6.5)	.00
II)	**Unclassified exposure**					
	Any use of an unknown drug to lose weight*	4	(4.2)	1	(0.3)	
	Anorexigen used at an undetermined date	5	(5.3)	1	(0.3)	
	Anorexigen used the same date as index date	2	(2.1)	0	(0.0)	
III)	**Use after index date**	6	(6.3)	20	(5.6)	
IV)	**No anorexigen used**	58	(61.1)	310	(87.3)	
TOTAL		95	(100)	355	(100)	

Categories I, II, III & IV are mutually exclusive.

* Patient reported having used drugs "to lose weight" but it was not clear whether those were anorexigens or any other pharmaceutical products (diuretics, homeopathy, etc.).

** Matched.

Table 21 Exposure of cases and controls to individual anorexigens (all past exposures)

	Cases (%) n		Controls (%) n		p value **
I) Definite exposure					
F/DF	18	(19)	20	(5.6)	.00
Fenfluramine	3		3		
Dexfenfluramine	16		19		
ALA	6	(6.3)	6	(1.7)	.02
Amfepramone	2		2		
Clobenzorex	3		3		
Fenosolone	0		1		
Fenproprorex	3		3		
Preludine	1		0		
II) Unclassified exposure					
Unknown	9		2		
Same index date	2		0		
III) Use after index date	6		20		
IV) No anorexigens used	58		310		
TOTAL	95		355		

F/DF = fenfluramine and/or dexfenfluramine (at least)

ALA = amphetamine-like anorexigens (at least)

Numbers are not mutually exclusive due to simultaneous exposure to different individual products

** Matched

DO NOT CITE OR QUOTE

Table 22 Exposure of cases and controls to individual anorexigens (one-year time-window before index date)

	Cases (%) n	Controls (%) n	p value**
I) Definite exposure +			
F/DF	10 (15.4)	7 (3.0)	.00
ALA	2 (3.1)	2 (0.9)	.14
II) Unclassified exposure	3	1	
III) & IV) Use after index date or no anorexigen used	50	224	
TOTAL	65	234	

F/DF = fenfluramine and/or dexfenfluramine

ALA = amphetamine-like anorexigens

\+ Numbers in subclasses are mutually exclusive: no subjects had used different individual products within the one-year time-window.

** Matched.

Table 23 Distribution and odds ratios (matched) for exposure to any anorexigen in cases and controls, according to the presence of other risk factors (all past exposure)

	Cases		Controls			
	n in stratum (% exposed)		n in stratum (% exposed)		Odds Ratios*	(95% CI)
Exposure to any anorexigen	95	(21.1)	355	(6.5)	4.4	(2.1-9.3)
BMI						
≥ 30	34	(32.4)	65	(10.8)	5.0	(1.5-16.2)
< 30	61	(14.8%)	290	(5.5%)	2.9	(1.1-7.4)
Hypertension**						
yes	11	(25.0)	21	(8.0)	5.5	(1.1-28.3)
no	84	(13.0)	334	(5.4)	3.8	(1.7-8.8)

* Matched (crude)

** Systemic hypertension (excluding portal hypertension)

95% CI = 95% confidence intervals limits

Table 24 Matched odds ratios of exposure to retained risk factors in PPH cases and controls: global and stratified by status of exposure to anorexigens

	Odds Ratios	Anorexigen non-users	Anorexigen users
High BMI*	3.0 (1.7-5.1)	2.1 (1.0-4.2)	3.6 (1.3-9.8)
Hypertension**	2.8 (1.1-7.0)	2.2 (0.7-6.6)	3.1 (0.5-19.3)

Numbers in parenthesis are 95% confidence interval limits.

95 cases and 355 matched controls are used.

* Body Mass Index ≥ 30

** Systemic hypertension (excluding portal hypertension)

NC: Not calculated for lack of convergence.

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Table 25 Adjusted odds ratios from multivariate conditional logistic regression of main risk factors on PPH (all past exposures before index date)

	All past exposure OR	(95% CI)	One-year time-window OR	(95% CI)
Anorexigens**	4.1	(1.8-9.7)	5.9	(2.1-16.5)
High BMI +	2.6	(1.3-5.0)	2.7	(1.2-6.2)
Hypertension#	2.4	(0.8-7.1)	2.5	(0.7-8.3)
Smoking	1.3	(0.7-2.3)	1.2	(0.6-2.3)
Weight Loss	0.9	(0.5-1.7)	1.2	(0.6-2.5)

* Adjusted for unclassified drugs, cirrhosis and IVD use (withdrawn). Interactions were tested and not retained.

** Exposure is to defined drugs (Category I).

\+ BMI greater than or equal to 30 (at least once in life).

\# Treated Systemic hypertension.

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Table 26 Adjusted odds ratios for subclasses of anorexigens (all past exposures and one year before index date)

Anorexigens +	All past exposure		One-year time-window	
	OR*	(95% CI)	OR*	(95%CI)
F/DF only	3.8	(1.5-9.7)	5.8	(1.6-16.2)
F/DF at least	4.1	(1.7-10.0)	NA**	
ALA (only)	4.0	(0.2-65.8)	6.4	(0.7-56.2)
ALA (at least)	5.4	(1.2-24.2)	NA**	
F/DF + amphetamine -like	5.8	(1.0-33.1)	NA**	

\+ Exposures are category I (defined exposures) in each time-window

* Adjusted odds ratios are estimated by separate models for each subclass (conditional logistic regressions controlled for BMI, hypertension, smoking, weight-loss behaviour, unclassified drugs) cirrhosis and IVD use are withdraw. References are categories III + IV in each time-window.

ALA = Amphetamine-like anorexigens (any indicated drug)

F/DF = Fenfluramine/dexfenfluramine

NA** = Not applicable, no cases or controls in this category (F/DF at least = F/DF only and ALA at least = ALA only).

95%CI = 95% confidence interval limits

Le produit ne met rien

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Table 27 Adjusted odds ratios for exposure to anorexigens before and after a one-year time-window preceding the index date

Exposure timing	Cases n	Controls n	Adjusted* Odds ratios	(95% CI)
Within one-year** before index date	12	9	5.9	(2.1-16.9)
Terminated more than one year before index date	7	13	2.4	(0.6-8.8)
Undetermined timing	1	1	--	--
TOTAL	20	23	3.9	(2.0-7.6)

* Adjusted for BMI, hypertension, smoking, weight loss behaviour, unclassified drugs, cirrhosis (withdrawn), hard drug use (conditional logistic regression).

** Exposure which terminated and/or started during this time-window.

Table 28 Distribution of use and adjusted odds ratios for duration of use of anorexigens (all past exposure before index date)

Duration of use	Cases N = 95	Controls N = 355	Adjusted* Odds ratios	(95% CI)
. 3 months or less	5	10	1.9	(0.5-6.9)
. More than 3 months	9	5	9.1	(2.6-31.5)
. Undetermined duration	6	8	2.2	(0.5-9.1)
. High BMI +	34	65	2.4	(1.2-4.8)

* The odds ratios are adjusted for systemic hypertension, smoking, weight-loss behaviour, unclassified exposures, cirrhosis and ivd use (withdrawn). (conditional logistic regression)

** Numbers depend on duration of exposure.

\+ Body Mass Index ≥ 30

IV. VALIDATION STUDIES

4.1 Selection of cases

4.1.1 Identification and reporting biases

Several sources of identification and reporting biases were analyzed.

4.1.1.1 Delay of diagnosis

The median delay of onset of symptoms and diagnosis was 12 months in the exposed cases vs 16 months in the unexposed.

4.1.1.2 Severity of diagnosis

Exposed cases were slightly more severely affected at time of diagnosis than non-exposed (80% vs 63% respectively in NYHA class III or IV).

4.1.1.3 Main reporting centres vs other centres

In France, 22.8% (8/35) of the cases from the main reporting centre were exposed, as opposed to 30.1% (9/29) for all other cases from that country. Numbers were too small in other countries to allow for comparisons (Table 29).

4.1.1.4 Included vs non-included cases; "A" vs "B" cases

Of the 109 cases which were not included but had been interviewed, 11 (10.1%) had used an anorexigen in the past. Two additional cases had been exposed to an unknown weight-loss product.

Twenty (25.0%) out of the 80 cases classified as "A" by the Expert Review panel had used an anorexigen vs none (0%) of the 15 "B" cases and 4 (17.4%) of the 23 incident, interviewed, rejected, or screened-out cases (Table 29).

4.1.1.5 Field study of participating centres

The survey of all centres revealed that all cases which had not been reported, in fact, did not meet the inclusion criteria, or had already been reported by another centre, with the exception of 3 Belgian cases which were omitted. These were later considered for the study but could not be included in the case-control analysis because of time constraints. The study on the process of diagnosis is still ongoing at the time of this report.

4.2 Selection of controls

4.2.1 Non-included controls

Out of the 114 controls in our database which could not be used for the case-control analysis, 7 (6.1%) had used anorexigens (Table 29).

4.2.2 Sales figures

Table 30 compares the proportion of controls exposed to the expectations based on sales figures. Approximately three (3) million packages containing F/DF and seven hundred and fifty thousand (750,000) containing an ALA were sold in France in 1991. In the U.K. and The Netherlands, sales figures were much lower. Taking into account the mean duration of use, it was estimated that altogether 5% of controls would be exposed to at least one anorexigen, all countries combined (see Table 31 and sample size calculations in the protocol in Appendix B1). The actual percentage of controls exposed in the study was 6.5% when all past exposures were considered. We had calculated that in France 5% of the population in the age groups and with the gender distribution considered used at least one anorexigen each year. Exactly 5.0% of the French controls had used an anorexigen in the one-year time window. We had guessed that up to 10% of the controls could have used an anorexigen at least once in the past in France and that the prevalence would be 1% or less in the U.K. (no estimates were done for Belgium and The Netherlands). The actual percentages varied from 8.6% in France to 5.1% in Belgium, 0% in the UK and Netherlands, probably paralleling sales figures. Also, the F/DF to ALA ratio in the controls in the study was 3.3 to 1, which is similar to the ratio observed in the sales figures (see above).

4.3 Sensitivity analysis on exposure misclassification

4.3.1 Index Date

The estimates of the odds ratio for anorexigen use after the index date are presented in Table 31. The ratio was close to one.

4.3.2 Protopathic bias

The above-mentioned odds ratio for anorexigens after the index date were considered as a good indication that little protopathic bias, if any had occurred. It is however conceivable that two opposite phenomena could have occurred in cases: on the one

hand, they were more likely withdrawn from exposure when the diagnosis was made; on the other hand, some obese patients presenting with dyspnea could have been prescribed anorexigens if the physician attributed the dyspnea to the obesity. If they had occurred, these two phenomena would have cancelled each other out.

4.3.3 Unclassified exposures

If all the unclassified exposures (Category II) were considered as actual exposures to anorexigens, the odds ratio for all exposure in the past climbed sharply [OR 7.6 (3.6-16.7)] but remained similar to the general estimate for the one year time-window [OR = 5.4 (2.2-13.7)]. (Table 31)

4.3.4 Validation of questionnaires

The results of the validation of questionnaires against computerized pharmacy records or GP's notes were not available to us at the time of this report.

4.4 Country effect

The adjusted odds ratios for all past anorexigen use was 4.0 (1.6-10.2) in France. It could not be estimated independently in other countries (lack of subjects in some cases).

4.5 Recruitment

We had planned to obtain 100 validated cases in two years; we in fact included 95 validated cases in the case control analysis recruited between September 1992 and the end of September 1994. Table 32 compares the expectations of recruitment that we presented at the ACCP conference in Chicago and the actual numbers. They are almost identical.

There are marked difference, however, between the recruitment of each country. Belgium should be taken as the "gold standard" for comparison because we had publicized our efforts to obtain an exhaustive recruitment there. The idea was to produce an estimate of the annual incidence of the disease. Thirty (30) centres participated in the Belgian study. Only a few of the cardiology and pulmonary centres were missing. To the cases included (13), one should add the cases not evaluated by the Expert Review Panel (3), those not available to us on time but diagnosed during the relevant 2 year-period (7), the cases who died before the interview (4), the other incident cases not rejected by the Expert Review Panel (ERP) which were not included (3). These numbers can be found

in Appendix A8. This addition leads to 30 cases, which is a maximum since some of the added cases, if they had been evaluated by the ERP, might have been rejected. On the other hand, we probably missed some cases. Considering that there are 10 millions inhabitants in Belgium, our data led to an estimate of the annual incidence of diagnosed PPH in adults of 1.5 per million inhabitants and per year. This is very close to the 2 per million expected, which included pediatric cases.

It is not easy to directly compare this estimate with numbers obtained in other countries because the identification of all potential cases was not conducted in the same fashion. It is however obvious that the same level of recruitment was not achieved in all countries. One centre reported 35 included cases in France and the other 17 centres reported 29 cases for an average of 1.7 cases per centre. The average number of cases per centre in Belgium was 1.5, in the U.K. it was 1.1 and in The Netherlands it was 1.0 (without counting the main reporting centres). Only one case was observed by a centre in Switzerland by one active centre, thus, besides the high reporting by one centre in some countries, the participating centres reported similar numbers of included cases (Table 33). (A number of centres were active but did not report any case, because they apparently did not observe any during this period).

So it seems that the differences in recruitment are in large part explained by the differences in the number of active centres per country, besides the main reporting centre. The mean number of cases per million inhabitants are quite similar for the main reporting centre in France, Belgium and the Netherlands (and in Switzerland, actually). In the U.K., several important centres did not contribute to the study, which could explain a large part of the difference in the recruitment.

The differences in the number of participating centres are in large part explainable by the publicity given to the study in different countries (e.g. The "Tour de France" and the incidence study in Belgium) as well as the a priori definition of the centres to be contacted in some countries for logistical reasons. As a whole, the recruitment can be considered satisfactory, as the objectives were met in due time. Yet, since the recruitment is obviously not exhaustive whatever the country, it is important to discuss the potential sources of selection bias which could have occurred.

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Table 29 Variation in the exposure of cases and controls to anorexigens.

	Exposed %	(n/N)
Exposure of cases		
. Overall	21.1	(20/95)
. Main reporting centre in France	22.8	(8/35)
. Other centres in France	30.1	(9/29)
. "A" cases	25.0	(20/80)
. "B" cases	0.0	(0/15)
. "C" cases +	17.4	(4/23)
Exposure of controls		
. Overall	6.5	(23/355)
. Non-included controls*	6.1	(7/114)

* 114 of the 137 non-included controls were entered in the database by the time of this report.

\+ Includes cases not retained by the Export Review Panel and interviewed.

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Table 30 Exposure of controls vs. estimations based on sales figures

	A priori estimate (%)	Actual exposure(%)
. One-year exposure,* France	5	5.0
. One-year exposure, * UK, Netherlands	<1	0.0
. All past exposure, ** all countries combined	5	6.5

* Estimates calculated on the basis of annual number of packages sold, the mean duration of treatment and the proportion of renewal.

** Estimates used in the protocol.

	Apriori	Actual exposure.
# Pays Cumulés	5	6,5
France	5	5,0
Hollande Angleterre	<1	0

Irlande + Irlande et Irlande du Nord

Table 31 Sensitivity Analysis: Variations of the odds ratio according to several definitions of exposure to anorexigens

	OR	(95% CI)
. Odds ratio after index date	0.9	(0.3-2.7)
. Category II* considered as anorexigens; all past exposures	7.6	(3.6-16.4)
. Category II* considered as anorexigens; one-year time-window	5.4	(2.2-13.7)
. Odds ratio for France only		
. All past exposure	3.6	(1.4-9.2)
. One-year time-window	5.0	(1.6-15.1)
. Odds ratio without HIV cases (all past exposures)	4.5	(1.9-10.7)

* Considered unclassified in previous analysis. Models are controlled for hypertension, BMI, undetermined exposures (when applicable), cirrhosis, IVD use (or hard drug use) and weight-loss behaviour (except for index date analysis).

NC: not calculated

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Table 32 Expectations vs. actual recruitment

	Expectations	Actual
Cases reported	300	298
Would not meet inclusion criteria or died	150	165
Rejected or not processed	50	38
Included	100	95

Plus de hasard de lancer. Autre exemple
22,8 Canard
30,1 autre

Table 33 Number of cases reported by main reporting centre in each country

	Main Reporting* Centre # cases reported	Other Reporting* Centres # centres	# cases/centre
France	35	17	1.7
Belgium	4	6	1.5
UK	5	5	1.1
The Netherlands	4	3	1.0

* At least one case included in case control analysis.

V. DISCUSSION

5.1 General Findings

The mean age, sex-ratio, and clinical presentation of cases included in the study are very similar to those observed in published case-series, and in particular to the patients included in the NIH registry. The mean age of the NIH registry was lower (38 y.o.), but included children, while we only included cases over 18 years old. It is felt that the cases included in the study represent the classical definition of primary pulmonary hypertension.

In summary, the study confirmed the role of AIDS and HIV infection and cirrhosis as risk factors for PPH. The role of IVD use is not clear since it could be partly confounded by HIV infection. Also, some cases of IVD may have a different pathology from PPH. Therefore, IVD users were withdrawn from the main analysis. Patients suffering of primary pulmonary hypertension were more frequently anorexigen users and, also had more often experienced a BMI over 30 once in their life, with a small partial confounding between those variables. The odds ratio is more important for long durations of use of anorexigens and was much smaller one year after cessation of drug use. There was no obvious difference between the different classes of anorexigens, except that some were more used than others. However, one should discuss the potential bias of the study before making any conclusions.

5.2 Selection bias

5.2.1 Selection of cases

Biases in the selection of cases could have occurred in several ways. Only the biases vis-à-vis the exposure to anorexigens will be addressed below as this is the main focus of this report.

Identification bias could have occurred if patients exposed to anorexigens were more likely to be diagnosed PPH than were non-exposed cases. Considering the severity of the disease, which is uniformly fatal in the absence of treatment, it is unlikely that a large number of these normally young patients suffering from severe dyspnea would evolve without being referred to a specialized centre at some point. The main centres specialized in PPH participated in the study in each country, plus a very large number of pulmonary medicine and cardiology centres. A similar bias would occur if exposed cases were more likely to be referred to hospitals than unexposed. This referral bias is not likely to be a significant issue in this case, for the same reasons: most of the cases originating in the community would end up in a specialized centre. Besides, if the potential association between exposure to anorexigens and PPH is known by highly specialized pulmonary physicians and cardiologists who treat those patients, it is not as well known by GPs and

other community doctors (even some specialists). The bias mentioned above would still hold, however, if there was a "forme fruste" of the disease which would be more likely to be diagnosed in cases exposed to anorexigens. The existence of even a form of the disease is not known. Exposed PPH cases actually presented with very severe dyspnea on the time of diagnosis (75% in NYHA class III).

Identification bias could also occur if exposed patients suffering from conditions closely resembling PPH were wrongly diagnosed as PPH because of their exposure to anorexigens. This was first controlled in this study by the strict, blind, review of cases by the Panel. We examined the exposure of cases according to their quality or validity of their diagnosis. If anything, "B" cases were less frequently exposed than "A" cases. The non-included interviewed cases were less frequently exposed than the included cases but more frequently than controls. This series however included true prevalent PPH cases, and some cases rejected on the basis of lack of date rather than mis-diagnosis.

As a whole it does not seem that non-PPH cases were more likely to be wrongly diagnosed PPH and reported only because of their exposure to anorexigens. The delay in the diagnosis of exposed cases was shorter than in the non-exposed. This indicates that physicians are more rapid to suspect PPH in a dyspneic patient who had used an anorexigen than in others. (The potential information bias related to this issue is discussed further below). The shortening of the delay in diagnosis would not lead to a selection bias per se, under the hypothesis that most cases will end up being diagnosed independently of exposure. It is not known to what extent the latter hypothesis is verified.

Another selection bias could originate in the preferential reporting of exposed vs non-exposed cases to the research teams. Efforts were made to obtain an exhaustive recruitment from the centres who reported at least one case. We also frequently checked with non-reporting centres. Despite numerous attempts with each centre, we were unable to find a significant number of non-reported cases (3 in the end). The proportion of cases exposed in the main reporting centre in France was similar to the proportion from other centres. If reporting bias cannot be fully excluded, it is in our opinion not likely to be a large phenomenon.

It is also possible that exposed cases were advised by their physicians to stop taking their medication which resulted in a resolution of symptoms and consequently these cases were never diagnosed.

5.2.2 Selection of controls

Another source of selection bias could originate from the selection of controls. The question is whether they adequately represent the so-called source population from which

cases originated. The rationale behind the choice of controls in this study is explained in the methods section. There is no difference between cases and controls in their sociodemographic composition, their familial history of morbidity, their personal history of disease (except for some of the suspected health-related risk factors). They also are very similar in their use of broad classes of drugs. The controls series is thus similar to the cases series as to several extraneous determinants of morbidity (other than the suspected risk factors). This is reassuring, although it is not per se a proof of the adequacy of the controls series.

Another reassuring fact is that the exposure of controls to the main risk factors studied (anorexigens) closely parallels the expectations based on sales figures for all past exposure, for the one-year time-window for all past exposure and by country.

Another concern with the selection process of controls could be the so-called "overmatching" due to the selection of controls through GPS. Overmatching is not a bias per se (it should not affect the direction of any observed relation). It is rather a question of efficiency (in other words, it would make it more difficult to observe "significant" associations if they exist). The associations were found significant for the most suspected risk factors, which makes the issue of efficiency less relevant. Also, it is theorically difficult to envision how an overmatching could have led to the observed results.

5.3 Information bias

5.3.1 Recall bias

Recall bias is a classical issue in studies based on interviews. The blinding of interviewers and interviewees on the specific objectives of the study, as well as the multiple precautions taken all along the conduct of the study, might not have controlled completely for this bias. Cases are likely to be more aware of the potential association between their disease and some risk factors, especially anorexigens, than controls. Thus they might recall more easily the use of anorexigens than controls did. The fact that controls reported anorexigen usage in proportions very close to sales figures is comforting in this respect. In the absence of under-reporting by controls, the results observed for anorexigens, if biased, would be due to an over-reporting by cases. This could happen if cases had some vested interest in reporting exposures which had not actually occurred. In Europe, liability is not a significant issue and it is not likely that such over-reporting could have a large magnitude, if any. Also, it is possible that some cases could be inclined to not report actual exposure to anorexigens, maybe because of the fear of being "blamed" for their disease (this was documented in one case). The most convincing

argument against the existence of an important recall bias in this study is the lack of difference between cases and controls as to their exposure after the index date.

5.3.2 Protopathic bias

Another source of exposure misclassification could have stemmed from the so-called "protopathic bias". Such a bias could have occurred if cases had received anorexigens after the onset of their symptoms, with the intention of mitigating these symptoms. They would thus have been wrongly classified as exposed. The fact that the odds ratio for anorexigens and PPH drops to almost one when only exposure after the index date is taken into account, excludes this hypothesis. This also is an indirect validation of the index date used in this study.

5.3.3 Time-window

In a case-control study, delays between first symptoms, diagnosis, reporting and interview could be the source of bias in several ways. Here the long delay between symptoms and diagnosis posed a problem. This could have been a source of bias if the date of diagnosis had been used as the index date, with a fixed time-window of investigation. The use of the first symptom as the index date controlled for this phenomenon (see the discussion on the validity of the index date further below). In the absence of a validated model for the disease process, we explored two different "time-window": all past exposure and exposures which occurred within one year previously to the event. When only recent exposures were taken into account, the odds ratios for anorexigens slightly increased as compared to all past exposures. Also, the odds ratio after drug discontinuation for more than one year was smaller than the odds ratio for recent exposures. This could support the notion of a physiological process with little remaining effects after exposure discontinuation. However, the number of unclassified exposure of cases more than one year before the index date was important (11 unclassified for all past exposures vs 3 in the last year, or 8 for the time-window of more than one year). The observed decrease in the odds ratio could be an artifact. It seems in any case more appropriate to chose a one-year time-window for the assessment of the odds ratio.

5.4 Confounding

Confounding is the last source of bias to be addressed. All the factors which are associated with PPH and anorexigen use are at stake here.

The first concern was that the use of anorexigens is obviously associated with the desire to lose weight, which is in turn more likely to exist in obese individuals. As obesity

appears to be a risk factor for the disease, the question is to what extent could the observed association for anorexigens be explained by confounding by obesity or any other factor associated to high BMI?

The association between the exposure to anorexigen and the experience of a high BMI (ECOR) was elevated, but it could not totally explain the observation. Indeed, when the high BMI was omitted from the multivariate analysis, the odds ratio observed for anorexigens was higher, but it did not decrease so notably when the model was controlled for BMI. This was already indicated by the matched odd ratios for anorexigens exposure which did not differ greatly whether individuals had experimented a high BMI or not although there was an indication of partial confounding. Conversely, the role of high BMI on the estimated relative risk of PPH was not significantly affected by the use of anorexigens or not. Thus, one can conclude that the experience of a high BMI only partially confounds the effect of anorexigens, but that the adjusted odds ratio produced by modelling satisfactorily controlled for this bias. No other source of confounding was obvious.

5.5 Role of risk factors

5.5.1 Anorexigens

The study confirms that the exposure to anexorigens is associated with a higher risk of PPH. The study more specifically documents the role of fenfluramine and dexfenfluramine. The estimate of the risk associated with other products such as amphetamine-like agents pointed in the same direction. The estimates were more unstable, due to the much smaller use of these later products in the recent past. (In the recent past, F/DF was used as a replacement to ALA). The fact that the use of both F/DF and ALA was associated with an estimated relative risk almost double that of the use of F/DF in isolation indicates that ALA may play a role per se in the risk of PPH.

The study of the time-window indicates that a more recent exposure (less than one year before the index date) is more relevant. It is however possible that a "depletion of susceptibles" occurred. This will have to be further analyzed. The study of the duration of use provided some important insights.

The estimate of the relative risk increased with longer duration, with a small, but not significant, increase in the odds ratio for short-duration users and a significantly higher odds ratio observed with long duration of use. There was no difference in the distribution

of obesity between users of short and long duration.

The consistency of the results was supported by the sensitivity analyses. Although the estimates of the relative risks could be lower or higher according to several hypotheses on exposure, in most cases the results did not change significantly in direction nor in magnitude. In the very extreme hypothesis where all drugs reported "to lose weight" are classified as anorexigens, the odds ratio was somewhat more elevated for the "all past" time-window, but was not for the more relevant one-year time-window. Also consistent is the fact that the exposure to several products (F/DR and amphetamines) was associated with an odds ratio superior to the one obtained for the exposure to one of these products alone. Finally, the results observed in the one-year time window, the duration of use and the stability of the estimates over different analyses all point to the consistency of the relation between exposure to anorexigens and primary pulmonary hypertension.

5.5.2 Obesity

The study indicates that obesity could be a risk factor for PPH. The odds ratio was slightly greater than 2. There is no clear explanation for this finding. Our measure of obesity was not very accurate in time since we could only interview several months after the onset of symptoms. We obtained the information on the higher BMI in life rather than the exact BMI at the time of the index date. Having experienced a high BMI could have been followed by a series of exposure which would confound the results observed. This is why we controlled all the analyses for any indication of weight-loss behaviour, use of undefined weight-loss drugs and the like. The effect of the high BMI was not affected at all. Also, obesity remained a risk factor whatever the use of anorexigens. One may wonder how obesity could increase the risk of PPH. Sleep apnea, which has been proposed as a risk factor for PPH, is known to occur more frequently in obese patients. Other physiological factors should be considered. Obesity and hypertension are known to be linked, the former being a known risk factor for the later.

5.5.3 Hypertension

The role of systemic hypertension was of borderline significance in the preliminary analysis. It remained elevated in all the multivariate models, whatever the time-window, but the estimates were unstable. This finding awaits confirmation, since this is the first empirical evidence of the possibility of such a relation.

5.5.4 Other risk factors

The study was unable to confirm the role of several alleged risk factors such as recent pregnancy, stays in high altitudes, dietary habits. The study confirmed the role of risk factors such as AIDS and HIV infections and cirrhosis. Many cases (11) were rejected because they had AIDS and 3 other had HIV infections, which confirms the significance of this risk factor, as reported recently. The relative risk in cirrhosis patients could not be estimated precisely. Two (2) out of 4 IVD users had HIV and 2 out of 3 HIV infected patients reported IVD use. Cocaine alone was not reported more frequently by PPH cases than controls.

The observations of the differences in the exposure to certain class of drugs (antiasthmatics, analgesics, haematological drugs) will have to be further explored. For antiasthmatics, the result is not confirmed by the data on preexisting morbidity; it is possible that the higher exposure of cases actually indicates the beginning of symptoms in some cases. Some of these drugs have cardiac effects and have been reported to be associated with higher mortality. Also, it could be a difference due to chance alone. No explanation can be found for the lesser use of analgesics by cases. The number for haematologic drugs are very small.

Finally, it is possible that anorexigens were used within other medications (such as phenylpropylamine which is used as a nasal degongestant and an anorexigen). Exposure to these possibilities needs further study.

5.5.5 Role of risk factors in PPH

When all of the risk factors were combined, more than half of the cases of PPH had an identifiable associated risk factor. Although causal relationships between these risk factors and PPH are largely unknown, it now appears that PPH may have clearly defined causes.

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APPENDIX A5

Feasibility study

A feasibility study was conducted in May in France. Four approaches were taken:

1. One hundred and ten (110) Departments of Pneumology and/or Cardiology of University Hospitals in France received a letter asking them to participate in the study (two mailings). Seventy-eight of them (78%) responded and 1 refused. The remainder have not responded. All of the major centres have consented to participate, including the referring centres and transplantation centres. Of the respondents, 22 had seen no cases in the past year, 28 had seen 1 to 2 cases per year, and 9 had seen more than 2 cases per year. Nineteen (19) did not report the number of cases that they had seen. Nine other centers later on accepted to participate.

2. A field feasibility study was conducted during the month of May 1992 (4 weeks) in the Aquitaine region of France (around Bordeaux). This region represents a catchment population of approximately 4.2 million inhabitants. The heads of the divisions of Pneumology (3), Cardiology (8), Internal Medicine (6), Chest Surgery (2) and Intensive Care units (4) of the five University and Military Hospitals in the region were contacted. Three (3) large private clinics were also surveyed. Finally, 32 local hospitals were contacted. They were all visited whenever they declared that they had diagnosed a PPH case in the preceding 16 months. Seventeen (17) cases were found. After applying an algorithm for case-ascertainment, 7 cases were considered meeting the inclusion criteria for the study. Extrapolating these results to the whole of France, this figure would lead to 72 potential "validated" cases per year in this country.

3. Forty-two (42) private cardiologists and 18 pneumologists were randomly selected among the list of cardiologists practising in the Aquitaine region. They were contacted by telephone. The objectives of this survey were: (i) to validate the patterns of referral of PPH cases seen by private cardiologists; (ii) to possibly identify more cases of PPH that would have been missed in the hospital centres. Forty-one declared that they would refer a case of PPH for treatment and/or confirmation of diagnosis to a University Hospital, 8 to a private clinic and 10 to local hospitals. It was confirmed that most of these cases would however end up in a University Centre. These centres were among the 23 surveyed. Two potential cases of PPH had been seen by the private cardiologists in the 16 months preceding the interview. These 2 cases were among the 17 found in the survey of the university Centres.

4. Mortality data from France (INSERM) and The Netherlands indicate that approximately 2 individuals per million inhabitants die each year with a primary or secondary diagnosis of PPH.

From these results, we concluded that the incidence of PPH in a country like France was in the order of 2 per million inhabitants per year.

The five countries involved in the study altogether have 150 million inhabitants altogether, with a maximum expected number of 300 incident cases per year. It was estimated that 50% of the cases would meet the inclusion criteriae for the study and that 50% of them could be recruited, i. e. a maximum of 75 per year. To allow for the uncertainty in the incidence, it was planned that 100 cases could be recruited over 2 years.

APPENDIX A6

EXPERT REVIEW PANEL REPORT

February 20, 1995

FINAL REPORT FROM IPPHS SUBCOMMITTEE TO REVIEW CASE REPORT FORMS FEBRUARY 20, 1995

A panel of experts from North America was selected to review all of the case report forms submitted to the IPPHS, to ascertain as to whether or not they were not appropriate for inclusion into the study. The rationale behind this came from the experience of the NIH Registry on Primary Pulmonary Hypertension where 18% of the cases submitted were felt not to be consistent with primary pulmonary hypertension. Because the Data and Coordinating Center for the study was based in Montreal, it was felt that committee members should be residing in North America to make frequent travel to Montreal realistic.

The members of the IPPHS Subcommittee where as follows:

1. Dr. Stuart Rich (Chairman). Dr. Rich is Professor of Medicine and Chief of the Section of Cardiology at the University of Illinois at Chicago. He was co-principal investigator for the NIH Registry on Primary Pulmonary Hypertension, and was responsible for reviewing all of the case report forms submitted to the Registry.

2. Dr. Lewis Rubin. Dr. Rubin is Professor of Medicine and Head of the Division of Pulmonary and Critical Care Medicine at the University of Maryland School of Medicine. He has an extensive experience in the management of patients with primary pulmonary hypertension and has published extensively on this topic. He is a recognized world authority.

3. Dr. Michael McGoon. Dr. McGoon is Associate Professor of Medicine in the Division of Cardiology at the Mayo Clinic. Dr. McGoon has a career interest in primary pulmonary hypertension and is currently principal investigator at the Mayo Clinic for their diagnostic and therapeutic trials in patients with primary pulmonary hypertension.

4. Dr. David Langleben. Dr. Langleben is a member of the Cardiology Department at the Jewish General Hospital in Montreal. Dr. Langleben has both basic science and clinical science interest in primary pulmonary hypertension and its mechanisms.

Meetings

Eight meetings were held between January 1, 1993 and December 31, 1994 where all of the submitted case report forms to the IPPHS were reviewed. The meetings were held at the Jewish General Hospital in Montreal (five times), O'Hare Airport in Chicago (two times), and a hotel in Washington, DC (one time). At every instance all of the available case report forms were reviewed by the Committee and work was completed.

Case report forms were censored prior to being submitted to the Committee so that any information regarding exposure to anorexigens or other medications was removed from the case report form. The Committee went through each report form on a page by page basis to ascertain as to whether or not the information seemed to be consistent with PPH. Actual chest X-rays and lung scans were requested and reviewed when available. If errors in transcription of the data was identified it was so indicated on the form. There was open dialogue and free discussion regarding the information provided on each individual case.

Classification

All of the case report forms were characterized in one of the three classifications.

Group A. Cases based on the data presented to the Committee that were felt to have unexplained pulmonary hypertension and were appropriate to be included in the study.

Group B. Cases where important data elements were missing or some data presented was uncertain, but felt to be possibly applicable to the study. More information on these cases were requested for further review.

Group C. Cases where the diagnosis of primary or unexplained pulmonary hypertension was felt to be inaccurate and thus the case should not be included into the study.

In addition, there were cases where the Committee felt there was not enough information even to classify. In those instances, it was requested that more data be provided so that a judgement could be made.

It was also noted when chest X-rays and/or lung scans were available for review. Cases for which they were provided were designated with a plus(+), and those where it was not provided designated with a minus(-). Other information such as pulmonary angiograms and CT scans were occasionally available for review as well.

Results

In total 193 cases were reviewed by the Committee. Their classifications were as follows:

1. INCIDENT ALIVE CASES

	GROUP A	GROUP B	GROUP C
NETHERLANDS	3	4	5
BELGIUM	12	1	5
FRANCE	61	8	9
U.K.	14	4	7
TOTAL	90	17	26

2. INCIDENT DECEASED CASES

	GROUP A	GROUP B	GROUP C
NETHERLANDS	4	1	0
BELGIUM	1	1	1
FRANCE	6	4	3
U.K.	3	1	0
TOTAL	14	[illegible]	4

3. PREVALENT ALIVE CASES

	GROUP A	GROUP B	GROUP C
NETHERLANDS	3	0	1
BELGIUM	6	1	1
FRANCE	6	3	3
U.K.	5	0	0
TOTAL	20	4	5

	GROUP A	GROUP B	GROUP C
NETHERLANDS	1	1	0
BELGIUM	0	0	0
FRANCE	1	0	1
U.K.	1	0	1
TOTAL	3	1	2

As a check on the validity of the review, 10 cases were resubmitted to the Committee for re-review without their knowledge. In those 10 cases, the classification made by the Committee was identical to the initial review in nine instances. In one instance the Committee reclassified a case from Group A to Group B. In no instance was a case felt to be acceptable (Group A or B), which then on re-review was felt to be unacceptable or vice versa.

All in all the Committee felt that the case review was useful and contributed to making sure that appropriate cases were included in the study. The Committee also commended the reporting centers for their excellent job in acquiring and collating the material, and making it easy to read and interpret.

Sincerely,

Stuart Rich, M.D.
Professor and Chief
Section of Cardiology
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SR/ks

APPENDIX A7

Reasons for the non-inclusion of cases (by country)

	FRANCE
TOTAL REPORTED	149
Did not meet inclusion criteria:	56
. <18 or >70 y.o	5
. diagnosed before September 1, 1992	24
. No date of catherization	6
. Secondary PH	4
. AIDS	8
. Crest syndrome	1
. Connective tissue disease	1
. Non-resident	4
. Reported after September 1994	3
. Pickwick syndrome	0
. Chart not found	0
Dead or died before interview	14
Rejected by Expert Review Panel	8
Not interviewed by end of recruitment	0
Lost to follow-up	2
Refused	1
Not evaluated by December 12, 1994	4
TOTAL INCLUDED	64

APPENDIX A9

Reasons for the non-inclusion of cases (by country)

UNITED KINGDOM

TOTAL REPORTED		44
Did not meet inclusion criteria:		17
. <18 or >70 y.o	0	
. diagnosed before September 1, 1992	10	
. No date of catherization	0	
. Secondary PH	5	
. AIDS	0	
. Crest syndrome	0	
. Connective tissue disease	0	
. Non-resident	2	
. Reported after September 1994	0	
. Pickwick syndrome	0	
. Chart not found	0	
Dead or died before interview		3
Rejected by Expert Review Panel		6
Not interviewed by end of recruitment		6
Lost to follow-up		0
Refused		1
Not evaluated by December 12, 1994		0
TOTAL INCLUDED		11

APPENDIX A10

Reasons for the non-inclusion of cases (by country)

THE NETHERLANDS

TOTAL REPORTED		30
Did not meet inclusion criteria:		13
. <18 or >70 y.o	0	
. diagnosed before September 1, 1992	6	
. No date of catherization	0	
. Secondary PH	7	
. AIDS	0	
. Crest syndrome	0	
. Connective tissue disease	0	
. Non-resident	0	
. Reported after September 1994	0	
. Pickwick syndrome	0	
. Chart not found	0	
Dead or died before interview		5
Rejected by Expert Review Panel		5
Not interviewed by end of recruitment		0
Lost to follow-up		0
Refused		0
Not evaluated by December 12, 1994		0
TOTAL INCLUDED		7

APPENDIX A11

Reasons for the non-inclusion of cases (by country)

SWITZERLAND

TOTAL REPORTED		**29**
Did not meet inclusion criteria:		29
. <18 or >70 y.o	8	
. diagnosed before September 1, 1992	1	
. No date of catherization	0	
. Secondary PH	15	
. AIDS	3	
. Crest syndrome	0	
. Connective tissue disease	0	
. Non-resident	0	
. Reported after September 1994	0	
. Pickwick syndrome	1	
. Chart not found	1	
Dead or died before interview		0
Rejected by Expert Review Panel		0
Not interviewed by end of recruitment		0
Lost to follow-up		0
Refused		0
Not evaluated by December 12, 1994		
TOTAL INCLUDED		**0**

APPENDIX A13

Age distribution of cases by country

Country	N	Mean	SD	Median	Min.	Max.
France	64	45.2	±12.5	45	21	70
Belgium	13	42.9	±10.0	46	22	60
United Kingdom	11	44.4	±15.2	41	24	67
Netherlands	7	44.3	±11.1	42	31	56
TOTAL	95	44.7	±12.3	45	21	70

APPENDIX A14

Female to male ratios of cases per country
(potential cases & included cases)

Country	Male	Female	Total	Sex ratio
France	19	45	64	45/19 = 2.4
Belgium	5	8	13	8/5 = 1.6
United Kingdom	3	8	11	8/3 = 2.7
The Netherlands	2	5	7	5/2 = 2.5
TOTAL	29	66	95	66/29 = 2.3

APPENDIX A15

Median delays for diagnosis by country

	Months				
	N	Median	Min.	Max.	Missing
France	62	18	2	104	2
Belgium	13	7	1	39	
United Kingdom	10	14	2	47	1
Netherlands	6	16	11	73	1
TOTAL	91	16	1	104	4
MEAN	16.7				
SD	19.3				

APPENDIX A16

Exposure to all drugs except anti-obesity preparations and drugs used to lose weight

ATC sub-classes	Cases	(%)	Control	(%)	p value
Alimentary tract & metabolism					
Stomatological preparation	3	(3.2)	4	(1.1)	.15
Antacids & gastroprot. agents	19	(20.0)	54	(15.2)	.26
Antispasmodics. Antichol.	2	(2.1)	13	(3.7)	.46
Antimetics & antinauseants	0	(0.00)	1	(0.3)	.61
Antidiarrheals, antiifect.	0	(0.0)	6	(1.7)	.20
Digestives, incl. enzymes	1	(1.0)	3	(0.8)	.85
Antidiabetic therapy	1	(1.13)	4	(1.1)	.95
Vitamins	4	(4.2)	30	(8.4)	.17
Mineral supplements	2	(2.1)	19	(5.3)	.18
Tonics	8	(8.4)	30	(8.4)	.99
Antiparasistic products					
Antiprotozoals	1	(1.1)	1	(0.3)	.38
Ectoparasiticides	0	(0.0)	0	(0.0)	--

Appendix A16 (continued)

Respiratory					
Nasal preparations	2	(2.1)	13	(3.7)	.46
Throat preparations	0	(0.0)	1	(0.3)	.99
Anti-asthmatics	9	(9.5)	15	(4.2)	.07
Cough & cold preparations	6	(6.37)	13	(3.7)	.25
Antihistamines for systemic use	6	(6.3)	36	(10.1)	.26
Sensory organs					
Ophtalmological	0	(0.0)	10	(2.8)	.13
General nutrients	2	(2.1)	2	(.6)	.15
Phytotherapy (non specified)	3	(3.2)	16	(4.5)	.57
Unknown drugs	2	(2.1)	4	(1.2)	.46
Musculo-skeletal system					
Antiinflammatory & antirheumatic	17	(17.9)	94	(26.4)	.09
Topical prod. for joints & musc. pain	0	(0.0)	3	(0.8)	.99
Muscle relaxants	2	(2.1)	11	(3.1)	.61
Antigout preparations	2	(2.1)	1	(0.3)	.11

Appendix A16 (continued)

					24
Nervous system					
Analgesics	48	(50.3)	209	(58.7)	.15
Antiepileptics	1	(1.1)	2	(0.6)	.6
Psycholeptics	24	(25.3)	88	(24.7)	.91
Psychoanaleptics	1	(1.1)	26	(7.3)	.02
Other CSN drugs including parasympathomimetics	0	(0.0)	2	(0.6)	.99
Systemic hormonal prep. excl. sex hormones					
Corticosteroides for systemic use	0	(0.0)	5	(1.4)	.59
Thyroid therapy	2	(2.1)	11	(3.1)	.61
Calcium homeostatis	0	(0.0)	2	(.6)	.99
Antibacterials for systemic use	28	(29.5)	108	(30.3)	.87
Antimycotics for systemic use	0	(0.0)	2	(0.6)	.46
Antivirals for systemic use	0	(0.0)	2	(0.6)	.46
Cytostatic agents	0	(0.0)	0	(0.3)	.99
Endocrine therapy	0	(0.0)	0	(0.0)	-
Immunosuppressive agents	0	(0.0)	0	(0.0)	-

Appendix A16 (continued)

Dermatological					
Antifungual for dermato. use	0	(0.0)	2	(0.6)	.46
Prep. for treat of wounds & ulcers	0		0		-
Antipruritics, incl. antihistamines	2	(2.1)	1	(0.3)	.114
Antipsoriatics	1	(1.1)	0	(0.0)	.21
Antibiotics & chemotherapy dermato.	2	(2.1)	5	(1.4)	.62
Corticosteroids, dermato.	4	(4.2)	9	(2.5)	.38
Antiseptics & disinfectants	1	(1.1)	3	(0.8)	.85
Anti-acne preparation	0	(0.0)	5	(1.4)	2.5
Genito-urinary & sex hormones					
Gyneco & antiseptics	0	(0.0)	3	(0.8)	.32
Urologicals	0	(0.0)	2	(0.6)	.46
Sex hormones & modulators	27	(28.6)	87	(24.4)	.43
Blood and blood forming organs					
Antithrombotic agents	7	(7.4)	8	(2.3)	.02
Antihemorrhagic prep.	1	(1.1)	1	(0.03)	.32
Antianemic prep.	0	(0.0)	5	(1.4)	.25
Serum lipid reducing agents	2	(2.1)	18	(5.1)	.21

Appendix A16 (continued)

					26
Plasma substitute and perf. soln.	0	(0.0)	1	(0.3)	.61
Cardiac therapy	2	(2.1)	12	(3.4)	.53
Antihypertensives	12	(12.6)	21	(5.9)	.02
Diuretics	15	(15.8)	17	(4.8)	.00
Peripheral vasodilators	0	(0.0)	2	(0.6)	.46
Vasoprotectives	13	(13.7)	57	(16.0)	.58
Beta-blockers	6	(6.3)	21	(5.9)	.88

Annexe 1-55

REPUBLIQUE FRANCAISE

AGENCE DU MEDICAMENT

Saint-Denis, le 03 MAI 1995

DIRECTION DE L'EVALUATION

UNITE DE PHARMACOVIGILANCE

CONFIDENTIEL
DOCUMENT
DE
TRAVAIL

SYNTHESE DES DONNEES DISPONIBLES SUR LE RAPPORT BENEFICE/RISQUE DES ANOREXIGENES A LA SUITE DE LA COMMISSION NATIONALE DU 28 AVRIL 1995

Rappel des mesures prises lors de la Commission National e de Pharmacovigilance du 10 mai 1994 :.
Au vue de l'analyse intermédiaire de l'étude IPPHS et des résultats de l'enquête nationale de Pharmacovigilance portant sur la fenfluramine et dexfenfluramine, il a été décidé :

- de poursuivre l'étude IPPHS jusqu'à son terme
- d'étendre l'enquête Nationale de Pharmacovigilance à l'ensemble des anorexigènes
- d'encadrer strictement la prescription des spécialités fenfluramine et dexfenfluramine : respect des indications, de la posologie et de la durée de prescription maximale de 3 mois.
- de mentionner le risque d'hypertension arterielle pulmonaire à la rubrique "mise en garde".
- d'informer les prescripteurs de ces dispositions.

La Commission Nationale de Pharmacovigilance du 28 Avril 1994 a pris connaissance du dossier actualisé de pharmacovigilance relatif à l'ensemble des anorexigènes et a examiné :

- les résultats finaux de l'étude IPPHS (International Primary Pulmonary Hypertension Study).
- l'enquête nationale de Pharmacovigilance coordonnée par le CRPV de Besançon.

Avec la participation d'experts pneumologues et nutritionistes, e lle a tenté d'évaluer le risque et le rapport bénéfice/risque des anorexigènes.

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I) Le risque

I-1) L'étude IPPHS montre une association significative entre la prise d'anorexigènes (toute classe) et la survenue d'Hypertension Arterielle Pulmonaire.

Facteurs de risque	Odds ratio
Anorexigènes	4,1· (1,8-9,7)
BMI≥ 30	2,6· (1,3-5)
Hypertension artérielle	2,4 (0,8-7,1)
Tabagisme	1,3 (0,7-2,3)
Perte de poids	0,9 (0,5-1,7)

Odds ratio ajustés (étude de régression logistique multivariée) des principaux facteurs de risque d'Hypertension Artérielle Pulmonaire (toute durée d'exposition confondue avant la date index)
· significatif

Anorexigènes	Odds ratio
Fenfluramine/Dexfenfluramine uniquement	3,8· (1,5-9,7)
et/ou Fenfluramine/Dexfenfluramine	4,1· (1,7-10)
Amphétaminiques uniquement	4 (0,2-65,8)
et/ou Amphétaminiques	5,4· (1,2-24,2)
Fenfluramine/Dexfenfluramine + amphétaminiques	5,8· (1-33,1)

Odds ratio ajustés par sous classe d'anorexigènes
· significatif

Durée d'utilisation	Cas : 95	Témoins : 355	Odds ratio ajustés
≤ 3 mois	5	10	1,9 (0,5-7,3)
> 3 mois	9	5	10,6· (2,8-39,5)

Odds Ratio ajustés en fonction de la durée d'exposition
· significatif

Les anorexigènes et un fort indice de masse corporelle (BMI > 30) apparaissent comme des facteurs de risques possiblement indépendants. Une durée d'exposition supérieure à 3 mois augmente considérablement le risque.

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Cette association suggère d'autant plus une causalité que : critères de Bradford Hill

- l'odd ratio est significativement élevé,
- l'étude ne présente pas de biais majeur,
- les résultats sont cohérents avec ce que l'on connait de la physiopathologie de l'Hypertension Arterielle Pulmonaire (femme jeune, obèse ...),
- elle est confirmée par des approches différentes (en particulier l'enquête de pharmacovigilance basée sur la notification spontanée),
- il existe une analogie avec l'Aminorex,
- l'intensité de l'exposition (durée et association d'anorexigènes) conduit à une augmentation du risque.

I-2) Les résultats de l'enquête officielle de Pharmacovigilance confiée au CRPV de Besançon confirme les conclusions de l'étude épidémiologique : l'Hypertension Artérielle Pulmonaire est un effet rare mais très grave (78 cas notifiés en France de 1985 à Décembre 1994 dont 22 décès, 4 transplantations pulmonaires et 4 attentes de greffe) fortement associé à la prise prolongée d'anorexigène de type amphétaminique et/ou serotoninergique.
(Les volumes des ventes en mois-traitement figurent en annexe)

La Commission Nationale de Pharmacovigilance estime, que le risque d'Hypertension Artérielle Pulmonaire lié à la prise d'anorexigène représente un problème de santé publique, en raison de la gravité de l'atteinte pulmonaire.

II) le bénéfice

Un groupe de travail DEV " stratégie thérapeutique de l'obésité " (réunion du 31 Mai 1994) avait défini les indications et apprécié le niveau d'efficacité.

II-1) **Les indications :**

Les spécialité ISOMERIDE® (dexfenfluramine) et PONDERAL® (fenfluramine) ont fait l'objet d'une modification du RCP conformément aux mesures prises. (cf annexe)

- l'indication doit être restreinte au traitement de 2ème intention , après echec d'un traitement diététique adapté, d'obésité patente ayant un indice de masse corporelle supérieure à 30 (ce type de patient représente 6 % de la population française).

- la durée du traitement ne doit pas dépasser 3 mois

- Le traitement est contre-indiqué chez l'enfant.
(NB: Cependant dans de rares cas, des traitements plus prolongés peuvent être conduits par des spécialistes hospitaliers en nutrition et en pédiatrie, sous couvert d'un suivi attentif)

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II-2) Le niveau d'efficacité avait été apprécié de façon différente :

→ *De l'avis de certains spécialistes en nutrition, la fenfluramine et dexfenfluramine sont efficaces et utiles notamment chez les obèses ayant un indice de masse corporelle > 30, plus particulièrement lorsque l'obésité est androïde ou s'associe à d'autres facteurs de risque.*
L'efficacité de ces produits a été montrée pour des durées de traitement de 3 mois à 1 an, en traitement adjuvant du régime. Le taux de répondeurs est de l'ordre de 33 % après un an de traitement (perte supérieure à 10 % du poids initial).
L'obésité tend à être reconnue comme un état chronique justiciable d'une pharmacothérapeutique adaptée à long terme.
L'usage intermittent de ce traitement est nocif, la variance du poids étant un risque propre indépendant du poids initial.

→ *D'autres spécialistes ("hypertensologues" cardiologues, endocrinologue, diabétologues, gynécologues, pédiatres, internistes), estiment l'efficacité de ce traitement comme mineure, voire marginale ou même inexistante. A long terme, ce traitement est jugé comme ayant un taux constant d'échec sur l'obésité. On ne dispose pas de données montrant que les anorexigènes permettent effectivement de réduire la mortalité et la morbidité cardio-vasculaire liées à l'obésité.*

III) le rapport bénéfice/risque

Les experts pneumologues ont souligné l'insuffisance des mesures prises au vue des résultats intermédiaires, prises sur les seules fenfluramine et dexfenfluramine. Etant donné l'évolution fatale de l'Hypertension Artérielle Pulmonaire, ils demandent un contrôle étroit des prescriptions ainsi qu'une information pertinente mettant en exergue le risque vital.

Si certaines firmes ont présenté des propositions visant à renforcer le respect du bon usage (information des professionnels de santé, du public, recommandations strictes, mise en garde...), d'autres attendent les propositions de la Commission. Toutes sont convaincues qu'il s'agit d'un effet de classe, que le risque est important et qu'il faut limiter les indications à l'obésité vraie morbide.

Les membres de la Commission Nationale de Pharmacovigilance du 28 Avril 1995 ont envisagé 4 possibilités :

a) la suspension de l'ensemble des anorexigènes, dans la mesure ou un traitement court serait sans interêt et un traitement prolongé trop dangereux.

b) la limitation à certains spécialistes hospitaliers pour traiter un nombre limité de patients dont l'obésité serait associée à un risque vital.

c) la limitation des prescriptions aux spécialistes hospitaliers et libéraux, dans la mesure ou un traitement de 3 mois ou moins présenterait quelque interêt. La définition de ces spécialités sera difficile.

d) la prescription laissée aux généralistes.

Bien entendu, des mesures adéquates d'information s'imposent pour les 3 dernières situations et singulièrement pour les les 2 dernières, ainsi qu'un contrôle régulier des volumes de vente et si possible du bon usage thérapeutique.
Les restrictions devraient s'appliquer aux préparations magistrales.

ANNEXES

CONFIDENTIEL

Annexe 1-55

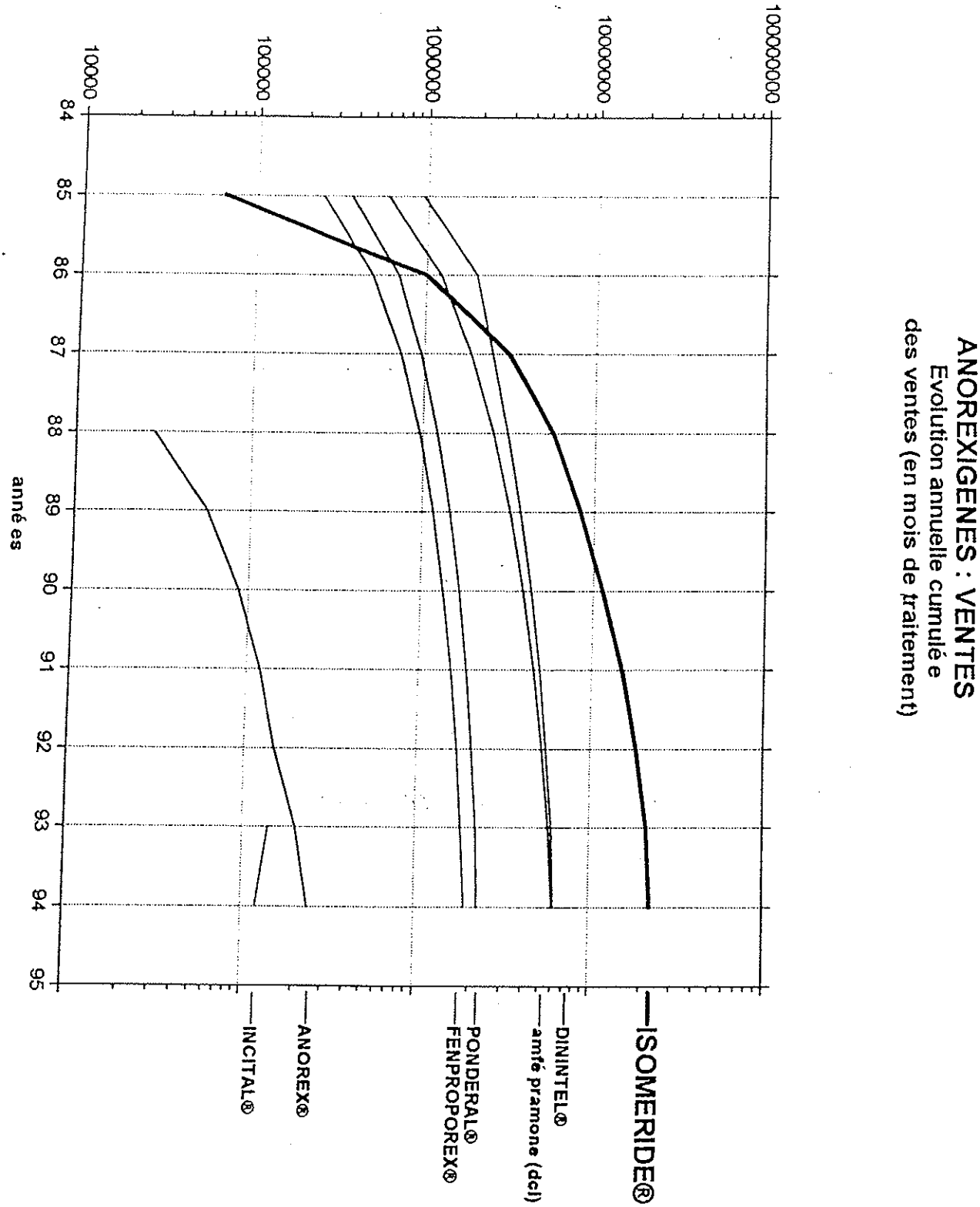
VOLUMES DE VENTES

	VENTES* EN MOIS-TRAITEMENT
ISOMERIDE	22 927 716
PONDERAL	2 232 038
TENUATE DOSPAN	3 164 849
MODERATAN	1 843 514
PREFAMONE	682 732
ANOREX	246 713*
amfépramone DC	
Préparations magistrales	
TOTAL Amfépramone	*5 937 808*
DININTEL	5 196 120
INCITAL	233 600**
FENPROPOREX	1 831 965
TOTAL	

* Le chiffre de ventes est donné pour les années allant de 1985 à juin 1994
sauf pour ANOREX* de 1988 à juin 1994
pour INCITAL** de 1993 à juin 1994
TENUATE DOSPAN majoritairement vendu.

ANOREXIGENES : VENTES

Evolution annuelle cumulée
des ventes (en mois de traitement)



Enfants : 1 pulvérisation dans chaque narine 3 fois par jour.
Adultes : 1 pulvérisation dans chaque narine 4 à 6 fois par jour.

DC CONTRE-INDICATIONS
- Sensibilisation préalable connue à l'un des constituants, en particulier à la framycétine ou aux autres aminoglucosides, notamment streptomycine, kanamycine ou gentamicine (allergie croisée).
- Ne pas administrer par la méthode de déplacement de Proëtz.

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI
Mises en garde :
- Risque d'allergie.
- Risque de sélection de souches résistantes.

Précautions d'emploi :
Le traitement usuel ne dépassera pas 10 jours ; au-delà la conduite à tenir devra être réévaluée.

DC EFFETS INDÉSIRABLES
L'emploi par voie nasale peut induire une allergie aux aminoglucosides se traduisant par des manifestations cutanées de fréquence exceptionnelle.

PP PHARMACODYNAMIE
La framycétine, antibiotique bactéricide, appartient à la famille des aminoglucosides, à usage local exclusif. La framycétine, aux concentrations obtenues en applications locales, est, en raison de son activité in vitro, potentiellement active in vivo sur de nombreux germes à Gram + et à Gram - pouvant être rencontrés au niveau des voies aériennes supérieures.

AMM 328 477.1 (1978).
PRIX : 14,80 F (flacon de 15 ml).
Remb. Séc. soc. à 35 % - Collect.

Laboratoires du Docteur E. BOUCHARA
68, rue Marjolin - 92300 LEVALLOIS-PERRET
Tél. : (1) 45-19-10-00

☆ ISOMÉRIDE 15 mg
dexfenfluramine

FORMES et PRÉSENTATIONS
Gélule (blanche) : Boîte de 60.

COMPOSITION	*p. gélule*	*p. boîte*
Dexfenfluramine (DCI) chlorhydrate ..	15 mg	900 mg

Excipient : amidon de maïs, cellulose microcristalline, lactose, silice colloïdale, stéarate de magnésium, talc. *Calibrage* : n° 3.

DC INDICATIONS
Traitement de deuxième intention, après échec d'un traitement diététique adapté, d'obésité patente ayant un indice de masse corporelle supérieur à 30.

DC POSOLOGIE et MODE D'ADMINISTRATION
2 gélules par jour, réparties en 2 prises quotidiennes, à savoir 1 gélule le matin et 1 gélule le soir, de préférence au cours des repas.
Durée du traitement :
La durée du traitement ne doit pas dépasser 3 mois. Cependant dans de rares cas, des traitements plus prolongés peuvent être conduits par des spécialistes hospitaliers en nutrition, sous couvert d'un suivi attentif.

DC CONTRE-INDICATIONS
- Glaucome, enfant à l'exception de cas spécifiques sous couvert d'un suivi attentif par des spécialistes hospitaliers en pédiatrie, antécédents d'anorexie mentale, antécédents dépressifs, antécédents psychiatriques, propension aux abus médicamenteux, alcoolisme avéré.
- Du fait du mécanisme d'action sérotoninergique d'Isomérides, l'association aux IMAO est contre-indiquée (un intervalle d'au moins 15 jours doit être respecté).

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI
Mises en garde :
Des observations d'hypertension artérielle pulmonaire ont été rapportées chez des patients ayant reçu un traitement par la dexfenfluramine.
Compte tenu de ce risque rare mais grave,
- l'indication doit être respectée ;
- la durée du traitement est limitée à 3 mois, et le traitement ne doit pas être renouvelé ;
- toute apparition ou augmentation d'une dyspnée d'effort doit faire évoquer la possibilité d'hypertension artérielle pulmonaire, et faire arrêter le traitement.

Bien que n'appartenant pas à la classe I (stimulants) des substances interdites par la commission médicale du Comité International Olympique, l'attention des sportifs est attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors de contrôles antidopage.

Précautions d'emploi :
- Les causes organiques d'obésité doivent être éliminées avant la prescription de ce produit.
- Chez des patients généralement porteurs de facteurs de risque vasculaire et souvent à la suite d'une perte de poids rapide, de rares observations d'infarctus du myocarde et d'accidents vasculaires cérébraux ont été rapportées. L'attention est attirée sur la nécessité chez de tels sujets d'un amaigris-
- Ce produit doit être utilisé avec précaution chez les sujets présentant des troubles du rythme.
- Insuffisants hépatiques et insuffisants rénaux : en l'absence d'étude spécifique, l'administration de ce produit devra être évitée chez de tels patients.

DC INTERACTIONS MÉDICAMENTEUSES
Ne pas associer à un anorexigène à action centrale ni à un IMAO (cf. Contre-indications).
La dexfenfluramine peut potentialiser :
- les médicaments dépresseurs du système nerveux central (sédatifs),
- les antihypertenseurs,
- les effets hypotenseurs des antidépresseurs tricycliques,
- les sulfamides hypoglycémiants.

DC GROSSESSE et ALLAITEMENT
Grossesse : la dexfenfluramine n'est pas tératogène et n'altère pas la reproduction chez l'animal. Cependant, elle ne doit pas être administrée chez la femme enceinte.
Allaitement : en l'absence de données sur le passage dans le lait maternel, l'allaitement est déconseillé pendant la durée du traitement.

DC EFFETS INDÉSIRABLES
- Les plus fréquemment rapportés sont : sécheresse de la bouche, nausée, constipation, diarrhée. Ces effets cèdent à la poursuite du traitement.
- Ont été plus rarement observés : asthénie, céphalées, frissons ; variations tensionnelles, hypertension, hypotension, syncope, lipothymie (spécialement en début de traitement) ; élévation des transaminases, hépatite (exceptionnellement) ; somnolence, étourdissement, troubles de l'humeur, insomnie, nervosité, dépression, état confusionnel ; diplopie, mydriase ; rash cutané, prurit, œdème de Quincke, urticaire ; pollakiurie.
- Des observations d'hypertension pulmonaire ont été rapportées chez des patients ayant reçu un traitement par la dexfenfluramine (cf. Mises en garde).

DC SURDOSAGE
Peu de données sont disponibles sur les accidents de surdosage.
Le traitement d'urgence comporte :
- un lavage d'estomac,
- une diurèse forcée avec acidification des urines pour accélérer l'excrétion du produit,
- une réanimation avec surveillance cardiaque dans les cas les plus sévères,
- à la différence des anorexigènes sympathomimétiques, l'administration de barbituriques ne doit pas être systématique.

PP PHARMACODYNAMIE
Isomérides agit sur la régulation pondérale en diminuant le niveau de réglage du pondérostat, système physiologique central qui détermine et maintient stable le poids d'un individu.
Isomérides possède une action spécifique sur les comportements alimentaires susceptibles d'induire une obésité :
- en inhibant électivement la consommation de glucides tout en respectant la consommation de protéines.
- en inhibant l'hyperphagie induite par l'insuline,
- en inhibant l'hyperphagie de situation anxiogène.

Isomérides a un mécanisme d'action sérotoninergique qui sous-tend son activité pharmacodynamique.
Isomérides inhibe la recapture et augmente la libération de sérotonine.
Dans l'obésité avec trouble du comportement alimentaire (compulsion pour les hydrates de carbone), Isomérides inhibe de façon sélective la consommation de glucides et diminue ainsi la consommation calorique globale, tout en respectant la prise de protéines.
Isomérides se différencie radicalement des anorexigènes amphétaminiques :
- absence d'effet psychostimulant,
- absence d'effet hypertenseur,
- absence de potentiel d'addiction.

PP PHARMACOCINÉTIQUE
Après administration orale, l'absorption d'Isomérides est pratiquement totale. Le pic de concentration plasmatique est atteint 4 heures après la prise.
En administration répétée, à dose thérapeutique, une gélule le matin et une gélule le soir, l'état d'équilibre est atteint vers le quatrième jour et reste stable à la concentration moyenne de 40 ng/ml.
La liaison aux protéines plasmatiques est faible (36 %).
Le produit est fortement métabolisé avec formation de d-norfenfluramine qui participe à l'activité globale du produit. Aucun dérivé de l'amphétamine n'a été mis en évidence. La clairance plasmatique est de 45 litres par heure.
L'élimination est presque exclusivement urinaire, plus de 90 % de la dose étant recueillis en 3 à 4 jours par cette voie. Le temps de demi-vie d'élimination est d'environ 18 heures.

LISTE I

PRIX indicatif : 169,00 F (60 gélules).
Non remboursable Sécurité sociale.

Laboratoires ARDIX
25, rue Eugène-Vignat - BP 1749 - 45007 ORLÉANS
Tél. : 38-81-60-00
Information médicale : Tél. : (1) 46-41-60-60

☆ ISOMYRTINE
pholcodine, isomyrtol

FORMES et PRÉSENTATIONS
Capsule (verte) : Boîte de 20, sous plaquettes thermoformées (PVC/ALU).

COMPOSITION	*p. capsule*
Pholcodine (DCI)	18 mg
Isomyrtol	20 mg

Excipient : terpinéol, cire d'abeille jaune, lécithine de soja d'arachide. *Enveloppe de la capsule* : gélatine, glycérol, hydroxybenzoate d'éthyle sodé, parahydroxybenzoate méthyle sodé, dioxyde de titane (E 171), jaune de quinoléine (E 104), bleu patenté (E 131), eucalyptol.

DC INDICATIONS
Traitement symptomatique des toux non productives gênantes.

DC POSOLOGIE et MODE D'ADMINISTRATION
Le traitement symptomatique doit être court (quelques jours).
Réservé à l'adulte.
Chez l'adulte, la posologie maximale est de 90 mg/jour de pholcodine à répartir en 4 prises espacées de 6 heures. La posologie usuelle est de 20 à 60 mg/jour soit, en l'absence de tout autre forme pharmaceutique apportant de la pholcodine ou tout autre antitussif central : 1 capsule/prise, 3 à 4 fois par jour.
Coût du traitement journalier : 3,94 à 5,26 F.

DC CONTRE-INDICATIONS
Celles liées à la présence de pholcodine, c'est-à-dire :
- toux de l'asthmatique. L'association antitussif + bronchodilatateur n'est pas justifiée ;
- en règle générale, insuffisance respiratoire quel qu'en soit son degré en raison de l'effet dépresseur des antitussifs sur les centres respiratoires et de la nécessité de respecter la toux pour éviter l'encombrement bronchique.

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI
Mises en garde :
- Les toux productives qui sont un élément fondamental de la défense bronchopulmonaire sont à respecter.
- Avant de prescrire un traitement antitussif, il convient de rechercher les causes de la toux qui requièrent un traitement étiologique spécifique, par exemple asthme, dilatation des bronches, vérification des stases intrabronchiques, cancer, affections ORL, bronchiques, insuffisance ventriculaire gauche, quelle qu'en soit l'étiologie, embolie pulmonaire, toux cardiaque.
- Si la toux résiste à un antitussif administré à la posologie usuelle, on ne doit pas procéder à une augmentation des doses, mais à un réexamen de la situation clinique.

Précautions d'emploi :
- Sujet âgé et insuffisant hépatique : la posologie initiale sera diminuée de moitié par rapport à la posologie conseillée chez l'adulte, et pourra ensuite être augmentée en fonction de la tolérance et des besoins.
- La prise de boissons alcoolisées et de médicaments contenant de l'alcool (cf. Interactions médicamenteuses) pendant le traitement est déconseillée.

DC INTERACTIONS MÉDICAMENTEUSES
Association déconseillée :
- Alcool : majoration par l'alcool de l'effet sédatif des antitussifs centraux. L'altération de la vigilance peut rendre dangereuse la conduite de véhicules et l'utilisation de machines.
Éviter la prise de boissons alcoolisées et de médicaments contenant de l'alcool.

Associations à prendre en compte :
- Autres dépresseurs du SNC (analgésiques morphiniques, certains antidépresseurs, les antihistaminiques H_1 sédatifs, barbituriques, benzodiazépines, clonidine et apparentés, hypnotiques, neuroleptiques, anxiolytiques autres que benzodiazépines) : Majoration de la dépression centrale pouvant être à l'origine des conséquences importantes, notamment en matière de conduite automobile ou d'utilisation de machines.
- Autres dérivés morphiniques (analgésiques antitussifs) : Dépression respiratoire (synergie potentialisatrice des effets dépresseurs des morphiniques), en particulier chez le sujet âgé.

DC GROSSESSE et ALLAITEMENT
Grossesse : en l'absence de données expérimentales et cliniques, le risque tératogène n'est pas connu. Par précaution, il est recommandé de ne pas utiliser cet antitussif pendant le premier trimestre.
Allaitement : par prudence, éviter l'administration pendant l'allaitement en raison du manque de données.

BOIRON
...
...E-FOY-LÈS-LYON
...72-32-40-20

...E AU CALENDULA
...R DIGESTION

...ENTATIONS
...20 g

	p. 100 g
...pure fraîche	20 g

...ilisé dans les brûlures et les plaies ...ète étendue, gerçures, crevasses.

...t MODE D'ADMINISTRATION
...r jour, après nettoyage des lésions ...sans pansement.

...YNAMIE
...icatrisante.

...68).
...e de 20 g).
...65 %.

BOIRON
...ue de la Libération
...AINTE-FOY-LÈS-LYON
...él. : 72-32-40-20

...MADE LELONG
...érou, sulfapyridine, rétinol

...ENTATIONS
...e 30 g.

	p. 100 g	*p. tube*
.....	1,60 g	0,48 g
.....	10 g	3 g
...mine A, ...	25 000 UI	7 500 UI

...e.

...aitement symptomatique des der-...s, érythèmes, prurits, intertrigo, ...du sein, gerçures, engelures.

...t MODE D'ADMINISTRATION
...a pommade sur la région à traiter.

...CATIONS
...u baume du Pérou, aux sulfamides ...e.

...RDE et PRÉCAUTIONS D'EMPLOI
...taine résorption transcutanée de la ...que d'hypervitaminose en cas de ...e est possible, tout particulièrement

...ploi :
...ques sont d'autant plus à redouter ...st appliquée de façon répétée, sur ...ce, sous occlusion, sur une peau ...brûlée), sur une muqueuse, sur une ...e et chez le nourrisson et l'enfant en

...NS MÉDICAMENTEUSES
...nt éminemment oxydable, ne pas ...e Lelong avec ou après un antisep-...es oxydantes.

...SIRABLES
...ibilité d'eczéma de contact.

...YNAMIE
...e (sulfapyridine).
...antes (baume du Pérou et vita-

...(1952) – CIP 333 634.4.
...oc.

...TERLING MIDY
...ictor-Hugo – 92115 CLICHY
...l. : (1) 41-06-83-83

...PHTALMIQUES ALLERGAN
...es produits figure au classement

...S

...bstances et procédé dopants ...figure page 6

POMMADES ET GELS OPHTALMIQUES CHAUVIN 544

L'information sur les produits figure au classement alphabétique :

ANTISEPTIQUE-CALMANTE
BLÉPHASEPTYL
CÉBÉMYXINE
CÉBÉNICOL
FRAKIDEX
OPHTAGRAM
OXYDE MERCURIQUE JAUNE ... CHAUVIN

Voir aussi :
COLLYRES CHAUVIN

☆ PONDÉRAL LONGUE ACTION 60 mg
☆ PONDÉRAL 20 mg
fenfluramine

FORMES et PRÉSENTATIONS
Pondéral longue action 60 mg :
Gélule (bleu et incolore, contenant un granule blanc) Boîte de 30.
Pondéral 20 mg :
Comprimé (blanc) : Boîte de 40.

COMPOSITION

Pondéral longue action 60 mg :	*p. gélule*	*p. boîte*
Fenfluramine (DCI) chlorhydrate ...	60 mg	1,8 g

Excipient : acetyltributylcitrate, cellulose microcristalline, hydroxypropylméthylcellulose, dihydrogénophosphate de sodium anhydre, résine acrylique, saccharose, silice colloïdale anhydre, talc, dioxyde de titane. *Enveloppe de la gélule :* gélatine, dioxyde de titane. *Colorant :* bleu indigotine. *Calibrage :* n° 3.

Pondéral 20 mg :	*p. comp.*	*p. boîte*
Fenfluramine (DCI) chlorhydrate ...	20 mg	800 mg

Excipient : amidon de maïs, gomme adragante, gomme arabique, lactose, saccharose, silice hydratée, stéarate de magnésium, talc.

DC INDICATIONS
Traitement de deuxième intention, après échec d'un traitement diététique adapté, d'obésité patente ayant un indice de masse corporelle supérieur à 30.

DC POSOLOGIE et MODE D'ADMINISTRATION
- Pondéral longue action 60 mg : la posologie est de 1 gélule par jour. Au bout de 3 à 4 semaines de traitement, la posologie pourra, si nécessaire, être portée à 2 gélules par jour en une seule prise. Dans ce cas, l'arrêt du traitement devra comporter un palier de 8 jours à 1 gélule par jour.
- Pondéral 20 mg : la posologie est de 3 comprimés par jour.

Il est préférable d'adopter un mode de traitement discontinu par périodes de 3 à 6 semaines.
Durée du traitement :
La durée du traitement ne doit pas dépasser 3 mois. Cependant dans de rares cas, des traitements plus prolongés peuvent être conduits par des spécialistes hospitaliers en nutrition, sous couvert d'un suivi attentif.

DC CONTRE-INDICATIONS
- Glaucome.
- Enfant, à l'exception de cas spécifiques sous couvert d'un suivi attentif par des spécialistes hospitaliers en pédiatrie.
- Antécédents d'anorexie mentale, antécédents dépressifs, antécédents psychiatriques, propension aux abus médicamenteux, alcoolisme avéré.
- Du fait du mécanisme d'action sérotoninergique de la fenfluramine, l'association aux IMAO est contre-indiquée (un intervalle d'au moins 15 jours doit être respecté).

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI
Mises en garde :
Des observations d'hypertension artérielle pulmonaire ont été rapportées chez des patients ayant reçu un traitement par la fenfluramine.
Compte tenu de ce risque rare mais grave,
- l'indication doit être respectée,
- la durée du traitement est limitée à 3 mois, et le traitement ne doit pas être renouvelé,
- toute apparition ou augmentation d'une dyspnée d'effort doit faire évoquer la possibilité d'hypertension artérielle pulmonaire, et faire arrêter le traitement.
- Bien que n'appartenant pas à la classe I (stimulants) des substances interdites par la Commission Médicale du Comité International Olympique, l'attention des sportifs est attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors de contrôles antidopage.

Précautions d'emploi :
- Les causes organiques d'obésité doivent être éliminées avant la prescription de Pondéral.
- Pondéral doit être utilisé avec précaution chez les sujets présentant un trouble du rythme.

DC INTERACTIONS MÉDICAMENTEUSES
Ne pas associer à un anorexigène à action centrale.
Pondéral peut potentialiser :
- les médicaments dépresseurs du système nerveux central (sédatifs),
- les antihypertenseurs,
- les effets hypotenseurs des antidépresseurs tricycliques, des neuroleptiques,
- les sulfamides hypoglycémiants.

Annexe 1-55

DC GROSSESSE et ALLAITEMENT
Grossesse : les études réalisées chez l'animal n'ont pas mis en évidence d'effet tératogène ; en l'absence de données cliniques humaines précises, ces résultats expérimentaux ne permettent pas de préjuger d'un effet malformatif dans l'espèce humaine, bien qu'à ce jour aucune malformation n'ait été rapportée.
Par mesure de prudence, éviter de prescrire pendant la grossesse.
Allaitement : en l'absence de données sur le passage dans le lait maternel, l'allaitement est déconseillé pendant la durée du traitement.

DC EFFETS INDÉSIRABLES
Les plus fréquemment rapportés sont : sécheresse de la bouche, nausées, constipation, diarrhée. Ces effets cèdent à la poursuite du traitement.
Ont été rarement observés :
- asthénie, céphalées, frissons,
- variations tensionnelles, hypertension, hypotension, syncopes, lipothymies (spécialement en début du traitement),
- élévation des transaminases, hépatite (exceptionnellement),
- somnolence, étourdissement, troubles de l'humeur, insomnie, nervosité, dépression, état confusionnel,
- diplopie, mydriase,
- rash cutané, prurit, œdème de Quincke, urticaire,
- pollakiurie.

Des observations d'hypertension artérielle pulmonaire ont été rapportées chez les patients ayant reçu un traitement par la fenfluramine (cf. Mises en garde).

DC SURDOSAGE
Peu de données sont disponibles sur les accidents de surdosage. Les cas rapportés de surdosage en prise unique se rapportent à des posologies de 300 à 2 000 mg.
Les symptômes consistent en agitation et somnolence, confusion mentale, rougeur de la face, tremblements, fièvre, sueurs, douleurs abdominales, hyperventilation, dilatation des pupilles ; les réflexes peuvent être exagérés ou diminués, certains patients peuvent présenter un nystagmus rotatoire. On peut noter une tachycardie, la tension artérielle peut être normale ou légèrement élevée. Des convulsions, un coma, des extrasystoles ventriculaires aboutissant à une fibrillation peuvent survenir à des doses plus élevées.
Le traitement d'urgence comporte :
- un lavage d'estomac,
- une diurèse forcée avec acidification des urines pour accélérer l'excrétion du produit,
- une réanimation avec surveillance cardiaque dans les cas les plus sévères.

A la différence des anorexigènes sympathomimétiques, l'administration de barbituriques ne doit pas être systématique.

PP PHARMACODYNAMIE (Uhlik '84)
La fenfluramine est un agent thérapeutique intervenant dans la régulation de l'équilibre pondéral et qui possède les propriétés suivantes :
Chez l'animal, ont été mis en évidence :
- Un mécanisme sérotoninergique :
  L'étude du site d'action de la fenfluramine permet de la distinguer des dérivés des amines sympathomimétiques psychostimulantes ; alors que l'amphétamine et ses dérivés mettent en jeu le système noradrénergique, la fenfluramine agit par l'intermédiaire des voies sérotoninergiques. Elle interviendrait davantage sur le centre de la satiété que sur celui de la faim et est dépourvue d'effets neuroexcitants. Ces particularités contribuent à conférer à la fenfluramine son originalité pharmacologique.
- Un effet sur la prise alimentaire :
  Cet effet, chez l'animal normal aussi bien que chez l'animal obèse (rat, souris, cobaye, chien et singe), se traduit par une diminution importante de la prise alimentaire globale journalière, diminution réalisée aux dépens de la taille des prises, mais sans modifier le nombre de prises alimentaires journalières physiologiques.
- Une activité métabolique :
  Chez l'animal, la fenfluramine augmente la pénétration du glucose au niveau du muscle aux dépens de la conversion et du stockage de ce substrat sous forme de graisses. La part jouée par ces propriétés métaboliques dans les effets sur la prise alimentaire et sur le poids n'est pas encore complètement précisée.
- Un effet sédatif :
  La fenfluramine est dépourvue d'effets neuroexcitants. Elle exerce de plus, chez l'animal, un effet anticonvulsivant.

Chez l'homme, en pharmacologie clinique :
- La fenfluramine réduit la prise alimentaire, mais la sécrétion salivaire à la présentation des aliments, utilisée comme témoin de l'appétit, n'est pas modifiée par la fenfluramine alors qu'elle est supprimée par l'amphétamine et ses dérivés.
- La fenfluramine accroît l'utilisation périphérique du glucose consécutive à une charge glucosée, et

entraîne une mobilisation des graisses se traduisant par une augmentation sérique des acides gras libres et du glycérol circulant.
- La fenfluramine n'entraîne habituellement pas d'effets sympathomimétiques sur le plan cardiovasculaire ; au contraire, le traitement prolongé entraîne une diminution des catécholamines circulantes qui se traduit cliniquement par une bradycardie modérée et une légère baisse tensionnelle.

Au total, la fenfluramine :
- réduit la prise alimentaire ;
- exerce une activité métabolique (augmentation de l'utilisation musculaire du glucose et mobilisation des graisses) ;
- produit un effet sédatif ;
- n'entraîne le plus souvent ni tachycardie, ni hypertension.

Ces caractéristiques expliquent la possibilité d'utiliser la fenfluramine dans certains cas où la dexamphétamine et ses dérivés sont déconseillés.

PP PHARMACOCINÉTIQUE

Administrée par voie orale, la fenfluramine est complètement absorbée au niveau du tractus gastro-intestinal et est distribuée dans tout l'organisme, puis est éliminée avec une demi-vie de 24,2 heures. La forme galénique particulière de Pondéral longue action 60 mg, comportant des granulés dont l'enrobage se dissout à des vitesses différentes, permet une absorption du médicament étalée sur le nycthémère.
Ainsi, la cinétique des taux sanguins en fenfluramine observés après la prise unique d'une gélule de Pondéral longue action 60 mg reproduit celle que l'on observe après la prise fractionnée de trois comprimés de Pondéral 20 mg. Cette forme galénique simplifie donc la posologie, permettant une seule prise quotidienne.

LISTE I
AMM 319 478.9 (1976, validée 1987, révisée 1994).
308 522.1 (1977, validée 1987, révisée 1994).
PRIX conseillé : 163,90 F (30 gélules).
52,50 F (40 comprimés).
Non remb. Séc. soc.

Laboratoires Biopharmaceutiques de France « BIOPHARMA »
29, rue du Pont - 92200 NEUILLY-SUR-SEINE
Tél. : (1) 46-41-60-00

☆ PONSTYL
acide méfénamique

FORMES et PRÉSENTATIONS

Gélule (bleu émail et ivoire) : Boîte de 20, sous plaquettes thermoformées de 10.
Suppositoire : Boîte de 8.

COMPOSITION

Gélules :	*p. unité*	*p. boîte*
Acide méfénamique (DCI)	250 mg	5 g

Excipient : lactose, stéarate de magnésium, gélatine, oxyde de fer jaune, oxyde de titane, indigotine. *Conservateur :* anhydride sulfureux. *Calibrage :* n° 1.

Suppositoires :	*p. unité*	*p. boîte*
Acide méfénamique (DCI)	500 mg	4 g

Excipient : glycérides semi-synthétiques.

DC INDICATIONS

- Traitement symptomatique des affections douloureuses et (ou) fébriles.
- Douleurs de l'appareil locomoteur.
- Dysménorrhées primaires.
- Ménorragies fonctionnelles.

DC POSOLOGIE et MODE D'ADMINISTRATION

Gélules (ne pas ouvrir les gélules) :
Adulte et enfant à partir de 12 ans :
- traitement des algies et des états fébriles : 1 g à 1,5 g par jour, soit 4 à 6 gélules par jour, en 3 prises au moment des repas.
Coût du traitement journalier : 5,28 à 7,92 F ;
- traitement de la dysménorrhée : dès le début de la douleur, 1,5 g par jour, soit 2 gélules 3 fois par jour, au moment des repas, jusqu'à disparition des symptômes.
Coût du traitement journalier : 7,92 F ;
- traitement des ménorragies : dès le premier jour des règles, 1,5 g par jour, soit 2 gélules 3 fois par jour, au moment des repas, jusqu'à la normalisation des règles, sans dépasser 5 jours.
Coût du traitement journalier : 7,92 F.

Suppositoires :
- Patients présentant des antécédents récents de rectite ou de rectorragie (suppositoires).
- Dernier trimestre de la grossesse (cf. Grossesse et Allaitement).

Relatives :
- Patients souffrant ou ayant souffert d'asthme bronchique ou d'affection allergique à survenue d'un bronchospasme pouvant être précipitée.
- Association avec un autre anti-inflammatoire, avec l'aspirine (cf. Interactions médicamenteuses).
- Association avec les anticoagulants oraux, l'héparine, les sulfamides hypoglycémiants, les sels de lithium, la ticlopidine (cf. Interactions médicamenteuses).

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI

Mises en garde :
- En raison de la gravité possible des manifestations gastro-intestinales chez les patients soumis à un traitement anticoagulant, il convient de surveiller particulièrement l'apparition d'une symptomatologie digestive ; en cas d'hémorragie gastro-intestinale, il faut interrompre le traitement.
- La survenue d'une diarrhée liée au traitement impose l'arrêt de celui-ci.

Précautions d'emploi :
- L'acide méfénamique ne doit pas être administré chez les enfants de moins de 12 ans.
- Il y a lieu de réduire la posologie chez le sujet âgé.
- L'acide méfénamique sera utilisé avec précaution en cas d'antécédents d'ulcères gastroduodénaux.
- En début de traitement, une surveillance attentive du volume de la diurèse et de la fonction rénale est nécessaire chez les malades insuffisants cardiaques, cirrhotiques et néphrotiques, chez les patients prenant un diurétique, chez les insuffisants rénaux chroniques, et particulièrement chez les sujets âgés.
- Lors des traitements de longue durée, une surveillance hématologique complète, au moins mensuelle, est conseillée.
- Avant d'envisager le traitement des ménorragies par l'acide méfénamique, il est indispensable que les examens gynécologiques, cliniques et paracliniques habituels aient été effectués dans le but d'éliminer une cause néoplasique ou infectieuse de ménorragie, ainsi que toute cause organique relevant d'un traitement spécifique.
- S'il a été décrit une possibilité de diminution d'efficacité du stérilet, chez les patientes traitées par les anti-inflammatoires non stéroïdiens au long cours, cette possibilité semble improbable lors de leur utilisation, exclusivement en période menstruelle, pour le traitement des dysménorrhées et des ménorragies.

DC INTERACTIONS MÉDICAMENTEUSES

Associations déconseillées :
- AINS entre eux (y compris les salicylés à fortes doses) : augmentation du risque ulcérogène et hémorragique digestif (synergie additive).
- Anticoagulants oraux, héparine (voie parentérale) : augmentation du risque hémorragique (inhibition de la fonction plaquettaire et agression de la muqueuse gastroduodénale).
Si la prescription de l'AINS ne peut être évitée, surveillance clinique et biologique étroite.
- Dispositifs intra-utérins : diminution de leur efficacité.
- Lithium (décrit pour le diclofénac, le kétoprofène, l'indométacine, la phénylbutazone, le piroxicam, le pipropfène) : augmentation de la lithémie pouvant atteindre des valeurs toxiques (diminution de l'excrétion rénale du lithium).
Si nécessaire, surveiller étroitement la lithémie et adapter la posologie du lithium pendant l'association et après l'arrêt de l'AINS.
- Méthotrexate (par extrapolation à partir de l'indométacine, du kétoprofène, des pyrazolés, des salicylés) : augmentation de la toxicité hématologique du méthotrexate en particulier lorsque celui-ci est administré à haute dose.
- Sulfamides : augmentation de l'effet hypoglycémiant des sulfamides (déplacement de leurs liaisons aux protéines plasmatiques).
- Ticlopidine : augmentation du risque hémorragique (synergie de l'activité antiagrégante plaquettaire conjuguée à l'effet agressif sur la muqueuse gastroduodénale des AINS).
Si la prescription de l'AINS ne peut être évitée, surveillance clinique et biologique étroite (temps de saignement).

Associations nécessitant des précautions d'emploi :

DC GROSSESSE et ALLAITEMENT

Grossesse :
- Dans l'espèce humaine, aucun effet malformatif particulier n'a été signalé. Cependant, des études épidémiologiques complémentaires sont nécessaires afin de confirmer ou infirmer cette notion.
- Au cours du 3e trimestre, tous les inhibiteurs de la synthèse des prostaglandines peuvent exposer le fœtus à une toxicité cardiopulmonaire (hypertension pulmonaire avec fermeture prématurée du canal artériel) et rénale et, en fin de grossesse, la mère et l'enfant, à un allongement du temps de saignement. En conséquence, toute prise d'AINS est absolument contre-indiquée pendant le 3e trimestre.

Allaitement : des traces d'acide méfénamique ont été retrouvées dans le lait maternel, son utilisation est déconseillée pendant l'allaitement en raison des effets possibles sur l'appareil cardiovasculaire du nourrisson.

DC CONDUITE et UTILISATION DE MACHINES

Prévenir les malades de l'apparition possible d'étourdissements (conducteurs de véhicules, utilisateurs de machines).

DC EFFETS INDÉSIRABLES

- Effets gastro-intestinaux : à l'occasion d'études contrôlées et de traitements prolongés pendant 6 mois, ont été observées : diarrhée (5 %), nausées avec ou sans vomissement, gastralgies, dont la fréquence a pu entraîner chez certains patients l'interruption du traitement ; la fréquence des effets secondaires est diminuée par l'absorption de l'acide méfénamique pendant les repas ; l'intensité de ces effets, étant liée à la dose, diminue habituellement avec la réduction posologique et éventuellement après l'arrêt du traitement. D'autres troubles ont été rapportés : anorexie, pyrosis, ballonnement, constipation, ulcérations digestives avec ou sans hémorragie.
- Réactions d'hypersensibilité :
  - dermatologiques (éruption, rash, prurit...) ;
  - respiratoires (possibilité de survenue de crise d'asthme, en particulier chez les sujets allergiques à l'aspirine et aux autres anti-inflammatoires non stéroïdiens).
- Effets rénaux : particulièrement chez les patients âgés et déshydratés, une insuffisance rénale a été rapportée incluant une nécrose papillaire ; occasionnellement, hématurie et dysurie.
- Effets sur l'hématopoïèse : des cas d'anémie hémolytique auto-immune ont été rapportés après utilisation prolongée d'acide méfénamique pendant 12 mois et plus, généralement réversibles à l'arrêt du traitement ; ont également été observés, diminution de l'hématocrite, chez 2 à 5 % des patients en cas d'utilisation prolongée : exceptionnellement, leucopénie, éosinophilie, purpura thrombopénique, agranulocytose, pancytopénie, hypoplasie médullaire.
- Effets neurologiques : vertiges, somnolence, nervosité, céphalées, vision trouble.
- Autres effets : irritation oculaire, otalgie, transpiration, anomalies hépatiques légères, augmentation des besoins en insuline chez le diabétique, accès de palpitations, dyspnée et perte réversible de la vue colorée.
- Effets liés à la voie d'administration : l'utilisation de la voie rectale peut être la cause d'une irritation locale.

DC SURDOSAGE

En cas d'intoxication accidentelle, un lavage gastrique doit être pratiqué suivi de l'utilisation de charbon activé, absorbant puissant de l'acide méfénamique et de ses métabolites ; une surveillance des fonctions vitales doit être instaurée ainsi que le traitement symptomatique adéquat ; en raison de la forte liaison aux protéines de l'acide méfénamique et de ses métabolites, l'hémodialyse et la dialyse péritonéale sont vraisemblablement de peu d'activité.

PP PHARMACODYNAMIE

L'acide méfénamique est un anti-inflammatoire non stéroïdien, de la famille des fénamates :
- activités antalgique, anti-inflammatoire et antipyrétique ;
- activité inhibitrice de la synthèse des prostaglandines (F2α et E2), par inhibition de la cyclo-oxygénase et antagoniste des prostaglandines préformées au niveau des sites récepteurs.

PP PHARMACOCINÉTIQUE

Annexe 1-56

REPUBLIQUE FRANCAISE

AGENCE DU MEDICAMENT

Saint-Denis, le 9 MAI 199

DIRECTION DE L'EVALUATION

UNITE DE PHARMACOVIGILANCE

DOSSIER TECHNIQUE

ENQUETE NATIONALE DE PHARMACOVIGILANCE ET ANOREXIGENES

Suite à la Commission Nationale de Pharmacovigilance du 10 Mai 1994, L'enquête de Pharmacovigilance relative aux anorexigènes serotoninergiques: la fenfluramine et dexfenfluramine, a été étendue à l'ensemble de la classe.

I) Présentation des produits

Les anorexigènes actuellement commercialisés sont au nombre de 10, il s'agit de :

ISOMERIDE® (dexfenfluramine) commercialisé par le Laboratoire ARDIX depuis 1985

PONDERAL® (fenfluramine) commercialisé par le Laboratoire BIOPHARMA depuis 1976

DININTEL® (clobenzorex) commercialisé par le Laboratoire DIAMANT depuis 1970

INCITAL® (mefenorex) commercialise par le Laboratoire PIERRE FABRE SANTE depuis 1974

FENPROPOREX DEGLAUDE (fenproporex) commercialisé par le Laboratoire DEGLAUDE depuis 1977.

MODERATAN DIFFUCAP (amfépramone) commercialisé par le Laboratoire THERANOL depuis 1974.

TENUATE DOSPAN (amfépramone) commercialisé par le Laboratoire MARION MERREL DOW depuis 1977.

PREFAMONE chronules (amfépramone) commercialisé par le Laboratoire DEXO SA depuis 1970

ANOREX (amfépramone) commercialisé par le Laboratoire CRINEX depuis 1979

et de l'Amfépramone préparations magistrales.

Les indications et modalités d'administration sont présentées dans le tableau suivant _:

Spécialités	indication	posologie	durée de traitement
ISOMERIDE® (dexfenfluramine)	Traitement de deuxième intention, après echec d'un traitement diététique adapté, d'obésité patente ayant un indice de masse corporelle supérieur à 30	30 mg/j	inférieure à 3mois
PONDERAL® (fenfluramine)	Traitement de deuxième intention, après echec d'un traitement diététique adapté, d'obésité patente ayant un indice de masse corporelle supérieur à 30	60 mg/j	inférieure à 3mois
DININTEL® (clobenzorex)	Medication adjuvante des régimes restrictifs des surcharges pondérales	60 mg/j à 90 mg/j	cure de 3 à 6 semaines
INCITAL® (mefenorex)	Medication adjuvante des régimes restrictifs des surcharges pondérales	40 mg/j	cure de 3 à 6 semaines
FENPROPOREX DEGLAUDE® (fenproporex)	Medication adjuvante des régimes restrictifs des surcharges pondérales	20 mg/j	cure de 3 à 6 semaines
MODERATAN DIFFUCAP® (amfépramone)	Medication adjuvante des régimes restrictifs des surcharges pondérales	75 mg/j	cure de 3 à 6 semaines
TENUATE DOSPAN® (amfépramone)	Medication adjuvante des régimes restrictifs des surcharges pondérales	75 mg/j	cure de 3 à 6 semaines
PREFAMONE® (amfépramone)	Medication adjuvante des régimes restrictifs des surcharges pondérales	75 mg/j	cure de 3 à 6 semaines
ANOREX® (amfépramone)	Adjuvants des régimes restrictifs au cours des traitements de l'excès pondéral de l'adulte et de l'adolescent	75 mg/j	cure de 3 à 6 semaines

I) Analyse des effets indésirables

Un total de 1098 effets indésirables a été déclarés au Système National de pharmacovigilance ou aux laboratoires entre 1985 et Juin 1994 (Les hypertensions artérielles pulmonaires ayant été collectées jusqu'au mois de Décembre 1994)

Spécialités	Nombre d'effets indésirables	Incidence par mois traitement
ISOMERIDE® (dexfenfluramine)	832	27 557
PONDERAL® (fenfluramine)	77	29369
TENUATE DOSPAN® (amfépramone)	47	71 928
MODERATAN® (amfépramone)	13	141 811
PREFAMONE® (amfépramone)	4	170 683
ANOREX® (amfépramone)	2	123 356
Amfépramone DC	7	
Preparations magistrales	15	
total Amfépramone	**88**	**69856**
DININTEL® (clobenzorex)	63	88 070
INCITAL® (mefenorex)	23	10 156
FENPROPOREX® (fenproporex)	15	122 131
TOTAL	**1098**	

Caractéristiques de la population (cf annexe 1) :
Les femmes sont majoritairement representées.
l'age moyen des patients varie de 38.3 à 42.3 ans selon les produits,
La moyenne des BMI est de 29.25 (de 23.8 à 29.2 pour la population générale)

La nature des effets indésirables

Les effets neurologiques sont majoritaires et essentiellement représentées par la pharmacodépendance (cf annexe 2).

● **Analyse des hypertensions artérielles pulmonaires** (les observations ont été recueillies jusqu'au 31/12/94).

Toutes les hypertensions artérielles pulmonaires ont été validées par un expert .
Le diagnostic d'hypertension artérielle pulmonaire a été posé sur les critères hémodynamiques suivants :

-HPA > 25 mmHg
- Pap < 15 mmHg

Les diagnostics différentiels ont été éliminés sur les données d'un examen pertinent :

- maladie thrombo-embolique pulmonaire : scintigraphie de perfusion, angiographie si nécessaire
- pathologie respiratoire (fibrose, insuffisance respiratoire, apnée grave du sommeil) : bilan fonctionnel respiratoire, gaz du sang.
- cardiopathie gauche évoluée.

117 observations d'hypertensions artérielles pulmonaires ont été notifiées, 78 ont finalement été retenues par l'expert.

Les hypertensions artérielles pulmonaires représentent respectivement :

6.1% des effets pour l'Amfépramone

6.1% " " " le DININTEL® (clobenzorex)

11.7% des effets pour le PONDERAL® (fenfluramine)

4.6 % pour l'ISOMERIDE® (dexfenfluramine) .

Les principales caractéristiques sont mentionnées dans le tableau suivant :

	HTAP	Age	F_H	Durée de traitement	
				< 3 m	≥ 3m
ISOMERIDE® (dexfenfluramine)	57	48,4	51_6	14	39
PONDERAL® (fenfluramine)	11	49,1	11_0	-	9
DININTEL® (clobenzorex)	4	52,0	5_1	-	3
TENUATE DOSPAN® (amfépramone)	4	43,0	4_0	-	4
Amfépramone DCI, Préparations magistrales	2	34,0	2_0	1	-
PREFAMONE® (amfépramone)	0	0,0	0		
FENPROPOREX® (amfépramone)	0	0,0	0		

- Dans la plupart des cas, la durée de traitement était supérieure ou égale à 3 mois.

- La dyspnée existait avant l'instauration du traitement dans 32 observations :
ISOMERIDE® (dexfenfluramine) : 22 cas
PONDERAL® (fenfluramine) : 7cas
TENUATE DOSPAN® (amfépramone) : 2
Amfepramone : 1

L'evolution a été marquée par :
-22 décès dont 13 sous ISOMERIDE® (dexfenfluramine) , 4 sous PONDERAL® (fenfluramine) , 1 sous DININTEL® (clobenzorex) et 4 sous amfépramone.
-4 transplantations pulmonaires : 3 sous ISOMERIDE® (dexfenfluramine) et 1 sous PONDERAL® (fenfluramine) ,
-7 patients sont en attente de greffe, 6 sous ISOMERIDE® (dexfenfluramine) et 1 sous PONDERAL® (fenfluramine) .
- 6 patients traités par ISOMERIDE® (dexfenfluramine) sont améliorés et 18 sont stabilisés.

Les incidences sont représentées dans le tableau suivant :

	Nombre de mois-traitement	Incidence des HTAP
ISOMERIDE® (dexfenfluramine)	24 264 059	1/425 685
PONDERAL® (fenfluramine)	6 548 869	1/595 352
DININTEL® (clobenzorex)	5 196 120	1/1 299 030
TENUATE DOSPAN® (amfépramone)	3 164 849	1/791 212
Amfépramone total	5 937 808	1/989 635

Au total, le risque d' hypertensions artérielles pulmonaires existe avec tous les anorexigènes.
IL s'agit d'un effet rare mais grave puisque potentiellement mortel.
Les résultats de la présente enquête sont conformes aux données de l'étude épidémiologique internationale IPPHS qui démontre une association significative entre la prise d'anorexigène quel qu'il soit et la survenue d'une hypertension artérielle pulmonaire dite primitive.

ANNEXE 1

POPULATION

	Femmes %	Hommes %	Inconnu %
Amfépramone	86,4	12,5	1,1
Dinintel	71,4	27	1,6
Fenproporex	80	20	
Incital	82,6	17,4	
Pondéral	88,3	11,7	
Isoméride	84,7	14,5	0,7

AGE

	Population totale (ans)	Femmes (ans)	Hommes (ans)
Amfépramone	38,5	38,8	36,3
Dinintel	38,7	37,8	40,8
Fenproporex	38,3	37,5	41,3
Incital	38,8	38,4	40,25
Pondéral	42,3	42,4	38,5
Isoméride	42	41,6	44

POIDS

	Population totale (kg)	Femmes (kg)	Hommes (kg)
Amfépramone	74,3	73,4	88
Dinintel	66,9	59,3	91
Fenproporex	75,8	71,8	96
Incital	77,9	68,9	105
Pondéral	72,2	69,9	84,7
Isoméride	72,5	69,5	90

BMI

	Population totale	Femmes	Hommes
Amfépramone	29,2	29,1	30,4
Dinintel	23,7	22,3	27,9
Fenproporex	23,8	23,8	
Incital	27,9	25,9	33,9
Pondéral	28,2	27,5	32,4
Isoméride	27,2	26,7	29,9

ANNEXE 2

Annexe 1-56

REPARTITION DES EFFETS INDESIRABLES (%)

	AMFEPRAMONE	DININTEL	FENPROPOREX	INCITAL	PONDERAL	ISOMERIDE
SNC	30	50,8	40	44,8	24,5	25,1
Ph.dependance sevrage	*15*	*33,9*	*20*	*3,4*	*5,3*	*4,8*
App.digestif	14,3	9,2		13,8	16	14,4
App.cutané	11,2	6,1		13,8	7,5	10,4
App.cardio vascu	10,2	9,2	33	13,8	9,6	14,1
App.respiratoire	9,2	9,2	6,6	0	23,4	7,6
HTAPP	*6,1*	*6,1*	*0*		*11,7*	*4,6*

Annexe 1-56

REPARTITION DES EFFETS INDESIRABLES (%)

	AMFEPRAMONE	DINTEL	FENPROPOREX	INCITAL	PONDERAL	ISOMERIDE
App.endocr et metab	6,1		6,6		3,2	4,2
App.urogénital	3,1	6,1	6,6			4,5
App.sensoriel	2			3,4	4,25	4,8
Sang	1	3,1			3,2	2,9
Divers	10,2			10,3	8,5	10,3
Tératogénèse	2	4,6	6,6			2,2

ANNEXE 3

ISOMERIDE - HYPERTENSION ARTERIELLE PULMONAIRE PRIMITIVE , DYSPNEE POSTERIEURE AU TRAITEMENT

N°	Age Sexe	Poso mg/j	Durée (j)	Description,circonstances	Facteurs associés
)60	42,F	?	240	Hypertension pulmonaire d'allure primitive,revelee par une dyspnee d'effort et des douleurs thoraciques . Pression capillaire élevée . ---------- Diagnostic 9 mois après l' arrêt d' Isoméride . Deces 30mois apres le diagnostic .	110kg pour 1m70 (IMC=38) Hypertension systemique traitee depuis 20ans . Nombreux anorexigenes (DININTEL, TRIACANA,FENPROPOREX,PONDERAL). Contraceptifs oraux .
)60k98 RENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 1)					
00	43,F	30	(365)	Hypertension pulmonaire d'allure primitive,revelee par une dyspnee d'effort.Recherche etiologique negative. Défauts de perfusion à la scintigraphie . ---------- Aggravation et deces 37mois apres le diagnostic.	80kg pour 1m70 (IMC=28) Hypertension systemique (moderee) Contraceptifs oraux
)60s21 RENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 6)					
)85	26,F	30	660 (60)	Hypertension pulmonaire d'allure primitive decouverte lors d'un bilan pre-operatoire et après l' arrêt d' Isoméride . Recherche etiologique negative . ---------- AMELIORATION PARTIELLE 2mois apres le diagnostic .	72kg pour 1m72 (IMC=24) Contraceptifs oraux . Prise contemporaine d' AMFEPRAMONE (préparation magistrale) .
)51j84 ROCHE N et Coll. Pulmonary hypertension and dexfenfluramine . Lancet 1992 ; 339 : 436-437 .					
)61	28,F	?	120	Hypertension pulmonaire d'allure primitive , révélée par une dyspnée d'effort . ---------- Décès 41 mois après le diagnostic .	67kg pour 1m62 (IMC=25) Hypertension gravidique . Grossesse recente . Contraceptifs oraux .
)61063 RENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 9)					
57	33,F	30	210	Hypertension pulmonaire d'allure primitive,revelee par une dyspnee d'effort.Recherche etiologique negative. ---------- Etat stationnaire 10mois apres le diagnostic. Traitement : ADALATE,NEPRESSOL puis LOPRIL,LASILIX . Aggravation et décès 35mois après le diagnostic .	93kg pour 1m64 (IMC=35) Hypertension gravidique Contraceptifs oraux
:N9100067 :N9300189)51r77 (D)					

559

Annexe 1-56

83 P92 Y9206451 51w13(D)	46,F	30 15	240 + 180	Hypertension pulmonaire d'allure primitive découverte lors d'un bilan pré-opératoire . Recherche étiologique négative . --- Etat inchangé 14mois après le diagnostic puis aggravation et décès 25mois après le diagnostic .	87kg pour 1m60 (IMC=34) Hypertension systemique ancienne traitee .
24 Y9100556 51w14 (D)	42,F	30	120 +150	Hypertension pulmonaire d'allure primitive revelee par une dyspnée s'aggravant rapidement . Recherche étiologique négative . --- Etat stationnaire (voire aggrave) 7mois apres le diagnostic . Traitement anticoagulant .	100kg pour 1m50 (IMC=44) Hypertension gravidique . Dyspnée ancienne . Contraceptifs oraux .
34 51z39	53,F	?	?	Hypertension pulmonaire d' allure primitive , révélée par une dyspnée dont l'ancienneté est imprécise mais qui s' aggrave . Bilan négatif (mais angiographie non faite) --- Etat inchangé 28mois après le diagnostic . Traitement : NIDREL puis ALPRESS .	72kg pour 1m59 (IMC=28) . Traitement anti-migraineux au long cours . Hypertension systémique traitée . Ovariectomie . Thyroidectomie . Syndrome de Raynaud . Varices des MI opérées .
92 T9200266 51z61 (D) PPHS (04-92) INCLUS	47,F	30	270	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d'effort et une douleur thoracique . --- Aggravation 17mois après le diagnostic , en attente de transplantation . Traitement par Prostacycline .	98kg pour 1m69 (IMC=34) . Phlébite 2ans auparavant . Pyélonéphrite (anomalie rénale ?) .
67 51z86	41,F	30	180	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d' effort . Angiographie pulmonaire normale . CIA de faible débit . --- AMELIORATION des pressions 15jours après l' arrêt du médicament .	62kg pour 1m56 (IMC=25) . Varices des membres inférieurs . Communication inter-auriculaire .
65 0920943 52090 (D) PPHS (09-92) NON-INCLUS	66,F	30	(500)	Hypertension pulmonaire sans preuve évidente de sa nature primitive , révélée par une dyspnée . Absence d' angiographie pulmonaire . --- Stabilité 3mois après le diagnostic .	81kg pour 1m44 (IMC=39) . Hypertension systémique traitée . Diabète NID (GLUCOPHAGE R) . Coronaropaphie importante justifiant une angioplastie . Pathologie veineuse .
89 B9300105 52288 (D) PPHS (11-92) INCLUS	57,F	?	(1100)	Hypertension pulmonaire d' allure primitive , révélée par une dyspnée , des troubles du rythme et une syncope d' effort . --- Stabilisation 9mois plus tard , sous anticoagulant .	96kg pour 1m56 (IMC=35) Cocktails amaigrissants . Hypertension systémique traitée .

687 840118	28,F	30	90 +90 (R)	Hypertension pulmonaire d' allure primitive révélée par une dyspnée au 5ème mois de grossesse . Recherche étiologique négative . --- Décès dans les suites de la césarienne motivée par le diagnostic . A l' histologie : prolifération fibreuse des branches artérielles de petite taille , artériolite diffuse et microthrombose extensive .	73kg pour 1m55 (IMC=30) Migraine . Contraception orale pendant 8ans . Anticorps anti-cardiolipides .
542 840121 IPPHS INCLUS	45,F	?	(700) + 15	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d'effort . Documentation incomplète (pression capillaire) . --- Absence de recul . Traitement diurétique .	66kg pour 1m58 (IMC=26) . Contraception orale pendant 20ans .
683 PB9300101 840128 BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 7)	54,F (F ou DF ?)	?	(390)	Hypertension pulmonaire d' allure primitive révélée par une dyspnée . --- Décès suite à une aggravation subite 6mois après le diagnostic .	Poids / taille non précisés . Syndrome de Raynaud et migraine .
684 840139 IPPHS (04-93) INCLUS	55,F	?	150	Hypertension pulmonaire d' allure primitive révélée par une décompensation cardiaque en altitude . Recherche étiologique négative mais découverte d'une maladie de Hashimoto . --- Etat stationnaire , 5mois après le diagnostic . Traitement anticoagulant .	105kg pour 1m70 (IMC=36) Hypertension systémique traitée (ADALATE) . Prise d' anorexigènes 15ans auparavant (Fenfluramine ?). Maladie de Hashimoto .
553 DJ94? 840193 (D) GUIARD-SCHMID JB et Coll. Hypertension artérielle pulmonaire et Isoméride . Rev Med Int 1994 ; 15 (Suppl.3) : 423s .	47,F	?	(730)	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d'effort mais bilan incomplet et pression capillaire limite . --- AMELIORATION transitoire 5mois après le diagnostic . Traitement : Nifédipine .	92kg pour 1m54 (IMC=39) Hypertension systémique traitée . Dyslipidémie , diabète .
659 840202 IPPHS (10-93) INCLUS	50,F	30	300 -420	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d'effort dans les suites d'une bronchite . --- Absence de recul . Traitement anticoagulant .	98kg pour 1m70 (IMC=34)

	53,F	30	(900)	Hypertension pulmonaire d'allure primitive révélée par une dyspnée d'effort et associée à une thyroidite auto-immune .	100kg pour 1m64 (IMC=37)
840799				Pas de données d'évolution (cas récent) . Traitement médical : Anticoagulants , Nifédipine , diurétiques.	Thyroidite à auto-anticorps . Hypertension systémique . Psychose maniaco-dépressive ancienne
768	23,F	?	>/=30	Hypertension pulmonaire pré-capillaire stade 3 , sans autre précision .	72kg pour 1m60 (IMC=28)
LY940333 840938 IPPHS (03-93) INCLUS				Greffe mono-pulmonaire 8 mois après le diagnostic .	Contraception orale pendant 5ans . Migraine .

655	36,F	30/60	120	Hypertension pulmonaire d' allure primitive révélée lors du diagnostic étiologique d' une dyspnée ancienne et d' une dysphonie . Recherche étiologique négative . Lésions athéromateuses des artères pulmonaires à l'histologie. --- Aggravation clinique 6mois après le diagnostic . Décès 21mois après le diagnostic .	61kg pour 1m55 (IMC=25) . Dyspnée précédant le début du traitement .
051z40					
BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 11)					
599	46,F	30	180	Hypertension pulmonaire d' allure primitive (données de l' angiographie non disponibles) révélée par une dyspnée et des douleurs à l' effort . Recherche étiologique négative , aspect d'artériopathie plexogénique avec microthromboses à l'histologie . --- Aggravation de la symptomatologie 10mois après le diagnostic . Traitement : Anticoagulants , TRIATEC , LASILIX . Transplantation bi-pulmonaire 25mois après le diagnostic .	78kg pour 1m65 (IMC=29) . Hypertension systémique traitée . Hyperlipidémie . Signes d'hypertrophie ventriculaire droite 7 ans avant le diagnostic .
LL9200138					
051z72 (D)					
BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 13)					
IPPHS (08-91) NON-INCLUS					
584	46,F	30	?	Hypertension pulmonaire d' allure primitive révélée par l' aggravation récente d' une dyspnée et de palpitations précédant le début du traitement . --- AMELIORATION RAPIDE (clinique et échographique) 1 à 2mois après l' arrêt du médicament puis réapparition des signes et à nouveau amélioration .	74kg pour 1m63 (IMC=28) . Dyspnée précédant le traitement . Varices des membres inférieurs opérées . Dépression .
052100					
636	55,M	15-30	70	Hypertension pulmonaire modérée ; révélée par une dyspnée d' effort . Une cardiopathie gauche ne peut être exclue . --- Pas de données d' évolution .	117kg pour 1m72 (IMC=40) . Un bilan cardiovasculaire avait révélé une possible hypertension pulmonaire avant le début du traitement .
052164					
IPPHS (09-92) INCLUS					
580	27,F	15/30	60 (R)	Hypertension pulmonaire d' allure primitive , révélée par une dyspnée et un malaise a l' effort . --- Traitement anticoagulant puis transplantation double monopulmonaire 7mois après le diagnostic . Histologie de type plexiforme .	77kg pour 1m61 (IMC=30) Migraine (MIGWELL) . Dyspnée d'effort depuis l'age de 16ans . Grossesse récente (<1an) .
052556					
699	44,F	30	180	Hypertension pulmonaire modérée , révélée par une dyspnée d' effort croissante . Recherche étiologique négative . --- AMELIORATION immédiate sous diurétiques et RENITEC (mais pas de recul) .	68kg pour 1m68 (IMC=24) Hypertension systémique traitée (LOPRIL puis TENORMINE) .
052597					

8	63,F	30	870	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d'effort.Bilan incomplet (diagnostic echographique). Absence de recul .	59kg pour 1m50 (IMC=26) Nombreux traitements anorexigènes (préparations,extraits thyroidiens.. Fenfluramine). Hypertension systémique traitée . Dyspnée d'effort ancienne .
0166					
5	52,F	?	90	Hypertension pulmonaire d'allure primitive . Peu documentée . Stabilité 2ans après le diagnostic . Traitement médical : ADALATE et SINTROM puis SINTROM seul .	Poids / taille non précisés . Antécédent veineux (chirurgie , phlébite) . Prise (non datée) de fenfluramine .
0377					
	31,F	?	?	Hypertension pulmonaire d'allure primitive révélée par une dyspnée d'effort progressive . Décès 11 mois après le diagnostic .	71kg pour 1m59 (IMC=28) Antécédents inconnus .
0399					
37	46,F	30	150	Hypertension pulmonaire d'allure primitive révélée par une insuffisance cardio-respiratoire . Décés 5mois après le diagnostic .	60kg pour 1m43 (IMC=29) Hypertension systémique . Alvéolite pulmonaire inexpliquée .
9407253					
40430					

HABOT F et Coll. Discordance anatomo-clinique au cours d'une hypertension artérielle pulmonaire primitive .
av Mal Respir 1994 ; 11 (2) : R86 .
PPHS (10-93) NON-INCLUS

Observations recueillies au deuxième semestre 1994

	48,M	30	210	Hypertension pulmonaire associée à un aspect de coeur pulmonaire chronique et d'embolie pulmonaire . Stabilité 16 mois après le diagnostic .	96kg pour 1m65 (IMC=35) Syndrome pulmonaire restrictif (post-traumatique) et obstructif (tabagisme) .
40663					

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Annexe 1-56

PONDERAL - HYPERTENSION ARTERIELLE PULMONAIRE PRIMITIVE , DYSPNEE POSTERIEURE AU TRAITEMENT

N°	Age Sexe	Poso mg/j	Durée (j)	Description,circonstances	Facteurs associés
	43,F	60	730	Hypertension pulmonaire d'allure primitive révélée par une dyspnée d'effort . Ni angiographie , ni scintigraphie pulmonaire .	77kg pour 1m58 (IMC=31) GYNOVLANE
NY9005759 060885				Regression complète dans un premier temps puis aggravation 3ans après le diagnostic . Traitement : Oxygénothérapie et anticoagulant .	
	56,F	60	60	Hypertension pulmonaire d'allure primitive , révélée par une dyspnée notée peu après le début du traitement.	60kg pour 1m47 (IMC=28) Hypertension systémique .
060b52				Aggravation 18mois après le diagnostic . Traitement : DIGOXINE,ALDACTONE,LOPRIL,Anticoagulant.	Prise d' Isomeride après l'arrêt de Ponderal .
	43,F	?	?	Hypertension pulmonaire d'allure primitive , révélée par une dypnée d'effort .	60kg pour 1m57 (IMC=24) Contraception orale .
060r91 BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 4)				Aggravation et décès 48mois après le diagnostic	Prise d' amfepramone .
	68,F	60	(1800)	Hypertension pulmonaire d'allure primitive , révélée par une dyspnée d'effort . Recherche étiologique négative .	68kg pour 1m68 (IMC=24) Prise alternée de TENUATE DOSPAN et d' ANOREX .
051x53 IPPHS INCLUS				Etat stationnaire 8mois après le diagnostic . Traitement Anticoagulant .	Thyroglobuline (hypothyroidie depuis l'age de 16ans. Facteurs rhumatoides positifs .
	35,F	?	?	Hypertension pulmonaire d'allure primitive , révélée en fin de grossesse . Recherche étiologique négative .	69kg pour 1m70 (IMC=24) Anticorps anti-microsomes positifs (confirmé) .
840130 BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 10)				Transplantation coeur-poumons 6mois après le diagnostic . 20mois de recul depuis . Artériopathie plexogénique à l' histologie accompagnée de quelques lésions thrombotiques .	
	65,F	24	?	Hypertension pulmonaire d'allure primitive , révélée par une dyspnée et des oedèmes .	82kg pour 1m60 (IMC=32) Cancer du sein (chirurgie , radiothérapie , chimiothérapie).
840160 IPPHS NON-INCLUS				Décès 18mois après le diagnostic ; aggravation progressive (traitement anticoagulant) . Histologie de type plexogénique .	Hypertension systémique ancienne traitée . Hypothyroidie . Traitements homéopathiques et préparations amaigrissantes (ANOREX ...).

PONDERAL - HYPERTENSION ARTERIELLE PULMONAIRE PRIMITIVE , DYSPNEE ANTERIEURE AU TRAITEMENT OU CHRONOLOGIE INCERTAINE

N°	Age Sexe	Poso mg/j	Durée (j)	Description,circonstances	Facteurs associés
061068	38,F	?	90	Hypertension pulmonaire d'allure primitive révélée par une dyspnée d'effort croissante . Décès 32mois après le diagnostic et en liste d'attente de transplantation depuis 2mois .	Poids et taille non précisés Syndrome de Raynaud primaire Facteur anti-nucléaire (1/20e) Dyspnée d'effort antérieure au traitement .
BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 3)					
051y65	37,F	60 à 120	730	Hypertension pulmonaire d'allure primitive , incomplètement explorée avec des éléments en faveur d'un coeur pulmonaire chronique . Décès accidentel 5mois après le diagnostic .	92kg pour 1m52 (IMC=40) Hypertension systémique Insuffisance respiratoire (fibrose ? désaturation nocturne)
DESJOBERT M et coll. Hypertension arterielle pulmonaire due à la fenfluramine . Rev Mal Respir 1992 ; 9 (Suppl.3) : R165.					
052732 IPPHS (01-93) INCLUS	48,F	90	380	Hypertension pulmonaire d'allure primitive , révélée par une dyspnée d'effort . Recherche étiologique négative . Pas de recul d' évolution . Traitement : anticoagulant et ADALATE .	84kg pour 1m51 (IMC=37) Insuffisance aortique modérée . Fenfluramine en préparation magistrale .
840129 IPPHS NON-INCLUS	52,F	?	?	Hypertension pulmonaire d' allure primitive révélée par une dyspnée d'effort au début imprécis . Stabilité 20mois après le diagnostic . Traitement anticoagulant et Prazosine .	57kg pour 1m58 (IMC=23) . Mise sous anorexigènes de façon quasi continue depuis l'âge de 23ans (85kg) : Phentermine , Clobenzorex , Phendimetrazine , Amfepramone . Migraine . Dépression . Hormonothérapie (PROGYNOVA,DUPHASTON)
BRENOT F et Coll. Primary pulmonary hypertension and fenfluramine use . Br Heart J 1993 ; 70 : 537-41 (Patient N° 12)					
840392	55,F	?	90	Hypertension pulmonaire d' allure primitive révélée à la suite de l'aggravation brutâle d'une dyspnée ancienne . Bilan non documenté . Inscription sur liste d'attente de greffe . Décès (délai) par aggravation progressive .	70kg pour 1m71 (IMC=24) . Hypertension systémique ancienne . Prise d'Amfépramone et de Dexfenfluramine .

DININTEL

SYSTEME RESPIRATOIRE

	MALADE			TRAITEMENT			EFFET INDESIRABLE			
N° DOSSIER	AGE	SEXE	REMARQUES	DOSE	DUREE	TRAIT. ASSOCIE	NATURE	DELAI	EVOL.	C S I
BX 9200590	52	F	HTP post-capillaire	60	1 mois	ISOMERIDE	Hypertension pulmonaire	11 ans apr. arrêt	U	1 1 1
PA 9001961	50	F	H.T.A	30	1 an	LISINOPRIL	Hypertension pulmonaire	1 an	F	1 1 1
PP8990081	42	F	Prep.magistrales		5 ANS	TENUATE DOSPAN (1,1) FRINGANOR (1,1) gelules amaigrissantes	Hypertension pulmonaire	16 ans	D	1 1 1
PB 9300103	52	F		?	?	fenfluramine LINYL FRINGANOR MODERATAN	Hypertension pulmonaire		F	1 1 1
ST 9300295	64	F	H.T.A syndrome de Raynaud	60	10 ans	ISOMERIDE	Hypertension pulmonaire	10 ans		1 1 1
DIN 6	29	M	observation non retenue par l'expert HIV+	60		élixir parégorique TRANXENE EQUANIL GARDENAL NOCTRAN	Hypertension pulmonaire			1 1 1

TENUATE DOSPAN

SYSTEME RESPIRATOIRE

	MALADE			TRAITEMENT			EFFET INDESIRABLE			
N° DOSSIER	AGE	SEXE	REMARQUES	DOSE	DUREE	TRAIT. ASSOCIE	NATURE	DELAI	EVOL.	C S I
NY 8703484	47	F			5 mois	RISORDAN (1,1) LASILIX (1,1)	hypertension pulmonaire	2 mois	D	1 1 1
MP 9202025 = TENU 29	31	F	tabac grossesse	225	6 mois	ALDACTAZINE (1,1) LOPRIL (1,1) PROPOFAN (1,1)	hypertension pulmonaire	2 ans après arrêt	D	1 1 1
PP 8900081	42	F			5 ans	DININTEL (1,1) FRINGANOR (1,1) gelules amaigrissantes: (amfepramone)	hypertension pulmonaire	16 ans	D	1 1 1
PB 9300104	52	F	H.T.A	75	+ mois	PONDERAL (1,1) ISOMERIDE (1,1) amphétamines (1,1)	hypertension pulmonaire	?	F	1 1 1
LY 9300283	44	F	H.T.A dyspnée aggravée observation non retenue par l'expert	0,075	22 j	FLUDEX (1,1) gel.amaigrissantes (1,1)	hypertension pulmonaire	3 ans avant trait.	F	1 1 1

PREPARATIONS MAGISTRALES

SYSTEME RESPIRATOIRE

	MALADE			TRAITEMENT			EFFET INDESIRABLE			
N° DOSSIER	AGE	SEXE	REMARQUES	DOSE	DUREE	TRAIT. ASSOCIE	NATURE	DELAI	EVOL.	C S I
PP8990081	42	F		51		extraits pancreas 900 theophylline 6mg metformine 150 fucus vesiculosus 300mg reine des prés 150mg HAVLANE MEDIATOR	Hypertension pulmonaire		U	1 1 1
MA 8901047	55	F	observation non retenue par l'expert			non précisé	Hypertension pulmonaire			1 1 1

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amfepramone (dc)

SYSTEME RESPIRATOIRE

	MALADE			TRAITEMENT			EFFET INDESIRABLE			
N° DOSSIER	AGE	SEXE	REMARQUES	DOSE	DUREE	TRAIT. ASSOCIE	NATURE	DELAI	EVOL.	C S I
LL 8700069	34	F		75	2 mois		Hypertension Pulmonaire	début trait.	D	1 1 1

Annexe 1-56

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT

Saint-Denis, le 12 Mai 1995

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Cher Confrère,

Une étude internationale, cas/témoin, visant à préciser les facteurs de risque des hypertensions artérielles pulmonaires d'allure primitive, vient de montrer l'existence d'une association entre **la survenue d'hypertension artérielle pulmonaire et la prise d'anorexigènes**.

Le risque de survenue de cet effet indésirable, dont vous connaissez la gravité du fait de son évolution le plus souvent fatale, augmente lorsque la durée du traitement dépasse trois mois ou lorsque les anorexigènes sont prescrits en association.

L'Agence du Médicament a donc décidé, sur proposition de la Commission Nationale de Pharmacovigilance et en accord avec les firmes commercialisant des spécialités contenant ces principes actifs* de :

- limiter l'indication de ces produits au traitement des obésités patentes des patients dont l'indice de masse corporelle est supérieur à 30, constituant un facteur de risque cardiovasculaire grave,
- limiter à 3 mois les durées cumulatives de traitement,
- contre-indiquer leur association.

Le rapport bénéfice/risque de ces traitements, dans la prise en charge thérapeutique globale de l'obésité, est en cours de réévaluation par l'Agence du Médicament qui prendra si nécessaire d'autres mesures complémentaires. Parallèlement, le Ministère chargé de la santé engage la procédure nécessaire pour interdire l'utilisation des substances anorexigènes dans les préparations magistrales.

Dès à présent, nous vous demandons d'assurer le strict respect de ces nouvelles règles, tant à l'occasion de la prescription que de la délivrance, en les expliquant aux patients afin d'en empêcher toute utilisation en dehors des modalités pré-citées.

Veuillez agréer, Cher Confrère, l'expression de ma considération distinguée.

Pr J.M. ALEXANDRE
Directeur de l'Evaluation

*Liste des principes actifs contenus dans les spécialités suivantes : amfépramone[1], clobenzorex[2], dexfenfluramine[3], fenfluramine[4], fenproporex[5], mefenorex[6].

1 ANOREX® (Laboratoire CRINEX)
MODERATAN® (Laboratoire THERANOL-DEGLAUDE)
PREFAMONE® (Laboratoire DEXO)
TENUATE DOSPAN® (Laboratoire MARION MERRELL DOW)
2 DININTEL® (Laboratoire DIAMANT)
3 ISOMERIDE® (Laboratoire ARDIX)
4 PONDERAL® (Laboratoire BIOPHARMA)
5 FENPROPOREX ACTION PROLONGEE DEGLAUDE® (Laboratoire THERANOL-DEGLAUDE)
6 INCITAL® (Laboratoire PIERRE FABRE SANTE)

Indice de masse corporelle = poids en kg/(taille en m)^2

Agence du Médicament : 07.38.07.77

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex Tel 48 13 20 00

AGENCE DU MEDICAMENT

RÉPUBLIQUE FRANÇAISE
DIRECTION GENERALE DE LA SANTE

16 MAI 1995

AVIS AUX PRESCRIPTEURS

La Commission Nationale de Pharmacovigilance réunie le 03/05/95 a pris connaissance des résultats d'une étude épidémiologique internationale sur l'Hypertension Artérielle Pulmonaire Primitive.

Cette étude montre qu'il existe une association entre la survenue de ces Hypertensions Pulmonaires et la prise de tout anorexigène* pour une durée de traitement supérieure à 3 mois.

Les résultats sont confirmés par la notification spontanée des Hypertensions Pulmonaires au système national de Pharmacovigilance.
Cette pathologie est de fréquence très faible mais de gravité extrême compte tenu de son évolution fatale. En conséquence, sur proposition de la Commission Nationale de Pharmacovigilance, l'Agence du Médicament a décidé de :

- restreindre l'indication au traitement de seconde intention, après échec d'un traitement diététique adapté, d'obésité patente avec indice de masse corporelle supérieur à 30.

- limiter la durée d'utilisation à 3 mois.

- de contre-indiquer leur association.

Parallèlement, un arrêté du ministre chargé de la santé interdit l'exécution et la délivrance de préparations magistrales et autres préparations à base de substances anorexigènes.

Un nouvel examen du rapport bénéfice/risque par la Commission Nationale de Pharmacovigilance aura lieu en Juin sur la base d'études complémentaires en cours.

Le Comité des Spécialités Pharmaceutiques de l'Agence Européenne (E.M.E.A.) a été saisi du problème.

* contenus dans les spécialités suivantes :

1° - ISOMERIDE® (dexfenfluramine) (laboratoires ARDIX)
2° - PONDERAL® (fenfluramine) (laboratoires BIOPHARMA)
3° - ANOREX® (amfepramone) (laboratoires CRINEX)
MODERATAN®amfepramone) (laboratoires THERANOL-DEGLAUDE)
PREFAMONE® (amfepramone) (laboratoires DEXO)
TENUATE DOSPAN® (amfepramone) (laboratoires MARION MERRELL DOW)
4° - DININTEL® (clobenzorex) (laboratoires DIAMANT)
5° FENPROPOREX ACTION PROLONGEE DEGLAUDE® (fenproporex) (laboratoires THERANOL-DEGLAUDE)
6° - INCITAL® (mefenorex) (laboratoires PIERRE FABRE SANTE)

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. 48.13.20.00

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MINISTÈRE DES AFFAIRES SOCIALES,
DE LA SANTÉ ET DE LA VILLE

16 MAI 1995

DIRECTION GÉNÉRALE DE LA SANTE

Direction Générale de la San...
S/Direction de la Pharmacie
Annexe 1-57
17 MAI 1995
COURRIER ARRIVÉE

AGENCE DU MÉDICAMENT

COMMUNIQUÉ DE PRESSE

Une étude épidémiologique internationale a récemment mis en évidence une relation entre la survenue de quelques cas de maladie vasculaire pulmonaire grave et souvent mortelle et la prise prolongée de médicaments anorexigènes (coupe-faim). Il s'agit des médicaments suivants :

Médicament	Laboratoire	Principe actif
ISOMERIDE	Laboratoires ARDIX	dexfenfluramine
PONDERAL	Laboratoires BIOPHARMA	fenfluramine
MODERATAN DIFFUCAP	Laboratoires THERANOL-DEGLAUDE	amfépramone
TENUATE D'OSPAN	Laboratoires MARION MERREL DOW	amfépramone
ANOREX	Laboratoires CRINEX	amfépramone
PREFAMONE	Laboratoires DEXO	amfépramone
FENPROPOREX ACTION PROLONGEE DEGLAUDE	Laboratoires THERANOL-DEGLAUDE	fenproporex
DININTEL	Laboratoires DIAMANT	clobenzorex
INCITAL	Laboratoires PIERRE FABRE SANTE	mefenorex

Ces principes actifs sont également présents dans certaines préparations magistrales à visée amaigrissante préparées en pharmacie, sur ordonnance.

Compte tenu de la gravité de cet effet indésirable, le directeur général de l'Agence du médicament a décidé, sur proposition de la Commission nationale de pharmacovigilance, de réserver ces spécialités aux obésités majeures répondant à des critères médicaux stricts, pour des durées de traitements inférieures à trois mois et uniquement après échec d'un traitement diététique adapté.

L'Agence du médicament rappelle que ces produits ne doivent en aucun cas être utilisés à des fins esthétiques.

Un nouvel examen du rapport bénéfice/risque par la Commission national de pharmacovigilance aura lieu en juin, sur la base d'études complémentaires en cours.

Parallèlement, un arrêté du ministre chargé de la santé interdit l'exécution et la délivrance de préparations magistrales et autres préparations à base de substances anorexigènes.

Pour toute information complémentaire, l'Agence du médicament met à disposition les numéros suivants : **48 13 22 99 et 48 13 23 14**

TOTAL PAGE(S) 01

« Norvège : yrkesmedisin.
« Suède : yrkesmedicin.

« Maladies rénales :

« Finlande : nefrologia, nefrologi.
« Islande : nýrnalækningar.
« Norvège : nyresykdommer.
« Suède : medicinska njursjukdomar (nefrologi).

« Neurochirurgie :

« Autriche : Neurochirurgie.
« Finlande : neurokirurgia, neurokirurgi.
« Islande : taugaskurðlækningar.
« Norvège : nevrokirurgi.
« Suède : neurokirurgi.

« Neurologie :

« Autriche : Neurologie.
« Finlande : neurologia, neurologi.
« Islande : taugalækningar.
« Norvège : nevrologi.
« Suède : nervsjukdomar (neurologi).

« Radiothérapie :

« Autriche : Radiologie-Strahlentherapie.
« Finlande : syöpätaudit ja sädehoito, cancersjukdomar och radioterapi.
« Norvège : onkologi.
« Suède : tumörsjukdomar (allmän onkologi).

« Ophtalmologie :

« Autriche : Augenheilkunde.
« Finlande : silmätaudit, ögonsjukdomar.
« Islande : augnlækningar.
« Norvège : oyesykdommer.
« Suède : ögonsjukdomar (oftalmologi).

« Oto-rhino-laryngologie :

« Autriche : Hals-, Nasen-und Ohrenkrankheiten.
« Finlande : korva-, nenä- ja kurkkutaudit, öron-, näs- och strupsjukdomar.
« Islande : háls-, nef- og eynalækningar.
« Norvège : ore-nese-halssykdommer.
« Suède : öron-, näs- och halssjukdomar (oto-rhino-laryngologi).

« Cardiologie :

« Finlande : kardiologia, kardiologi.
« Islande : hjartalækningar.
« Norvège : hjertesykdommer.
« Suède : hjärtsjukdomar.

« Pédiatrie :

« Autriche : Kinderheilkunde.
« Finlande : lastentaudit, barnsjukdomar.
« Islande : barnalækningar.
« Norvège : barnesykdommer.
« Suède : barnaålderns invärtes sjukdomar (pediatrik).

« Médecine des voies respiratoires :

« Autriche : Lungenkrankheiten.
« Finlande : keuhkosairaudet, lungsjukdomar.
« Islande : lungnalækningar.
« Norvège : lungesykdommer.
« Suède : lungsjukdomar (pneumologi).

« Psychiatrie :

« Autriche : Psychiatrie.
« Finlande : psykiatria, psykiatri.
« Finlande : geðlækningar.
« Norvège : psykiatri.
« Suède : allmän psykiatri.

« Radiodiagnostic :

« Autriche : Radiologie-Diagnostik.
« Finlande : radiologia, radiologi.
« Suède : röntgendiagnostik.

« Physiothérapie :

« Autriche : Physikalische Medizin.
« Finlande : fysiatria, fysiatri.
« Islande : orku- og endurhæfingarlækningar.
« Norvège : fysikalsk medisin og rehabilitering.
« Suède : medicinsk rehabilitering.

« Rhumatologie :

« Finlande : reumatologia, reumatologi.
« Islande : gigtlækningar.
« Norvège : revmatologi.
« Suède : reumatiska sjukdomar.

« Community medicine :

« Autriche : Sozialmedizin.
« Finlande : terveydenhuolto, hälsovard.
« Islande : embættislækningar.
« Norvège : samfunnsmedisin. »

Arrêté du 2 mai 1995 désignant le préfet de région chargé de l'organisation des épreuves nationales d'admissibilité du concours de l'internat en pharmacie

NOR : *SANH9501564A*

Le ministre de l'enseignement supérieur et de la recherche et le ministre délégué à la santé, porte-parole du Gouvernement,

Vu la loi n° 68-978 du 12 novembre 1968 modifiée d'orientation de l'enseignement supérieur ;

Vu le décret n° 89-739 du 12 octobre 1989 relatif aux concours de l'internat en pharmacie ;

Vu l'arrêté du 18 novembre 1983 modifié portant création du Centre national des concours d'internat ;

Vu l'arrêté du 17 juillet 1987 modifié relatif au régime des études en vue du diplôme d'Etat de docteur en pharmacie ;

Vu l'arrêté du 12 octobre 1989 modifié relatif à l'organisation des concours d'internat en pharmacie,

Arrêtent :

Art. 1er. – Conformément aux dispositions de l'article 1er de l'arrêté du 12 octobre 1989 susvisé, l'organisation des épreuves nationales d'admissibilité est placée sous la responsabilité du préfet de la région Ile-de-France.

Art. 2. – Le directeur général de l'enseignement supérieur et le directeur des hôpitaux sont chargés, chacun en ce qui le concerne, de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 2 mai 1995.

Le ministre délégué à la santé,
porte-parole du Gouvernement,
Pour le ministre et par délégation :
Par empêchement du chef de service :
Le sous-directeur
des personnels médicaux hospitaliers,
B. BOUQUET

Le ministre de l'enseignement supérieur
et de la recherche,
Pour le ministre et par délégation :
Par empêchement du directeur général
des enseignements supérieurs :
Le sous-directeur,
S. FRANÇOIS

Arrêté du 10 mai 1995 portant interdiction de l'exécution et de la délivrance de préparations magistrales ou autres préparations à base de certains principes actifs

NOR : *SANP9501560A*

Le ministre délégué à la santé, porte-parole du Gouvernement,

Vu le code de la santé publique, et notamment ses articles L. 605 (10°), R. 5144-9 et R. 5179 ;

Considérant qu'une étude épidémiologique internationale a mis en évidence une relation entre la survenue d'une maladie vasculaire pulmonaire grave et souvent mortelle et la prise prolongée de médicaments anorexigènes ;

Considérant l'avis de la Commission nationale de pharmacovigilance du 3 mai 1995,

Arrête :

Art. 1er. – Sont interdites, à compter de la date de publication du présent arrêté, l'exécution et la délivrance de préparations magistrales ou autres préparations à base des principes actifs suivants :

- dexfenfluramine ;
- fenfluramine ;
- amfépramone ;
- fenproporex ;
- clobenzorex ;
- mefenorex.

Art. 2. – Le directeur général de la santé est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 10 mai 1995.

Pour le ministre et par délégation :
Le directeur général de la santé,
J.-F. GIRARD

Sente
Theme principal
Groupe ad hoc

Annexe 1-59

REUNION ISOMERIDE - ANOREXIGENES
du 29 mai 1995

Mme le Docteur Arlette MOSSE Endocrino Diabeto Nutritionniste	54 boulevard du Général Leclerc 92200 NEUILLY SUR SEINE Centre cardiologique du Nord CCN SAINT DENIS	Tél : 47.22.03.14 Fax : 47.22.03.14 Tél : 49.33.41.41 ~~1 33 41 42~~
Mr le Professeur Patrick VEXIAU //	Hôpital Saint-Louis - Trèfle 4 1 avenue Claude Vellefaux 75010 PARIS	Tél : 42.49.96.88 (direct) Fax : 42.49.41.78
Mr le Docteur Thierry LEBLANC abs	Hôpital Saint-Louis - Trèfle 4 1 avenue Claude Vellefaux 75010 PARIS	Tél : 42.49.90.70 (direct) Fax : 42.49.41.78
Mr le Professeur Paul VALENSY //	Hôpital Jean Verdier Service du Prof. Attali Avenue du 14 Juillet 93143 BONDY CEDEX BOBIGNY	Tél : 48.02.65.92 (direct) ou 65.80 Fax : 48.02.65.79
Mr le Professeur LUBETZKI //	Hôpital Lariboisière Service Médecine B 2 rue Ambroise 75010 PARIS	Tél : 49.95.63.66 (63.71) Fax : 49.95.63.93
Mr le Docteur Henri SALTIEL //	25 bis rue Franklin 75116 PARIS	Tél : 47.04.71.96
Mr le Professeur Serge HERSON	Hôpital Pitié Salpétrière Service Médecine Interne Boulevard de l'Hôpital 75013 PARIS	Tél : 42.16.10.52 Fax : 42-16-10-58
Mr le Docteur CARLIER HG CNPV		Tél : 40.05.43.34 Fax : 69.41.25.83

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le 06 OCT 1995

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COMMISSION NATIONALE DE PHARMACOVIGILANCE
(PROCES-VERBAL DE LA REUNION DU 19 JUIN 1995)

Etaient présents :

M. IMBS : Président, M. HUGUES : Vice-Président,
M. BAUMELOU, M. BEGAUD, M. CARLIER, M. CARON, Mme CHICHMANIAN, M. EVREUX, M. GHISLAIN, M. GUIZE, Mme JOUAN-FLAHAULT, Mme JOUGLARD, M. THEVENEAU (suppléant de M. LABOURE), Mme ALBENGRES (suppléante de M. MERLE), M. MOORE (suppléant de M. MOULIN), M. PAUL, M. CHOISY, Mme SOUBRIE, Mme GOUJARD (représentant Monsieur le Directeur Général de l'INSERM), Mme BARON (représentant Monsieur le Directeur Général de la Santé), M. ALEXANDRE (représentant M. le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Assistaient à la réunion :

M. AMEDEE-MANESME
Mme BIVAS
M. CAULIN
M. LE COURTOIS
Mme MALOTAUX
Mme TISSIER

Unité de Pharmacovigilance :

Mme CASTOT
Mme LE BELLER
Mme LEREBOURS
Mme MORIN

Rapporteurs à la Commission :

Mme BAVOUX, Mme ELEFANT, Mme SOUBRIE, M. VIAL.

Experts :

M. APFELBAUM,
M. DUROUX,
M. GUY-GRAND,
M. HERSON,
M. LUBETSKY,
Mme MOSSE,
M. RODOR
M. SALTIEL,
M. BRENOT,
M. VALENSI,
M. VEXIAU,
M. WEIZENBLUM

Laboratoires :

ARDIX et BIOPHARMA :	M. HALIMI, Mme LAUDIGNON, M. de LAVENNE, Mme NATHAN, M. PERRET, M. WAGNIART
CRINEX :	M. BERGOGNE, Mme LEBRE
DEXO :	Mme GUERY
DIAMANT :	Mme AZOULAY, M. MATON, Mme VINCENT du LAURIER
LIPHA :	Mme BELLEVEGUE, M. MOSNIER, M. SCHMITT
MARION MERRELL DOW :	M. CANAVATE, Mme PRAYER
MENARINI :	M. SCHMITT pour M. BERTRAND
PIERRE FABRE SANTE :	M. DERQUENNE, M. RICARD
THERABEL :	M. MAS
THERANOL-DEGLAUDE :	M. BRUNEL, Mme LAGENTE, Mme SARTRE
WELLCOME :	Mme SAINTE CROIX LE BALEUR

Experts auprès des firmes (anorexigènes) :

M. CHARPENTIER
M. DANAN
M. FLAHAULT

Etaient excusés :

M. ANKRI, M. CHAST, M. DUPUIS, M. LARREY, M. LECOMPTE, M. LENOIR, M. LEVERGE, M. MUNERA, M. NETTER, M. ROUJEAU, M. le Directeur des Hôpitaux ou son représentant.

Annexe 1-60

I – ANOREXIGENES ET HYPERTENSION ARTERIELLE PULMONAIRE PRIMITIVE

La Commission Nationale de Pharmacovigilance a réexaminé le dossier relatif aux anorexigènes. Lors de la réunion du 3 mai 1995, les membres s'étaient jugés insuffisamment documentés sur le bénéfice de ces produits et avaient demandé à ce qu'il soit évalué en fonction des données disponibles.

Le directeur de l'évaluation a rappelé en préambule que ce dossier faisait l'objet d'un article 12 au niveau européen (sujet d'intérêt communautaire). Les conclusions de la réunion du Groupe de Travail Pharmacovigilance du C.S.P. du 2 Juin 1995 ont été communiquées aux membres de la Commission par le secrétariat de l'Unité de Pharmacovigilance.

1) Le bénéfice thérapeutique

Un groupe d'experts nutritionnistes/endocrinologistes nommés par la DEV s'est réuni, en présence du Président de la Commission Nationale de Pharmacovigilance le 29 Mai 1995, afin de définir la place des anorexigènes dans la prise en charge globale de l'obésité, à la lumière des études fournies par les firmes pharmaceutiques ; celles-ci ont été entendues le 30 Mai 1995.
Un rapport d'évaluation destinée aux Etats membres de l'Union Européenne a été rédigé et remis pour information à chaque membre de la Commission Nationale.

Ces rapporteurs affirment que l'obésité sévère constitue un facteur de risque cardio-vasculaire certain, direct ou indirect (hypertension artérielle, anomalies métaboliques...) et augmente la morbidité et la mortalité.
L'objectif d'un traitement est de diminuer de manière cliniquement significative (soit de 5% à 10% du poids initial) et durable le poids, les facteurs de risque associés s'en trouvant améliorés.
Actuellement, il n'existe cependant aucune étude démontrant un bénéfice direct des traitements de l'obésité en terme de morbidité/mortalité.

Les experts estiment que les traitements court terme ne sont pas justifiés dans une prise en charge globale de l'obésité. Dans ces conditions, les études disponibles montrent une perte pondérale modeste d'en moyenne de 3 à 4 kg seulement. A l'arrêt du traitement, le retour du poids initial se fait rapidement. Les rapporteurs estiment que cette demande n'initie jamais, comme un "starter", une perte de poids prolongée. Seul un traitement prolongé, s'il était possible, pourrait avoir un bénéfice à long terme.

Les anorexigènes "amphétamine-like"

Les experts ont analysé les études fournies par les laboratoires commercialisant les anorexigènes amphétamine-like. Elles objectivent une perte pondérale de 3 à 4 kg lors de durée d'utilisation de 3 mois en moyenne. Aucune étude suivant une méthodologie rigoureuse (contrôlée, en double aveugle) et avec un nombre suffisant de patients n'est disponible.

Les anorexigènes sérotoninergiques

Les experts ont étudiés l'analyse en terme de répondeurs et non-répondeurs de l'étude INDEX (étude internationale contrôlée en double aveugle de 1 an) fournie par les laboratoires commercialisant les fenfluramines. Le nombre de répondeurs définis par une perte de poids supérieure à 10 % du poids initial est 2 fois plus élevé chez les patients traités par dexfenfluramine que chez les patients recevant un placebo.

Les experts ont étudiés les réponses thérapeutiques enregistrées au cours du deuxième mois de traitement (perte de 1.8 kg en moyenne) qui permettraient de prévoir en partie les répondeurs (patients qui perdront 10 % de leur poids initial au court du traitement). L'importance de la perte pondérale notée au quatrième mois permettrait de recruter avec une plus grande précision l'ensemble des patients répondeurs : parmi les patients qui présentent une perte de poids d'au moins 10 % du poids initial, plus de 80 % le maintiendront à 12 mois.

2) le risque

Les experts pneumologues de l'hôpital Antoine-Béclère ont communiqué officiellement un bilan global de l'expérience de leur établissement concernant les hypertensions artérielles pulmonaires (HTAP) suivies entre 1984 et 1995 : 326 HTAP ont ainsi été répertoriées dont 67 associées à la prise d'un anorexigène.

Le Président de la Commission Nationale de Pharmacovigilance a fait état de plusieurs courriers adressés à l'Agence du Médicament par les pharmaciens responsables de plusieurs firmes. Certaines demandent que les observations françaises des anorexigènes amphétamine-like soient à nouveau revues sur le plan de l'imputation avec le CRPV de Besançon responsable de l'enquête nationale, d'autres soulèvent des questions quant aux modalités de l'analyse de l'étude IPPHS.

Les dossiers français pourront être revus avec le CRPV de Besançon si les laboratoires en font la demande.

Les questions relatives à l'étude IPPHS ont été examinées, en présence de plusieurs membres du Comité Scientifiques de l'étude mais en l'absence du Pr Abenhaim, coordinateur de l'étude, excusé.

3) Gestion du rapport bénéfice/risque

L'obésité est une pathologie chronique dont la prise en charge doit être globale et prolongée. Les traitements brefs dits "starter" ne sont pas efficaces.
Pour ce qui concerne la prise en compte du risque, la pratique d'un échodoppler ne garantit pas la détection précoce d'une HTAP, de plus l'arrêt du traitement en cas de d'HTAP modérée n'entraîne pas systématiquement la réversibilité de la symptomatologie.

4) Audition des firmes

4-1 les anorexigènes "amphétamine-like"

Les firmes commercialisant les anorexigènes amphétamine-like ont reformulé des questions à propos de l'étude IPPHS. Elle seront transmises au Pr Abenhaim. L'administration s'engage à fournir les réponses aux laboratoires concernés.

Les firmes proposent de mener une étude court terme (3 mois) pour démontrer l'efficacité de leurs produits prescrits en seconde intention en soutien d'un régime hygiéno-diététique.

4-2 les anorexigènes sérotoninergiques

Les laboratoires commercialisant les fenfluramines ont présenté les résultats de l'étude Index en terme de répondeurs . Le niveau d'efficacité était fixé à une perte de 10% du poids initial. Une réponse au cours des premiers mois serait prédictive d'une perte de poids de 10% sous traitement.

La firme propose une prescription de ces produits par des spécialistes, associée aux mesures diététiques, chez des patients répondeurs définis dès les premiers mois de traitement, avec analyse de la morbi-mortalité à long terme chez les patients traités.

5) Conclusion

Après cette audition des firmes pharmaceutiques, la Commission Nationale de Pharmacovigilance a proposé la suspension des anorexigènes amphétamine-like. Leur potentiel de pharmacodépendance ne permet pas d'en envisager la prescription pour des périodes longues et ce d'autant qu'aucune étude à long-terme sur un nombre suffisant de patients n'a été conduite.
Les fenfluramines pourraient être prescrite dans le cadre d'une prise en charge globale de l'obésité, après échec du traitement hygiéno-diététique en milieu hospitalier spécialisé :

- à long terme chez des patients répondeurs présentant un BMI $\geq$ 30 caractérisés comme répondeurs, au terme d'un traitement de 1 ou 2 mois ;
- ayant donné leur consentement éclairé.

Les Résumés des Caractéristiques devront comporter des mises en garde sur le risque de survenue accru d'hypertension artérielle pulmonaire lors des traitements prolongés (plus de 3 mois).

Ces mesures devront s'accompagner d'une étude d'efficacité en terme de morbi-mortalité de phase IV, menée avec les fenfluramines.

Les membres de la Commission ont demandé qu'un comité de pilotage soit créé pour cette étude et que les futurs prescripteurs soient sensibilisés à la notification des effets indésirables aux Centres Régionaux de Pharmacovigilance.

Pour ce qui concerne les préparations magistrales, la Commission Nationale de Pharmacovigilance souhaite étendre l'interdiction des préparations magistrales du 10 Mai 1995 à l'ensemble des principes actifs figurant dans la liste 3 de la loi Talon (Décret n° 82-253 du 16 Mars 1982 donné en annexe).

Annexe 1-60

II – ENQUETE OFFICIELLE SUR L'HEPATOTOXICITE DES FORMES ORALES DES SPECIALITES CONTENANT DU NAFTIDROFURYL

Dans le cadre de la réévaluation du rapport bénéfice/risque du naftidrofuryl, une enquête officielle de pharmacovigilance sur les effets indésirables hépatiques, lors de l'administration par voie orale des spécialités PRAXILENE® 200 mg, PRAXILENE® 100 mg, GEVATRAN® 200 mg LP, DI-ACTANE® 200 mg LP, NAFTILUX® 200 mg LP, a été confiée au Centre Régional de Pharmacovigilance de Lyon.

1. Données de pharmacovigilance :

De 1985 à fin 1994, parmi les 44 observations d'atteinte hépatique retenues, une seule décrit une réadministration positive chez une femme de 67 ans, probablement atteinte de la maladie de Gilbert. Le type d'atteinte paraît homogène (cytolyse hépatique dans 70% des cas) et d'évolution généralement favorable. La majorité des observations comporte des médicaments associés et l'incidence de l'ensemble des cas est très faible.

2. Données complémentaires :

Au niveau international, le laboratoire LIPHA rapporte 9 observations d'atteintes hépatiques, peu documentées dont une d'évolution fatale, chez des patients ayant reçu du naftidrofuryl.

La tolérance du naftidrofuryl (sous sa forme fumarate) a été évaluée dans le cadre d'un essai clinique comparativement à celle d'un placebo, lors d'un traitement de 180 jours, et aucune différence significative n'a été mise en évidence entre les deux groupes de traitement.

Lors de l'administration par voie injectable, la responsabilité du naftidrofuryl peut être évoquée dans 3 cas (avec un traitement associé de même imputabilité) recueillis par le système national de pharmacovigilance.
Dans la littérature, deux observations d'atteinte hépatique cytolytique aiguë ont été décrites.

3. Conclusions :

Au vu de ces données, les arguments en faveur de l'hépatotoxicité du naftidrofuryl ne paraissent pas décisifs. La Commission nationale de pharmacovigilance propose donc de ne pas mentionner les atteintes hépatiques dans les effets indésirables du naftidrofuryl par voie orale.

III - ACICLOVIR ET GROSSESSE

La Commission nationale de pharmacovigilance a pris connaissance des résultats de l'enquête officielle sur l'évaluation du risque éventuel d'exposition à l'aciclovir pendant la grossesse et l'attitude à adopter face à une prise d'aciclovir chez une femme enceinte.

Menée par le centre régional de pharmacovigilance de Lyon en collaboration avec les centres de Paris Saint-Vincent-de-Paul et Paris La Pitié-Salpêtrière prenant en compte les données des CRPV ainsi que celles du centre de renseignement sur les agents tératogènes (CRAT) et des laboratoires Wellcome, cette étude s'étend de 1985 à fin 1992 et distingue les cas dits "prospectifs" (suivi systématique de l'évolution de la grossesse après prise d'aciclovir) des cas rétrospectifs (notification enregistrée alors que l'évolution de la grossesse est connue chez des femmes ayant été traitées par aciclovir).

1/ Bilan de l'enquête :

L'analyse des 188 dossiers, d'évolution connue, n'a pas montré d'augmentation :
- du nombre d'interruption volontaire ou thérapeutique de grossesse (par rapport aux données DGS-INSERM),
- du nombre de fausses couches spontanées (par rapport au groupe témoin d'une étude sur la fluoxétine)
- ni du taux de malformation de 3,9% (par rapport au taux de base de la population générale estimé à 3%). Les quelques malformations observées, dans les dossiers prospectifs et rétrospectifs, touchent des appareils différents et n'évoquent donc pas un syndrome malformatif homogène et spécifique.

Le nombre de cas est trop faible pour mettre en évidence un effet délétère des formes topiques, à très faible passage systémique, utilisées au cours de la grossesse.

2/ Registre international :

Les données issues du registre international des laboratoires Wellcome concernant le suivi "prospectif" de 1117 grossesses exposées à un traitement par aciclovir sont comparables aux résultats de l'enquête.

3/ Conclusions :

L'ensemble des données n'a pas mis en évidence d'augmentation du risque malformatif ou foetotoxique, notamment après une exposition lors du premier trimestre ou en fin de grossesse. Il paraît donc possible d'être rassurant face à une prise accidentelle d'aciclovir au cours de la grossesse.

Cependant les effectifs sont trop limités pour qu'une augmentation faible du risque de malformation soit détectable ; d'autre part, les données n'ont pas été comparées à un groupe témoin issu de la même population, mais à celles observées dans la population générale. Enfin, cette enquête n'a pas évalué les éventuels effets délétères à long terme, notamment une altération potentielle de la fonction immunitaire suggérée par des études chez l'animal. Il apparait donc important de rappeler que seul l'herpès systémique grave justifie la mise en place d'un traitement par l'aciclovir chez la femme enceinte.
La Commission nationale de pharmacovigilance propose une rédaction plus informative et plus rassurante du libellé de la rubrique "grossesse et allaitement" du résumé des caractéristiques du produit.

Annexe 1-60

IV – RELEVE D'AVIS

La procédure des relevés d'avis, suite au Comité Technique, est entérinée par la Commission nationale de pharmacovigilance. Les dossiers de demande de modification de l'information médicale seront dorénavant présentés aux membres de la Commission nationale de pharmacovigilance sous forme de relevé d'avis suite au Comité technique. Ces avis, avec le rapport technique, seront adressés aux membres avant la Commission nationale. Ils seront validés ou modifiés lors de la réunion de la Commission.

A – DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE TRIATEC® FAIBLE 1,25mg, TRIATEC® 2,5mg, TRIATEC® 5mg (ramipril) (Laboratoires HOECHST)

Considérant :

- les notifications d'effets indésirables au système national de pharmacovigilance, les déclarations obligatoires de la firme et les données de la littérature,
- la rareté de survenue d'érythème polymorphe et de purpura vasculaire sous ramipril,

la Commission nationale de pharmacovigilance du 19/06/95 a approuvé le relevé d'avis suite au Comité technique du 18/05/95, soit :

Ajouter

– à la rubrique "Précautions d'Emploi" : hémodialyse : des réactions anaphylactoïdes (oedème de la langue et des lèvres avec dyspnée et baisse tensionnelle) ont été observées au cours de l'hémodialyse utilisant des membranes de haute perméabilité (polyacrylonitrile) chez des patients traités par inhibiteurs de l'enzyme de conversion. Il est prudent d'éviter cette association. *"Des réactions similaires ont été observées au cours de LDL aphérèses sur sulfate de dextran".*

– à la rubrique "Effets indésirables" :
Effets digestifs *"une augmentation des enzymes hépatiques a été notée dans des cas isolés, associée exceptionnellement à une hépatite cholestatique ou mixte, nécessitant l'arrêt du traitement".*
Effets respiratoires : toux, *"et plus rarement bronchospasme".*
Effets allergiques et cutanés : prurit, *"éruption cutanée maculopapuleuse ou urticarienne, flush, et exceptionnellement : dermatose lichénoïde ou psoriasiforme".*

B – DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE CEPOREXINE® 125 mg granulés en sachet, CEPOREXINE® 250 mg granulés en sachet, CEPOREXINE® 250 mg granulés pour suspension buvable, CEPOREXINE® 500 mg gélules, CEPOREXINE® 1000 mg comprimés enrobés sécables (cefalexine) (Laboratoires GLAXO)

Considérant :

- la possibilité de survenue de colites pseudo-membraneuses lors de traitement par cefalexine,
- que l'innocuité de la cefalexine n'a pas été établie durant la grossesse,
- les effets indésirables collectés par le système national de pharmacovigilance et le laboratoire,
- la dialysance de ce médicament,

La Commission nationale de pharmacovigilance du 19/06/95 a approuvé le relevé d'avis suite au Comité technique du 02/03/95, sous réserve d'une modification de forme :

Remplacer de la phrase "il a été convenu qu'un paragraphe mentionnant la dialysance de la cefalexine soit ajouté à la rubrique Pharmacocinétique." par

"il a été convenu que le paragraphe mentionnant la dialysance de la céfalexine soit déplacé à la rubrique Pharmacocinétique."

C - DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE SPORANOX® (itraconazole) (Laboratoires JANSSEN)

Au vu des données de pharmacovigilance et des résultats des études pharmacocinétiques, expérimentales ou sur volontaires sains, la Commission nationale de pharmacovigilance du 19/06/95 a approuvé le relevé d'avis du Comité technique du 18/05/95, il est nécessaire d'inclure les effets indésirables de type oedème de Quincke, syndrome de Stevens-Johnson, ainsi que la possibilité de survenue d'oedème, hépatites et neuropathies périphériques lors de traitements prolongés. Une surveillance du bilan hépatique est préconisée lors des traitements de plus d'un mois.

Suite à des études pharmacocinétiques et de pharmacologie clinique, de nouvelles associations contre-indiquées sont à mentionner : avec l'astémizole, le cisapride et le triazolam.
L'association avec le midazolam est à déconseiller.

Une mise en garde concernant l'hépatotoxicité apparaît nécessaire ainsi que des précautions d'emploi, lors d'associations avec la didanosine, les anti-acides, les antagonistes calciques de la famille des dihydropyridines, les quinidiniques dont hydroquinidine, les anticoagulants oraux.

D - DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE PRESTOLE® (triamtérène, hydrochlorothiazide) (Laboratoires SMITHKLINE BEECHAM)

Considérant :

- qu'afin d'éviter une hyperkaliémie, une précaution d'emploi est nécessaire lors d'association avec les inhibiteurs de l'enzyme de conversion,
- qu'il n'est pas établi qu'une association de type PRESTOLE® présente des risques de troubles du rythme,
- que la survenue de calculs riches en triamtérène est un argument en faveur d'un potentiel lithogène,
- que la survenue d'effets indésirables à type de modification de la formule sanguine et de thrombopénie est rapportée dans la littérature,
- qu'aucune étude n'a établi la sécurité d'emploi chez l'enfant,

La Commission nationale de pharmacovigilance du 19/06/95 a approuvé le relevé d'avis suite au Comité technique du 18/05/95, sous réserve des modifications suivantes :

- dans le libellé des associations nécessitant des précautions d'emploi : remplacer la phrase *"lorsqu'un traitement diurétique préalable peut avoir entraîné une déplétion..."* par "lorsqu'un traitement diurétique a entraîné une déplétion ..."

- remplacer "*médicaments donnant des torsades de pointes...*" par "médicaments pouvant entraîner des torsades de pointes..." et inclure ce libellé dans la rubrique "associations nécessitant des précautions d'emploi" et non "associations déconseillées".

E - DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE Spécialités injectables contenant de la noramidopyrine (Laboratoires HOECHST, LAFON, RIOM CERM, THERABEL LUCIEN PHARMA)

Considérant le risque de formation d'un précipité lors de l'association au cours de la même injection ou perfusion de phloroglucinol et de noramidopyrine (risque d'apparition de phlébothrombose), la Commission nationale de pharmacovigilance du 19/06/95 approuve le relevé d'avis suite au Comité technique du 30/03/95, sous réserve de la suppression du terme "connue" à la fin du libellé, soit : "Il est contre-indiqué de mélanger dans la même seringue [nom de la spécialité contenant de la noramidopyrine] et le SPASFON® (Phloroglucinol), en raison d'une incompatibilité physico-chimique."

F - DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE VOLTARENE® collyre (diclofenac) (Laboratoires CIBA VISION)

Considérant :

- que le laboratoire a retiré sa demande sur les effets du collyre sur l'aptitude à conduire des véhicules,
- qu'il n'y a pratiquement aucun risque d'effet toxique en cas d'ingestion accidentelle ou volontaire d'un flacon,
- que la kératite ponctuée est l'effet indésirable le plus fréquemment notifié,

la Commission nationale de pharmacovigilance du 19/06/95 a approuvé le relevé d'avis suite au Comité technique du 30/03/95

G - DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE ANSATIPINE® (rifabutine)

Considérant :

- qu'une diminution de la dose d'ANSATIPINE® doit être préconisée en cas d'insuffisance hépatique sévère,
- qu'une actualisation de la rubrique "interactions médicamenteuses" est nécessaire,
- que la survenue d'effets indésirables à type d'uvéites, notamment lors d'une augmentation des doses et de certaines associations médicamenteuses, a été rapportée au niveau du système national de pharmacovigilance, au laboratoire et dans la littérature,
- et que parmi les signes cliniques d'uvéite, la diminution de l'acuité visuelle mérite d'être signalée dans l'annexe II,

la Commission nationale de pharmacovigilance du 19/06/95 a approuvé le relevé d'avis suite au Comité technique du 20/04/95.

Annexe 1-60

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Annexe 1-61

Jim à EXANDER

le 16/07/95

Urgent

Note sur les annexigènes
à l'intention
de Mr TABUTEAU, Dir. Général de
l'Agence du Médicament

Objet = situation après le Comité des Spécialités Pharmaceutiques des 11-12 et 13 Juillet 95.

1) Position du CSP de Juillet

La procédure selon l'article 12 est prolongée de 60 jours, pour permettre d'obtenir des informations complémentaires des firmes pharmaceutiques, en terme de

- bénéfice(s) thérapeutique(s) selon les modes (continus ou discontinus) et durées de traitement
- profil global de sécurité, incluant d'autres effets indésirables que l'hypertension pulmonaire

L'annexe I correspond aux questions

qui seront adressées aux firmes
et au calendrier=

- réponses des détenteurs d'AMM 31 Août
- rapports d'évaluations et du rapporteur (FR) du co-rapporteur (SWE) pour le profil de sécurité 30 Oct
- avis du C.S.P 17 Oct

Ce délai permettra au C.S.P d'affiner sa position

2 Rappel des éléments du dossier

2.1) Une enquête de pharmacovigilance a recensé 78 cas d'hypertension artérielle pulmonaire primitive (PP) associés à la prise d'anorexigènes, survenus en France depuis 1985

Une étude épidémiologique cas-témoin (IPPH) menée, en 92-93, dans 4 pays, par le Pr Abenhaim, a confirmé le lien

suite

contre la survenue d'une HSA
la prise d'anorexigènes (fenfluramine(F)/dex fenfluramine(DF)/amfépramone/clobenzorex/fenproporex, phenmétrazine), les anorexigènes étant considérés comme une classe. L'analyse "rétrospective" par sous-groupe fait apparaître une association significative avec F/DFenfl; mais, par manque de puissance, l'association n'atteint pas le seuil de significativité pour les autres anorexigènes (amphétaminiques); cependant, il existe une forte tendance...

2.2) Les 2 Commissions Nationales de PV des 28 Avril et 03 Mai ont permis (annexes 2 et 3) dans l'attente de l'évaluation de données complémentaires d'efficacité, de prendre un ~~premier train de mesures~~:
- restriction des indications (2e intention, obésité avec IMC supérieur à 30
- limitation de la durée d'hospitalisation à 3 mois
- contre-indication des associations

Une large information a été diffusée visant le public et les professions de santé

à la suite d'une réunion du
Groupe de Travail Pharmacovigilance du C.S.P
(11 Mai) et du Comité lui-même (16-17 Mai)
l'Allemagne (Pr H. Polenbrandt) a saisi
le Comité, sur ce sujet d'intérêt communautaire
selon l'article 12 (17 Mai 95)

2.4) Un groupe d'experts sur l'obésité
(23 Mai) réuni à l'Agence du Médicament
a permis de faire le point sur l'efficacité
des anorexigènes. Les firmes ont été entendues, le 30.

Un rapport d'évaluation a été adressé
par le D.E.V. au C.S.P et à son groupe
de Travail de Pharmacovigilance, sur efficacité & sécurité

2.5) le groupe de Travail Pharmacovigilance
du CSP, au vu du rapport d'évaluation
français, a conclu (annexe 4), le 02/06, à :
- l'absence d'intérêt des dérivés amphétaminiques
qui n'ont pas de place dans le traitement
de l'obésité (absence de bénéfice long terme;
risque dépassant le bénéfice)
- la possibilité de maintenir F/DF

adré:
- avec les indications limitées ...
- et une prescription pour les spécialités

2.6 la Commission Nationale de Pharmacovigilance du 19/06 a émis les mêmes recommandations (cf compte-rendu personnel en annexe 5)
Lire =
- suspension des amphétaminiques
- maintien dans les conditions précitées de F/DF, notamment avec prescription (initiale) hospitalière.

2.7 le C.S.P des 11-12-13 Juillet

après 3 auditions de firmes a décidé de prolonger la procédure [M^me le Pr^e Abenhaim, amenée par la délégation française, a pu répondre aux questions des fabricants]

Au plan scientifique, le Comité a retenu les faits décrits par un document FRE "position statement" (annexe 6)

Annexe 1-61

La discussion a fait apparaître que :

a) - les représentants n'étaient pas prêts à répondre oui en Juillet 95

b) - cependant, ils n'étaient pas satisfaits (du tout) de laisser en le marché

c) - ils redoutaient de ne pas avoir des bases suffisamment solides pour un avis négatif (tenaient, par ailleurs, exclusivement aux empêchements que :

- pour F/D.F. la preuve d'un lien avec l'HPL est faite, mais que l'évitité est bien prouvé (à un an)
- pour les annexistes : il n'existe qu'une "suspicion" mais, fin en revanche, seul un effet contre terme est affiché, dont on peut douter de l'intérêt dans le cadre d'une prise en charge long terme de l'obésité et que les empêchements sont décriés depuis 20 ans pour leurs multiples effets indésirables (dépendance, effets

cerveaux, effets cardio-vasculaires...)

d) ils n'étaient pas convaincus de pouvoir faire une différence entre F/DF et amphétaminiques

Deux solutions ont été évoquées :

(A) suspension des amphétaminiques → [pré-vote 7/15 favorables à la suspension malgré la volonté de ne pas conclure en Juillet

(B) maintien de F/DF et amphétaminiques

un milieu spécialisé. Les cliniciens feraient la différence.

Cette position de compromis heurte SUE, DK, NL qui n'ont pas des amphétaminiques sur leur marché ... et qui, à la suite d'un article 12 favorable, pourraient être obligés de les adopter !!

Annexe 1-61

[illegible] que dans le pré-vote, [illegible] et DK n'devraient pas, pour autant, être le volonté de suspendre (immédiatement).

Il n'est pas impossible qu'en Octobre, l'avis soit négatif, mais, cela n'est pas certain.

De plus, en cas d'avis négatif (pour les amphétaminiques / ou l'ensemble des anorexigènes), il y aurait forcément des recours

Il paraît difficile d'entendre (cf lettre de Durand) les FR, comme souligné par PL en C.S

Je serais favorable à un passage en prescription hospitalière (initiale) [illegible]

Annexe 1-62

MINISTERE DE LA SANTE PUBLIQUE
ET DE L'ASSURANCE MALADIE

REPUBLIQUE FRANCAISE

PARIS, 19 OCT. 1995

1, Place de Fontenoy
75350 PARIS 07 SP
Tel.: 40.56.60.00

A Gabor

DIRECTION GENERALE DE LA SANTE

Sous-Direction de la Pharmacie

Dossier suivi par
Mme H. SAINTE MARIE, chargé de mission

N O T E
pour Monsieur le Directeur général de
l'Agence du médicament

OBJET : anorexigènes.

Par lettre du 12 octobre 1995, l'Agence du médicament a demandé l'interdiction de l'utilisation dans les préparations magistrales des principes actifs qui, ajoutés à ceux déjà interdits par l'arrêté du 10 mai 1995, sont en cours d'évaluation au niveau européen.

Par ailleurs, j'observe que la commission de pharmacovigilance, au cours de sa réunion du 19 juin 1995, avait souhaité voir cette interdiction étendue à l'ensemble des principes actifs figurant dans la liste 3 annexée au décret du 16 mars 1982.

L'Agence du médicament avait d'ailleurs sensibilisé mon service sur les risques de transfert en direction des principes actifs autres que ceux concernés par l'étude européenne, dans un courrier du 5 octobre 1995.

Dans ces conditions, et comme suite à votre conversation téléphonique de ce jour avec Mme MOREL, je vous serais obligée de bien vouloir me préciser le plus rapidement possible :

– d'une part, quelles sont les bases scientifiques sur lesquelles l'Agence du médicament s'est fondée pour demander l'interdiction des principes actifs étudiés au niveau européen et non interdits par l'arrêté du 10 mai 1995 ; à cet égard, je souhaiterais obtenir communication du rapport que l'Agence a fourni, en tant que rapporteur, au comité des spécialités pharmaceutiques ;

– d'autre part, pour quelles raisons l'Agence a limité cette demande aux seuls principes actifs précités, sans englober les autres principes actifs figurant dans le groupe III de l'annexe au décret de 1982 précité.

Le Chargé de Mission
auprès du Sous-Directeur de la Pharmacie

Hélène SAINTE MARIE

AGENCE DU MEDICAMENT

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le 20 OCT. 1995

NOTE
pour Monsieur le Directeur Général
de la Santé

Objet : anorexigènes

En réponse à votre note du 19 Octobre 1995, Je vous prie de bien vouloir trouver ci-joint les précisions demandées :

Les substances anorexigènes inclues dans l'article 12 sont les seules à avoir fait l'objet d'une évaluation au niveau européen et correspondent aux spécialités pharmaceutiques commercialisées dans divers Etats membres de la Communauté Européenne. Il semble donc pertinent d'en interdire l'utilisation dans les préparations magistrales.

Toutefois, en raison du risque de reports de prescription sur les principes actifs figurant dans le groupe 3 du Décret n° 82-200 du 25 Février 1982, la Commission Nationale de Pharmacovigilance lors de sa séance du 19 Juin 1995 a souhaité que l'arrêté du 10 Mai 1995 soit étendu à ce groupe. Ces produits, à l'exception de ceux inclus dans l'enquête européenne n'ont pas fait l'objet d'une évaluation spécifique ; leur interdiction dans des préparations magistrales vise à empêcher un report de prescription vers des principes actifs ayant les mêmes particularités que les anorexigènes inclus dans l'article 12.

Vous trouverez joint à ce courrier les rapports communiqués aux états de la Communauté Européenne, ainsi que la liste des principes actifs du groupe 3 du Décret pré-cité.

Le Directeur Général

D. TABUTEAU

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 48.13.20.00

NOM DU TITULAIRE	NOM DU FABRICANT
Biotech Passage des Halles, 45300 Pithiviers	Biotech Passage des Halles, 45300 Pithiviers

NOM DE LA FAMILLE	DATE DE FIN DE VALIDITÉ	NUMÉRO D'HOMOLOGATION
Chambre postérieure mixte	13 juin 1998	4433-95-3

CARACTÉRISTIQUES DE LA FAMILLE	MODÈLES	GAMME DE VERGENCE
Monobloc. Polyméthacrylate usiné avec filtre UV. Monofocal. Anses ouvertes en C. Chambre postérieure d'appui mixte ciliocapsulaire. Optique biconvexe. Stérilisé à l'oxyde d'éthylène.	B 60130 = 610. B 65130 = 620. B 70130 = 630.	De 14 à 25 dioptries par pas de 0,5 dioptrie. De 0 à 14 dioptries et de 25 à 30 dioptries par pas de 1 dioptrie.

Arrêté du 25 octobre 1995 portant interdiction d'exécution et de délivrance de certaines préparations magistrales

NOR : *SANP9503231A*

Le ministre de la santé publique et de l'assurance maladie,

Vu le code de la santé publique, et notamment les articles R. 5144-9 et R. 5179 ;

Vu l'avis de la Commission nationale de pharmacovigilance du 19 juin 1995 ;

Vu l'avis de la commission d'autorisation de mise sur le marché n° 208 du 15 septembre 1995 ;

Considérant qu'une étude épidémiologique internationale a mis en évidence une relation entre la survenue d'une maladie vasculaire pulmonaire grave et souvent mortelle et la prise prolongée de médicaments anorexigènes à base de certains principes actifs ;

Considérant que la législation et la réglementation spécifiques aux médicaments, et notamment celles relatives à leur mise sur le marché et à leurs conditions de prescription et de délivrance, permet de prendre les mesures nécessaires à la sécurité de ces produits ;

Considérant que les préparations magistrales ou autres préparations à base de ces principes actifs sont commercialisées sans autorisation de mise sur le marché et qu'il n'est pas possible d'assurer le même encadrement de leur prescription et de leur délivrance ;

Considérant que ces préparations présentent les mêmes risques graves pour la santé publique,

Arrête :

Art. 1er. – Sont interdites à compter de la publication du présent arrêté l'exécution et la délivrance de préparations magistrales ou autres préparations à base de principes actifs suivants :

Acridorex, amfécloral, amfépentorex, aminorex, amphétamine, benflurorex, benzphétamine, chlorphentermine, cloforex, clominorex, clotermine, dexamphétamine, difémétorex, étilamfétamine, étolorex, fénétylline, fénisorex, fénosolone, flucétorex, fludorex, fluminorex, formétorex, furfénorex, indanorex, levamphétamine, mazindol, métamfépramone, métamphétamine, morforex, norpseudoéphédrine, ortétamine, oxifentorex, pentorex, phenbutrazine (fenbutrazate), phendimétrazine, phenmétrazine, phentermine, picilorex, propylhexedrine, triflorex.

Art. 2. – Le directeur général de la santé est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 25 octobre 1995.

Pour le ministre et par délégation :
Le directeur général de la santé,
J.-F. GIRARD

MINISTÈRE DE L'AGRICULTURE, DE LA PÊCHE ET DE L'ALIMENTATION

Arrêtés du 29 juin 1995 relatifs à des groupements de producteurs

NOR : *AGRP9501972A*

Reconnaissances

Par arrêtés du ministre de l'agriculture, de la pêche et de l'alimentation en date du 29 juin 1995, les organismes ci-dessous sont reconnus en qualité de groupement de producteurs.

La coopérative Société coopérative agricole Ovins 27, agréée le 6 février 1995 sous le numéro 27/95/001, dont le siège social est établi au Neubourg (Eure), est reconnue en qualité de groupement de producteurs à compter du 1er janvier 1995 et jusqu'au 31 octobre 1996 pour les agneaux et les ovins de réforme sur la circonscription territoriale suivante :

Le département de l'Eure ;
L'arrondissement de Lisieux (Calvados).

La coopérative Société coopérative agricole Terres de Gascogne, Gers porcs, dont le siège social est établi à Condom (Gers), est reconnue en qualité de groupement de producteurs jusqu'au 31 octobre 1996 pour les porcelets et les porcs charcutiers sur la circonscription territoriale suivante :

Canton d'Astafort (Lot-et-Garonne) ;
Canton de Boulogne-sur-Gesse (Haute-Garonne) ;
Canton de Cadours (Haute-Garonne) ;
Canton de Léguevin (Haute-Garonne) ;
Arrondissement d'Auch (Gers) ;
Canton de Condom (Gers) ;
Canton d'Eauze (Gers) ;
Canton de Fleurance (Gers) ;
Canton de Lectoure (Gers) ;
Canton de Mauvezin (Gers) ;
Canton de Miradoux (Gers) ;
Canton de Montréal (Gers) ;
Canton de Saint-Clar (Gers) ;
Canton de Valence-sur-Baïse (Gers) ;
Canton d'Aignan (Gers) ;
Canton de Marciac (Gers) ;

Annexe 1-64

AGENCE DU MEDICAMENT
DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

20 DEC. 1996

Copie

Note
Pour Mr Philippe BAS, Directeur de Cabinet
du Ministre du Travail et des Affaires Sociales
et Mr Benoît PARLOS, Directeur de Cabinet
du Secrétaire d'Etat à la Santé et à la Sécurité Sociale
(A l'attention de Mr Pierre BIVAS, Conseiller Technique)

Objet : Synthèse du dossier anorexigènes

L'hypertension artérielle pulmonaire primitive est une maladie rare (deux cas pour un million d'habitants), mais d'évolution sévère et le plus souvent mortelle. Les ressources thérapeutiques sont limitées à des perfusions continues de prostacycline à visée vasodilatatrice et aux greffes pulmonaires ou cardiopulmonaires.

I anorexigènes et hypertension artérielle

En 1991, des cas d'hypertesion artérielle pulmonaire associés à la prise de fenfluramine ont été publiés. En France, plusieurs cas de notifications spontanées liées à l'utilisation d'anorexigènes, notamment defenfluramine et dexfenfluramine ont justifié la mise en place d'une enquête nationale de pharmacovigilance. Cette enquête conduite par le Centre de Pharmacovigilance de Besançon a permis de relever 78 cas d'hypertension artérielle pulmonaire primitive notifiés au système français de pharmacovigilance et associés à la prise d'anorexigènes entre 1985 et 1994.

Parallèlement une étude internationale prospective cas-témoin (étude IPPHS) dont les resultats définitifs ont été connus au printemps 1995, conduite en Europe entre 1992 et 1994 et coordonné par le Pr L.Abenhaim (Université Mc Gill, Montréal), a établi l'existence d'un lien significatif entre la prise d'anorexigènes et la survenue d'une hypertension artérielle pulmonaire primitive. Le risque augmente avec la durée du traitement ; il est significativement augmenté pour des durées supérieures à trois mois.

II Mesures prises en France

La relation établie entre la survenue d'hypertensions artérielles pulmonaires primitives et la prise de médicaments anorexigènes a conduit la Commission Nationale de Pharmacovigilance et la Commission d'Autorisation de Mise sur le Marché à proposer, dès le mois de Mai 1995, des mesures restrictives visà vis de l'utilisation de ces produits. L'Agence a donc pris les décisions suivantes :

- Harmonisation du Résumé des Caractéristiques des produits (RCP) de l'ensemble des spécialités avec restriction de l'indication au traitement de seconde intention, après échec d'un traitement diététique adapté, des obésités majeures (indice de masse corporelle supérieure à 30 kg/m2) représentant un facteur de risque grave :

- limitation de la durée totale de traitement à trois mois,
- identification claire d'un risque potentiellement mortel.

Parallèllement, un arrêté du Ministre de la Santé a interdit l'exécution et la délivrance des préparations magistrales à base de substances anorexigènes.

Ces mesures ont été portées à la connaissance des professionnels de santé et du public le 16 mai 1995 (Cf. Avis aux prescripteurs joint)

Parallèllement, un groupe d'experts spécialistes de diabétologie-endocrinologie-nutrition était chargé, à partir de l'ensemble des données fournies par les firmes pharmaceutiques concernées, de réévaluer l'intérêt thérapeutique des anorexigènes et leur place dans la prise en charge globale de l'obésité. Les conclusions ont été :

- Pour les amphétamines et apparentés : il n'est pas possible de prescrire ces produits à long terme en raison de leur potentiel de dépendance ; on ne peut donc attendre une perte de poids prolongée, d'autant que leur effet cesse dès l'arrêt du traitement. Le bénéfice thérapeutique, s'il existe, est donc insuffisant au regard du risque potentiel d'hypertension artérielle pulmonaire.

- Pour les fenfluramines : il existe une étude long terme (un an) menée avec la dexfenfluramine. Le nombre de patients répondeurs au traitement (perte prolongée de 10 % du poids initial) double par rapport à un placebo. Ce produit pourrait être utile dans le cadre d'une prescription à long terme, après une stricte sélection des patients, dans le cadre d'une prise en charge globale par des spécialistes. Il convient de vérifier par une étude épidémiologique l'impact réel d'un traitement long terme sur la morbidité et la mortalité.

La Commission Nationale de Pharmacovigilance du 19 juin 1995 a validé ces conclusions, après audition des firmes pharmaceutiques commercialisant des anorexigènes en France et envisagé la suspension des anorexigènes amphétaminiques et le maintien de la fenfluramine et desfenfluramine en milieu hospitalier sous le contrôle de spécialistes (cf. annexes). Ces propositions ne pouvaient être appliquées qu'après les conclusions du Comité des Spécialités Pharmaceutiques.

Toutefois, les délais règlementaires de réponse ainsi que la processus décisionnel européen ne permettaient pas d'espérer la mise en oeuvre de mesures concrètes avant la fin du premier trimestre 1996, en cas d'appel des firmes. La France étant le pays Européen qui compte le plus grand nombre de cas d'hypertension artérielle primitive, était confrontée à un problème de Santé publique majeur. Aussi, l'Agence du Médicament a t'elle saisi à nouveau la Commission d'Autorisation de Mise sur le Marché sur la nécessité de prendre des mesures à titre conservatoire dans l'attente de la décision européenne.

La Commission d'AMM du 15 septembre 1995 a estimé que :

- l'obésité était une maladie chronique nécessitant un traitement prolongé et une prise en charge globale pluridisciplinaire ;

- les anorexigènes, prescrits à long terme, pouvaient avoir une place dans cette prise en charge globale ;

- compte tenu du risque inhérent à la prescription des anorexigènes, la décision de prescription devait être soigneusement pesée et ne concerner que des obésités majeures de type androïde, représentant un réel facteur de risque de morbidité et mortalité cardio-vasculaires.

Dans ces conditions, la Commission a proposé une prescription restreinte avec prescription initiale hospitalière par des services spécialisés en diabétologie, endocrinologie, nutrition, médecine interne et/ou par des spécialistes d'endocrinologie et maladies métaboliques. Le relais de la prescription pouvant se faire en ville. La validité de la prescription initiale proposée était de un an. La réglementation ne permet en effet pas de réserver la prescription initiale à des spécialistes hospitaliers et libéraux assurant une prise en charge globale de l'obésité avec renouvellement possible par tout médecin.

Il a en outre, été rappelé que la durée cumulative de prescription des amphétaminiques ne devait pas excéder trois mois par cure de 4 à 6 semaines, en raison du risque de dépendance. Pour les fenfluramines, un traitement plus prolongé était autorisé pour les patients ayant atteint une perte de poids d'au moins 5 % de leur poids initial après 2 à 3 mois de traitement.

Ces mesures restrictives répondaient au double objectif :

- d'éliminer les risques de prescription à visée esthétique des anorexigènes ;

- de conserver la possibilité pour les spécialistes de disposer d'un moyen pharmacologique dans le cadre d'une prise en charge globale de l'obésité.

Ainsi, les patients pour lesquels une diminution possible du risque de mortalité cardio-vasculaire compensait l'éventualité rare de survenue d'une hypertension artérielle pulmonaire ont pu bénéficier du traitement.

Ces mesures ont été prises par l'Agence du Médicament dès l'approbation de l'avis de la Commission d'Autorisation de Mise sur le Marché et portées à la connaissance du public et des professionnels de santé (Cf communiqué de presse du 30 octobre 1995)

III Procédure Européenne

L'ensemble des données de tolérance ont été transmises au Comité des Spécialités Pharmaceutiques. L'Allemagne a saisi le Comité au cours de sa séance du mois de Mai 1995 en vertu de l'article 12 de la directive 75/319/EEC. La France a été nommée rapporteur du dossier.

Depuis cette date le dossier des anorexigènes a donc été évalué en parallèle en France et au niveau Européen .

Trois rapports ont ainsi été examinés au niveau du Comité des Spécialités pharmaceutiques au cours de l'année 1995 et les titulaires d'autorisation de mise sur le marché ont été entendus à deux reprises en juillet 1995 et en octobre 1995.

Un premier avis rendu par le Comités des Spécialités Pharmaceutiques le 15 février 1996, a fait l'objet d'un appel de certaines firmes pharmaceutiques. Aussi un avis final de ce Comité n'a été donné qu'au mois de juillet 1996.

- les anorexigènes représentent un traitement adjuvant du régime alimentaire chez des patients atteints d'obésité dont l'index de masse corporelle (IMC) est de 30 kg/m2 ou plus, qui n'ont pas répondu au régime amaigrissant adopté seul ;

- il est recommandé que ce traitement soit mené sous la surveillance d'un médecin expérimenté dans le traitement de l'obésité ;

- il est de plus indiqué pour les fenfluramines que le traitement ne pourra être prolongé au delà de 3 mois que chez les patients qui présentent , dans les 3 mois suivant le début du traitement , une perte de poids égale ou supérieure à 10 % du poids initial ;

- toute association médicamenteuse à un autre anorexigène à action centrale est contre-indiquée en raison du risque accru d'hypertension artérielle pulmonaire potentiellement fatale.

- Une mise en garde indique clairement que :

"Des cas d'hypertension artérielle pulmonaire sévère, souvent fatale, ont été rapportés chez des patients ayant reçu des anorexigènes.

Une étude épidémiologique a montré que la prise d'anorexigènes est un facteur de risque impliqué dans le développement de l'hypertension artérielle pulmonaire et que la prise d'anorexigène est fortement liée à un risque accru de survenue de cet effet indésirable.

Compte tenu de ce risque rare mais grave, il faut souligner :

- que l'indication thérapeutique et la durée de traitement doivent être soigneusement respectées ;

- qu'une durée de traitement supérieure à trois mois ainsi qu'un Index de Masse Corporelle ≥ 30 kg/m2, augmentent le risque d'hypertension artérielle pulmonaire ;

- que l'apparition ou l'aggravation d'une dyspnée d'effort doit faire suspecter la survenue d'une hypertension artérielle pulmonaire. Dans ces circonstances, le traitement doit être arrêté immédiatement et le patient orienté en milieu spécialisé pour investigations".

IV Position française

La décision de la Commission Européenne sur les conditions d'utilisation des médicaments anoexigènes ne remet pas en cause les mesures actuellement en vigueur en France.

En effet, depuis le mois d'octobre 1995, les autorisations de mise sur le marché de ces médicaments comportaient déjà les informations proposées par le Comité des Spécialités Pharmaceutiques :

- les anorexigènes étaient reservés au traitement de seconde intention, après échec d'un traitement hygiéno-diététique adapté , des obésités patentes de type androïde chez des patients ayant un indice de masse corporelle égal ou supérieur à 30 kg/m2 ;

- les anorexigènes étaient reservés au traitement de seconde intention, après échec d'un traitement hygiéno-diététique adapté , des obésités patentes de type androïde chez des patients ayant un indice de masse corporelle égal ou supérieur à 30 kg/m2 ;

- pour les fenfluramines, la prolongation du traitement au delà de 3 mois n'était envisagée qu'en cas de réponse clinique attestée par une perte de poids d'au moins 5 % du poids initial. (la décision de la Commission Européenne restreint encore l'indication en fixant à 10 % la perte de poids nécessaire pour justifier la poursuite du traitement).

- l'association à d'autres médicaments anorexigènes était contre-indiquée ;

- une mise en garde indiquait que :

"Des observations d'hypertensions artérielles pulmonaires graves,souvent mortelles, ont été rapportées chez des patients ayant reçu un traitement par anorexigènes.

Une relation avec la prise de ces médicaments a été établie. Compe tenu de ce risque rare mais grave :

- l'indication doit être respectée ;

- le traitement ne doit être poursuivi qu'en cas de réponse clinique dans les 3 premier mois (pour les fenfluramines) ;

- toute apparition ou augmentation d'une dyspnée d'effort doit faire évoquer la possibilité d'hypertension artérielle pulmonaire et faire arrêter le traitement .

Il est alors nécessaire d'adresser le patient en milieu spécialisé afin de pratiquer des examens respiratoires."

Ces traitements étaient reservés aux médecins ayant une parfaite expérience de la prise en charge de l'obésité et ayant les moyens d'appréhender complètement les risques liés à l'obésité elle même. La prescription initiale peut ainsi reposer sur une évaluation précise et individuelle de la balance bénéfice /risque de ces traitements.

Il apparait ainsi clairement que la position européenne est en accord avec les mesures prises à titre conservatoire en France en 1995. Les libellés des autorisations de mise sur le marché feront donc simplement l'objet d'une rectification pour reprendre les termes exacts de la décision européenne.

Cette position a été rendue publique par un communiqué de presse diffusé le 19 décembre 1996 après accord du cabinet du Ministre.(pièce jointe)

Un recours administratif a été formé devant l'Agence et sera examiné par la commission d'AMM notamment à la lumière de la nouvelle réglementation qui doit prochainement compléter le dispositif sur la prescription restreinte (articles R5143-5-1 et suivants du code de la santé publique).

Il convient de souligner que les décisions européenne et française permettent de maintenir ces médicaments à la disposition des patients pour lesquels le risque de morbidité et de mortalité cardiovasculaires dû à une forte obésité, justifie la prise de risque lié au traitement par des produits anorexigènes.

En revanche, il importe d'écarter tout risque d'une prise d'anorexigène en dehors des strictes indications de l'autorisation de mise sur le marché. Tel est l'objet des décisions arrêtées l'an dernier.

Dans ces conditions, le maintien des mesures prises par la France dès 1995 est une nécessité de santé publique.

Didier TABUTEAU

AGENCE DU MEDICAMENT

Saint-Denis, le 12 Mai 1995

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Cher Confrère,

Une étude internationale, cas/témoin, visant à préciser les facteurs de risque des hypertensions artérielles pulmonaires d'allure primitive, vient de montrer l'existence d'une association entre **la survenue d'hypertension artérielle pulmonaire et la prise d'anorexigènes**.

Le risque de survenue de cet effet indésirable, dont vous connaissez la gravité du fait de son évolution le plus souvent fatale, augmente lorsque la durée du traitement dépasse trois mois ou lorsque les anorexigènes sont prescrits en association.

L'Agence du Médicament a donc décidé, sur proposition de la Commission Nationale de Pharmacovigilance et en accord avec les firmes commercialisant des spécialités contenant ces principes actifs* de :

- limiter l'indication de ces produits au traitement des obésités patentes des patients dont l'indice de masse corporelle est supérieur à 30, constituant un facteur de risque cardiovasculaire grave,
- limiter à 3 mois les durées cumulatives de traitement,
- contre-indiquer leur association.

Le rapport bénéfice/risque de ces traitements, dans la prise en charge thérapeutique globale de l'obésité, est en cours de réévaluation par l'Agence du Médicament qui prendra si nécessaire d'autres mesures complémentaires. Parallèlement, le Ministère chargé de la santé engage la procédure nécessaire pour interdire l'utilisation des substances anorexigènes dans les préparations magistrales.

Dès à présent, nous vous demandons d'assurer le strict respect de ces nouvelles règles, tant à l'occasion de la prescription que de la délivrance, en les expliquant aux patients afin d'en empêcher toute utilisation en dehors des modalités pré-citées.

Veuillez agréer, Cher Confrère, l'expression de ma considération distinguée.

Pr J.M. ALEXANDRE
Directeur de l'Evaluation

*Liste des principes actifs contenus dans les spécialités suivantes : amfépramone[1], clobenzorex[2], dexfenfluramine[3], fenfluramine[4], fenproporex[5], mefenorex[6].

1 ANOREX® (Laboratoire CRINEX)
MODERATAN® (Laboratoire THERANOL-DEGLAUDE)
PREFAMONE® (Laboratoire DEXO)
TENUATE DOSPAN® (Laboratoire MARION MERRELL DOW)
2 DININTEL® (Laboratoire DIAMANT)
3 ISOMERIDE® (Laboratoire ARDIX)
4 PONDERAL® (Laboratoire BIOPHARMA)
5 FENPROPOREX ACTION PROLONGEE DEGLAUDE® (Laboratoire THERANOL-DEGLAUDE)
6 INCITAL® (Laboratoire PIERRE FABRE SANTE)

Indice de masse corporelle = poids en kg/(taille en m)²

Agence du Médicament : 07.38.07.77

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex Tel 48.13.20.00

AGENCE DU MEDICAMENT

AVIS AUX PRESCRIPTEURS

La Commission Nationale de Pharmacovigilance réunie le 03/05/95 a pris connaissance des résultats d'une étude épidémiologique internationale sur l'Hypertension Artérielle Pulmonaire Primitive.

Cette étude montre qu'il existe une association entre la survenue de ces Hypertensions Pulmonaires et la prise de tout anorexigène* pour une durée de traitement supérieure à 3 mois.

Les résultats sont confirmés par la notification spontanée des Hypertensions Pulmonaires au système national de Pharmacovigilance.
Cette pathologie est de fréquence très faible mais de gravité extrême compte tenu de son évolution fatale. En conséquence, sur proposition de la Commission Nationale de Pharmacovigilance, l'Agence du Médicament a décidé de :

- restreindre l'indication au traitement de seconde intention, après échec d'un traitement diététique adapté, d'obésité patente avec indice de masse corporelle supérieur à 30.

- limiter la durée d'utilisation à 3 mois.

- de contre-indiquer leur association.

Parallèlement, un arrêté du ministre chargé de la santé interdit l'exécution et la délivrance de préparations magistrales et autres préparations à base de substances anorexigènes.

Un nouvel examen du rapport bénéfice/risque par la Commission Nationale de Pharmacovigilance aura lieu en Juin sur la base d'études complémentaires en cours.

Le Comité des Spécialités Pharmaceutiques de l'Agence Européenne (E.M.E.A.) a été saisi du problème.

* contenus dans les spécialités suivantes :

1° - ISOMERIDE® (dexfenfluramine) (laboratoires ARDIX)
2° - PONDERAL® (fenfluramine) (laboratoires BIOPHARMA)
3° - ANOREX® (amfepramone) (laboratoires CRINEX)
MODERATAN®amfepramone) (laboratoires THERANOL-DEGLAUDE)
PREFAMONE® (amfepramone) (laboratoires DEXO)
TENUATE DOSPAN® (amfepramone) (laboratoires MARION MERRELL DOW)
4° - DININTEL® (clobenzorex) (laboratoires DIAMANT)
5° FENPROPOREX ACTION PROLONGEE DEGLAUDE® (fenproporex) (laboratoires THERANOL-DEGLAUDE)
6° - INCITAL® (mefenorex) (laboratoires PIERRE FABRE SANTE)

Annexe 1-64

Arrêté du 10 mai 1995 portant interdiction de l'exécution et de la délivrance de préparations magistrales ou autres préparations à base de certains principes actifs

NOR : *SANP9501560A*

Le ministre délégué à la santé, porte-parole du Gouvernement,

Vu le code de la santé publique, et notamment ses articles L. 605 (10°), R. 5144-9 et R. 5179 ;

Considérant qu'une étude épidémiologique internationale a mis en évidence une relation entre la survenue d'une maladie vasculaire pulmonaire grave et souvent mortelle et la prise prolongée de médicaments anorexigènes ;

Considérant l'avis de la Commission nationale de pharmacovigilance du 3 mai 1995,

Arrête :

Art. 1er. – Sont interdites, à compter de la date de publication du présent arrêté, l'exécution et la délivrance de préparations magistrales ou autres préparations à base des principes actifs suivants :

- dexfenfluramine ;
- fenfluramine ;
- amfépramone ;
- fenproporex ;
- clobenzorex ;
- mefenorex.

Art. 2. – Le directeur général de la santé est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 10 mai 1995.

Pour le ministre et par délégation :
Le directeur général de la santé,
J.-F. GIRARD

JO 16 mai 95

Arrêté du 25 octobre 1995 portant interdiction d'exécution et de délivrance de certaines préparations magistrales

NOR : *SANP9503231A*

Le ministre de la santé publique et de l'assurance maladie,

Vu le code de la santé publique, et notamment les articles R. 5144-9 et R. 5179 ;

Vu l'avis de la Commission nationale de pharmacovigilance du 19 juin 1995 ;

Vu l'avis de la commission d'autorisation de mise sur le marché n° 208 du 15 septembre 1995 ;

Considérant qu'une étude épidémiologique internationale a mis en évidence une relation entre la survenue d'une maladie vasculaire pulmonaire grave et souvent mortelle et la prise prolongée de médicaments anorexigènes à base de certains principes actifs ;

Considérant que la législation et la réglementation spécifiques aux médicaments, et notamment celles relatives à leur mise sur le marché et à leurs conditions de prescription et de délivrance, permet de prendre les mesures nécessaires à la sécurité de ces produits ;

Considérant que les préparations magistrales ou autres préparations à base de ces principes actifs sont commercialisées sans autorisation de mise sur le marché et qu'il n'est pas possible d'assurer le même encadrement de leur prescription et de leur délivrance ;

Considérant que ces préparations présentent les mêmes risques graves pour la santé publique,

Arrête :

Art. 1er. – Sont interdites à compter de la publication du présent arrêté l'exécution et la délivrance de préparations magistrales ou autres préparations à base de principes actifs suivants :

Acridorex, amfécloral, amfépentorex, aminorex, amphétamine, benfluorex, benzphétamine, chlorphentermine, cloforex, clominorex, clotermine, dexamphétamine, diféméthorex, diflamfétamine, étolorex, fénétylline, fénisorex, fénocolone, fluféthorex, fludorex, fluminorex, formétorex, furféthorex, isadorex, levamphétamine, mazindol, métamfépramone, métamphétamine, morforex, norpseudoéphédrine, ortétamine, oxifentorex, pentorex, phenbutrazine (fenbutrazate), phendimétrazine, phenmétrazine, phentermine, picilorex, propylhexedrine, triflorex.

Art. 2. – Le directeur général de la santé est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 25 octobre 1995.

Pour le ministre et par délégation :
Le directeur général de la santé,
J.-F. GIRARD

JO du 31 octobre 95

RÉPUBLIQUE FRANÇAISE

25 OCT. 1995

AGENCE DU MEDICAMENT

Le Directeur de l'Evaluation du Médicament

DIRECTION GENERALE DE LA SANTE

Le Directeur Général

Cher Confrère,

Comme vous le savez, au mois de Mai 1995, l'Agence du Médicament a pris une première série de mesures restreignant les conditions de prescription des anorexigènes, en raison du risque de survenue d'hypertension pulmonaire primitive, maladie rare mais d'évolution souvent mortelle associé à la prise de ces médicaments.

Dans l'attente d'une réévaluation du rapport bénéfice/risque, l'utilisation de cette classe a donc été restreinte aux patients présentant une obésité majeure avec des durées de traitement n'excédant pas 3 mois.

Les évaluations complémentaires conduites depuis cette date par les instances scientifiques de l'Agence ont établi que pour le traitement de l'obésité, et dans le cadre d' une prise en charge globale et prolongée, d'une part les fenfluramines* pouvaient être utiles, le cas échéant en prescription long terme, et que d'autre part les amphétaminiques* et apparentés induisaient une perte de poids significative mais que la durée de prescription devait être brève en raison du potentiel de pharmacodépendance.

En conséquence, et dans l'attente de l'avis du Comité des Spécialités Pharmaceutiques de l'Agence européenne pour l'évaluation des médicaments qui a été saisi du dossier, le Directeur Général de l'Agence du Médicament a décidé à titre conservatoire et conformément à l'avis de la commission d'AMM, de modifier les conditions de prescription des anorexigènes.

Ces nouvelles conditions de prescriptions qui visent à assurer une prise en charge globale de l'obésité en unités de soins spécialisées, consistent en :

une "prescription initiale hospitalière annuelle réservée aux services spécialisés en diabétologie/endocrinologie et maladies métaboliques /médecine interne et/ou aux spécialistes en endocrinologie et maladies métaboliques ou médecine interne".

La validité de cette prescription initiale est de un an.

Le renouvellement est possible en médecine de ville sur présentation de l'ordonnance hospitalière.

Annexe 1-64

Le pharmacien d'officine ne peut délivrer ces spécialités que sur présentation des 2 ordonnances : la première ordonnance hospitalière et l'ordonnance de renouvellement.

La prescription des Fenfluramines ne peut être maintenue que chez les patients "répondeurs" identifiés après une période de traitement de 3 mois.
En revanche, pour les amphétaminiques et apparentés, la durée de prescription reste limitée à 3 mois, par cure de 4 à 6 semaines, en raison du risque de dépendance.

En ce qui concerne les préparations magistrales, nous vous rappelons qu'un arrêté du ministre chargé de la santé du 10 mai 1995 a interdit l'exécution et la délivrance des préparations magistrales à base de principes actifs correspondant aux spécialités précitées. Un nouvel arrêté étend cette interdiction à l'ensemble des principes actifs qui figurent dans le groupe III du Décret n° 82-200 du 25 février 1982 et à des principes actifs qui sont inclus dans des spécialités faisant l'objet d'une évaluation par l'Agence européenne.

Nous vous prions d'agréer, Cher Confrère, l'assurance de notre considération distinguée.

Pr Jean-Michel ALEXANDRE

Pr Jean-François GIRARD

* Liste des spécialités concernées

Anorexigènes amphétaminiques :

- ANOREX® (amfépramone)
- DININTEL® (clobenzorex)
- FENPROPOREX® (fenproporex)
- INCITAL® (méfénorex)
- MODERATAN® (amfépramone)
- PREFAMONE® (amfépramone)
- TENUATE DOSPAN® (amfépramone)

Anorexigènes fenfluramines :

- ISOMERIDE® (dexfenfluramine)
- PONDERAL® (fenfluramine)

Liste des principes actifs interdits en préparations magistrales

- acridorex
- amfécloral
- amfépentorex
- amfépramone
- aminorex
- amphétamine
- benfluorex
- benzphétamine
- chlorphentermine
- clobenzorex
- cloforex
- clominorex
- clortermine
- dexamphétamine
- dexfenfluramine
- diférétorex
- étilamfétamine
- étolorex
- fenbutrazate (phenbutrazine)
- fénétylline
- fenfluramine
- fénisorex
- fénosolone
- fenproporex
- flucétorex
- fludorex
- fluminorex
- formétorex
- furfénorex
- indanorex
- lévamphétamine
- mazindol
- méfénorex
- métamfépramone
- métamphétamine
- morforex
- norpseudoéphédrine
- ortétamine
- oxifentorex
- pentorex
- phendimétrazine
- phenmétrazine
- phentermine
- picilorex
- propylhexédrine
- trifluorex

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT

AVIS AUX PRESCRIPTEURS

Au mois de Mai 1995, l'Agence du Médicament a pris une première série de mesures restreignant les conditions de prescription des anorexigènes, en raison du risque de survenue d'hypertension pulmonaire primitive, maladie rare mais d'évolution souvent mortelle associé à la prise de ces médicaments.

Dans l'attente d'une réévaluation du rapport bénéfice/risque, l'utilisation de cette classe a donc été restreinte aux patients présentant une obésité majeure avec des durées de traitement n'excédant pas 3 mois.

Les évaluations complémentaires conduites depuis cette date par les instances scientifiques de l'Agence du Médicament ont établi que pour le traitement de l'obésité, et dans le cadre d' une prise en charge globale et prolongée, d'une part les fenfluramines* pouvaient être utiles, le cas échéant en prescription long terme, et que d'autre part les amphétaminiques* et apparentés induisaient une perte de poids significative mais que la durée de prescription devait être brève en raison du potentiel de pharmacodépendance.

En conséquence, et dans l'attente de l'avis du Comité des Spécialités Pharmaceutiques de l'Agence européenne pour l'évaluation des médicaments qui a été saisi du dossier, l'Agence du Médicament a décidé à titre conservatoire et conformément à l'avis de la commission d'AMM, de modifier les conditions de prescription des anorexigènes.

Ces nouvelles conditions de prescriptions qui visent à assurer une prise en charge globale de l'obésité en unités de soins spécialisées, consistent en :

une "prescription initiale hospitalière annuelle réservée aux services spécialisés en diabétologie/endocrinologie et maladies métaboliques /médecine interne et/ou aux spécialistes en endocrinologie et maladies métaboliques ou médecine interne".

La validité de cette prescription initiale est de un an.

Le renouvellement est possible en médecine de ville sur présentation de l'ordonnance hospitalière.

Le pharmacien d'officine ne peut délivrer ces spécialités que sur présentation des 2 ordonnances : la première ordonnance hospitalière et l'ordonnance de renouvellement.

La prescription des Fenfluramines ne peut être maintenue que chez les patients "répondeurs" identifiés après une période de traitement de 3 mois.
En revanche, pour les amphétaminiques et apparentés, la durée de prescription reste limitée à 3 mois, par cure de 4 à 6 semaines, en raison du risque de dépendance.

En ce qui concerne les préparations magistrales, il vous est rappelé qu'un arrêté du ministre chargé de la santé du 10 mai 1995 a interdit l'exécution et la délivrance des préparations à base de principes actifs correspondant aux spécialités précitées. Un nouvel arrêté étend cette interdiction à l'ensemble des principes actifs qui figurent dans le groupe III du Décret n° 82-200 du 25 février 1982 et à des principes actifs qui sont inclus dans des spécialités faisant l'objet d'une évaluation par l'Agence européenne.

Pour toute information complémentaire, un service de renseignement téléphonique est assuré par l'Agence du Médicament de 9h00 à 18h00 au 48.13.22.82.

*** Liste des spécialités concernées**

Anorexigènes amphétaminiques :

- ANOREX® (amfépramone)
- DININTEL® (clobenzorex)
- FENPROPOREX® (fenproporex)
- INCITAL® (méfénorex)
- MODERATAN® (amfépramone)
- PREFAMONE® (amfépramone)
- TENUATE DOSPAN® (amfépramone)

Anorexigènes fenfluramines :

- ISOMERIDE® (dexfenfluramine)
- PONDERAL® (fenfluramine)

Liste des principes actifs interdits en préparations magistrales

- acridorex
- amfécloral
- amfépentorex
- amfépramone
- aminorex
- amphétamine
- benfluorex
- benzphétamine
- chlorphentermine
- clobenzorex
- cloforex
- clominorex
- clortermine
- dexamphétamine
- dexfenfluramine
- difémétorex
- étilamfétamine
- étolorex
- fenbutrazate (phenbutrazine)
- fénétylline
- fenfluramine
- fénisorex
- fénosolone
- fenproporex
- flucétorex
- fludorex
- fluminorex
- formétorex
- furfénorex
- indanorex
- lévamphétamine
- mazindol
- méfénorex
- métamfépramone
- métamphétamine
- morforex
- norpseudoéphédrine
- ortétamine
- oxifentorex
- pentorex
- phendimétrazine
- phenmétrazine
- phentermine
- picilorex
- propylhexédrine
- triflorex

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RÉPUBLIQUE FRANÇAISE

AGENCE DU MÉDICAMENT

DIRECTION GÉNÉRALE DE LA SANTÉ

COMMUNIQUÉ DE PRESSE

En raison de la survenue de quelques cas de maladie vasculaire pulmonaire grave et souvent mortelle associés à la prise de médicaments anorexigènes (coupe-faim), l'Agence du Médicament a restreint, au mois de mai 1995, les conditions d'utilisation de ces produits aux seules obésités majeures et uniquement après échec d'un traitement diététique adapté, pour des durées de traitement n'excédant pas 3 mois.

A la suite des évaluations complémentaires conduites depuis cette date par l'Agence du Médicament et dans l'attente de l'avis du Comité de Spécialités Pharmaceutiques de l'Agence européenne pour l'évaluation des médicaments qui a été saisi du dossier, le Directeur Général de l'Agence du Médicament a décidé à titre conservatoire et conformément à l'avis de la commission d'AMM, de modifier les conditions de prescription des anorexigènes.

En effet, ces évaluations ont montré que ces spécialités devaient être utilisées au sein d'unités permettant d'assurer une prise en charge globale de l'obésité, respectant des règles hygiénodiététiques et bénéficiant d'un encadrement psychothérapeutique.

Désormais pour ces médicaments, la prescription initiale est donc limitée aux services hospitaliers spécialisés en endocrinologie et maladies métaboliques, médecine interne, diabétologie et aux spécialistes hospitaliers : endocrinologues, diabétologues et médecins internistes.

La durée de validité de l'ordonnance initiale hospitalière est fixée à 1 an. Le renouvellement peut être réalisé par des médecins spécialistes ou généralistes de ville pour les patients qui présentent une ordonnance initiale hospitalière. Le pharmacien, ne peut délivrer ces spécialités que sur présentation des 2 ordonnances : la première ordonnance hospitalière et l'ordonnance de renouvellement.

En ce qui concerne les préparations magistrales, un arrêté du ministre chargé de la santé du 10 mai 1995 a interdit l'exécution et la délivrance des préparations à base de principes actifs correspondant aux spécialités précitées. Un nouvel arrêté complète la liste des substances interdites.

Pour toute information complémentaire, un service de renseignement téléphonique est assuré par l'Agence du Médicament de 9 h 00 à 18 h 00 au 48 13 22 82.

*** Liste des spécialités concernées**

Anorexigènes amphétaminiques :

- ANOREX® (amfépramone)
- DININTEL® (clobenzorex)
- FENPROPOREX® (fenproporex)
- INCITAL® (méfénorex)
- MODERATAN® (amfépramone)
- PREFAMONE® (amfépramone)
- TENUATE DOSPAN® (amfépramone)

Anorexigènes fenfluramines :

- ISOMERIDE® (dexfenfluramine)
- PONDERAL® (fenfluramine)

Liste des principes actifs interdits en préparations magistrales

- acridorex
- amfécloral
- amfépentorex
- amfépramone
- aminorex
- amphétamine
- benfluorex
- benzphétamine
- chlorphentermine
- clobenzorex
- cloforex
- clominorex
- clortermine
- dexamphétamine
- dexfenfluramine
- difémétorex
- étilamfétamine
- étolorex
- fenbutrazate(phenbutrazine)
- fénétylline
- fenfluramine
- fénisorex
- fénosolone
- fenproporex
- flucétorex
- fludorex
- fluminorex
- formétorex
- furfénorex
- indanorex
- lévamphétamine
- mazindol
- méfénorex
- métamfépramone
- métamphétamine
- morforex
- norpseudoéphédrine
- ortétamine
- oxifentorex
- pentorex
- phendimétrazine
- phenmétrazine
- phentermine
- picilorex
- propylhexédrine
- triflorex

Annexe 1-64

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT

Saint-Denis, le

19 DEC. 1996

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Communiqué de presse

La décision de la Commission Européenne sur les conditions d'utilisation des médicaments anorexigènes vient d'être portée à la connaissance des états membres de l'Union Européenne. Cette décision ne remet pas en cause les mesures actuellement en vigueur en France.

En effet, suite à la survenue de cas d'hypertension artérielle pulmonaire primitive, maladie rare mais d'évolution souvent mortelle associés à la prise des médicaments anorexigènes, l'Agence du Médicament a modifié, à titre conservatoire et dans l'attente de l'avis du Comité des spécialités Pharmaceutiques, les conditions de prescription des anorexigènes, au mois de mai et d'octobre 1995.

Le 17 juillet 1996, le Comité des Spécialités Pharmaceutiques après avoir examiné au cours de la procédure communautaire les données disponibles a proposé une mise en garde indiquant clairement :

> *"des cas d'hypertension artérielle pulmonaire sévère, souvent fatale, ont été rapportés chez des patients ayant reçu des anorexigènes.*
> *Une étude épidémiologique a montré que la prise d'anorexigènes est un facteur de risque impliqué dans le développement de l'hypertension artérielle pulmonaire et que la prise d'anorexigène est fortement liée à un risque accru de survenue de cet effet indésirable. Compte tenu de ce risque rare mais grave, il faut souligner :*
> *- que l'indication thérapeutique et la durée de traitement doivent être soigneusement respectées ;*
> *- qu'une durée de traitement supérieure à trois mois ainsi qu'un Index de Masse Corporelle ≥ 30 kg/m2, augmentent le risque d'hypertension artérielle pulmonaire ;*
> *- que l'apparition ou l'aggravation d'une dyspnée d'effort doit faire suspecter la survenue d'une hypertension artérielle pulmonaire ; dans ces circonstances, le traitement doit être arrêté immédiatement et le patient orienté en milieu spécialisé pour investigations".*

En outre, le Comité des Specialités Pharmaceutiques a recommandé que ce traitement soit mené sous la surveillance d'un médecin expérimenté dans le traitement de l'obésité. En France, afin de répondre à cet objectif et d'assurer une prise en charge globale de l'obésité, la prescription initiale de ces médicaments a été restreinte aux services spécialisés en diabétologie/endocrinologie et maladie métabolique/médecine interne, la durée de validité de l'ordonnance hospitalière étant fixée à un an.

La Commission Européenne a entériné les propositions du Comité le 9 décembre 1996. La décision est en accord avec les mesures adoptées en France depuis 1995 et les autorisations de mise sur le marché seront rectifiées pour reprendre les termes précis de la décision européenne.

Liste des anorexigènes concernés :

Anorexigènes fenfluramines :

ISOMERIDE® (dexfenfluramiue)
PONDERAL® (fenfluramine)

Anorexigènes amphétaminiques :

- DININTEL® (clobenzorex)
- FENPROPOREX® (fenproporex)
- INCITAL® (mefenorex)
- ANOREX® (amfepramone)
- MODERATAN® (amfepramone)
- PREFAMONE® (amfepramone)
- TENUATE DOSPAN® (amfepramone)

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VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE–PHENTERMINE

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ABSTRACT

Background Fenfluramine and phentermine have been individually approved as anorectic agents by the Food and Drug Administration (FDA). When used in combination the drugs may be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent and perhaps fewer side effects. Although the combination has not been approved by the FDA, in 1996 the total number of prescriptions in the United States for fenfluramine and phentermine exceeded 18 million.

Methods We identified valvular heart disease in 24 women treated with fenfluramine–phentermine who had no history of cardiac disease. The women presented with cardiovascular symptoms or a heart murmur. As increasing numbers of these patients with similar clinical features were identified, there appeared to be an association between these features and fenfluramine–phentermine therapy.

Results Twenty-four women (mean [±SD] age, 44±8 years) were evaluated 12.3±7.1 months after the initiation of fenfluramine–phentermine therapy. Echocardiography demonstrated unusual valvular morphology and regurgitation in all patients. Both right-sided and left-sided heart valves were involved. Eight women also had newly documented pulmonary hypertension. To date, cardiac surgical intervention has been required in five patients. The heart valves had a glistening white appearance. Histopathological findings included plaque-like encasement of the leaflets and chordal structures with intact valve architecture. The histopathological features were identical to those seen in carcinoid or ergotamine-induced valve disease.

Conclusions These cases arouse concern that fenfluramine–phentermine therapy may be associated with valvular heart disease. Candidates for fenfluramine–phentermine therapy should be informed about serious potential adverse effects, including pulmonary hypertension and valvular heart disease. (N Engl J Med 1997;337:581-8.)

FENFLURAMINE and phentermine are prescription medications that have been individually approved by the Food and Drug Administration (FDA) as appetite suppressants for the treatment of obesity. When used in combination they may be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent, fewer side effects, and improved patient tolerance.[1] Even though the FDA has not approved the use of the combination, in 1996 the total number of prescriptions for fenfluramine and phentermine in the United States exceeded 18 million.[2]

Pulmonary hypertension has been reported in association with treatment with fenfluramine[3,4] or phentermine[5] alone. The *d*-isomer of fenfluramine, dexfenfluramine, also increases the risk of pulmonary hypertension,[6] particularly when patients receive high doses for more than three months. These drugs may cause pulmonary hypertension through the vasoconstrictor action of serotonin or by altering the depolarization of pulmonary vascular smooth-muscle membrane.[7]

Valvular disease has been reported after exposure to serotonin-like drugs such as ergotamine and methysergide[8] and with increased serotonin levels associated with carcinoid disease.[9,10] Valvular heart disease has not been reported in patients taking anorectic agents. We report 24 cases of unusual valvular disease in patients taking fenfluramine–phentermine.

METHODS

All the patients (Table 1) were identified during the course of routine evaluation for various clinical problems. No attempt was

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TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS.*

PATIENT NO.	AGE (YR)/SEX	BEFORE APPETITE SUPPRESSANTS					APPETITE SUPPRESSANTS		
		WEIGHT	HEIGHT	BODY-MASS INDEX†	MEDICATIONS	CARDIOVASCULAR EXAMINATION	MAXIMAL DOSE OF PHENTERMINE	MAXIMAL DOSE OF FENFLURAMINE	DURATION OF THERAPY
		kg	cm				mg/day		mo
1	41/F	108	165	39.7	None	Normal	48	120	25
2	44/F	91	160	35.5	Lisinopril, conjugated estrogens, theophylline	Normal	30	60	12
3	48/F	85	157	34.5	Sertraline, hydrochlorothiazide	Normal	30	60	9
4	52/F	69	158	27.6	Fluoxetine	Normal	15	40	12
5	49/F	96	158	38.5	Nortriptyline, propylthiouracil	Normal	30	60	11
6	51/F	133	153	56.8	Conjugated estrogens, medroxyprogesterone acetate, hydrochlorothiazide–benazepril	Normal	30	60	7
7	44/F	85	167	30.5	None	Normal	60	220	12
8	41/F	100	161	38.6	None	Normal	15	60	6
9	50/F	92	158	36.9	None	Normal	30	40	4
10	50/F	84	152	36.4	None	Normal	15	40	6
11	42/F	67	150	29.8	Bronchodilators	Normal	30	60	1
12	41/F	124	157	50.3	Sertraline	Normal	30	40	6
13	48/F	93	158	37.3	None	Normal	30	20	15
14	34/F	152	163	57.2	None	1/6 SEM	30	60	15
15	35/F	91	157	36.9	None	Normal	30	40	14
16	63/F	68	153	29.0	Fluoxetine	Normal	30	60	8
17	38/F	101	165	37.1	None	Normal	30	40	6
18	43/F	78	150	34.7	None	Normal	30	20	28
19	56/F	62	150	27.6	None	Normal	30	40	17
20	44/F	98	165	36.0	None	Normal	30	40	17
21	41/F	94	162	35.8	Sertraline	1/6 SEM	30	40	7
22	33/F	122	170	42.2	None	Normal	30	40	2
23	30/F	70	165	25.7	None	Normal	30	60	20
24	38/F	NA	NA	NA	None	Normal	30	40	4
Mean ±SD	44±8	96±22.1	159±5.8	37.9±7.9			30.8±8.5	56.5±40.7	11±6.9

TABLE 1. CONTINUED.

CARDIOVASCULAR FINDINGS			SURGERY		
PRESENTATION	ECHOCARDIOGRAPHY	CARDIAC CATHETERIZATION	PROCEDURE	GROSS PATHOLOGICAL FINDINGS	MICROSCOPICAL PATHOLOGICAL FINDINGS
Murmur, dyspnea	Severe MR, thickened MV	Severe MR, normal coronary arteries	MV repair	Glistening white, thickened, tethered leaflets	NA
CHF, dyspnea, murmur	Severe AR and MR; moderate TR; EF, 40%	Severe AR and MR; PAP, 55/31 mm Hg	AVR, MVR, tricuspid-valve repair	No chordal rupture or flail segment; trileaflet aortic valve	"Stuck-on" appearance of plaque on leaflets‡
Dyspnea, edema	Severe MR, moderate AR	Severe MR; normal coronary arteries; PAP, 35/16 mm Hg	MVR	No prolapse or chordal rupture	"Stuck-on" appearance of plaque on leaflets‡
CHF, murmur, dyspnea	RVSP, 75 mm Hg; severe MR	Normal coronary arteries	MV repair	Distinctly unusual; posterior leaflet thickened, tethered	NA
Dyspnea	RVSP, 52 mm Hg; severe MR	Moderate MR; EF, 50%	MVR	Glistening white, thickened leaflets and chordae	"Stuck-on" appearance of plaque on leaflets‡
Murmur, dyspnea, edema	Moderate AR and TR, severe MR	Not done			
Dyspnea	RVSP, 74 mm Hg; moderate AR	PAP, 75/30 mm Hg			
CHF	Severe TR and MR; moderate AR; RVSP, 75 mm Hg; EF, 65%	Not done			
Dyspnea	Moderate MR; RVSP, 60 mm Hg	Not done			
Murmur, palpitations	Moderate AR, mild MR	Not done			
Murmur, edema	Moderate AR; severe MR and TR; RVSP, 72 mm Hg	Not done			
Murmur	Moderate MR; mild AR and TR; RVSP, 23 mm Hg; normal EF	Not done			
Murmur, edema	Moderate MR, TR, and AR; RVSP, 54 mm Hg; normal EF	Not done			
Murmur, edema, dyspnea	Severe MR; moderate AR and TR; RVSP, 93 mm Hg	Not done			
Murmur	Moderate AR; mild MR; EF, 75%	Not done			
Murmur, edema	Moderate AR, TR, and MR; EF, 65%	Not done			
Palpitations	Moderate AR; mild MR; EF, 70%	Not done			
Murmur	Moderate AR, mild MR and TR	Not done			
Supraventricular tachycardia	Mild MR and TR, normal left ventricle	Not done			
Dyspnea	Moderate AR; EF, 66%	Not done			
Murmur	Mild MR, AR, and TR	Not done			
Chest pain	Mild MR, TR, and AR; normal EF	Not done			
Murmur, dyspnea, edema	Severe AR and MR; RVSP, 45 mm Hg	Not done			
Palpitations, chest pain	Mild AR	Not done			

*MR denotes mitral regurgitation, MV mitral valve, NA not available, CHF congestive heart failure, AR aortic regurgitation, TR tricuspid regurgitation, EF ejection fraction, PAP pulmonary-artery pressure, AVR aortic-valve replacement, MVR mitral-valve replacement, RVSP right ventricular systolic pressure, and SEM systolic ejection murmur.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡"Stuck-on" refers to the fact that the valve architecture was intact.

made to identify patients by reviewing data bases, conducting cross-index searches of patient files, or soliciting reports of suspected cases from clinical practices. As increasing numbers of patients were identified with similar clinical features, a perceived association between these features and previous or current use of fenfluramine–phentermine evolved. The serendipitous connection between these individual cases was identified as a result of communication among several physicians beginning in May 1996.

May 1996

In May 1996, Patient 1 underwent mitral-valve repair at the Mayo Clinic for the treatment of severe mitral regurgitation. Intraoperatively, the valve was noted to have a glistening white appearance, suggesting ergotamine-induced valvular injury as observed in previous patients,[8] but the patient had no history of ergotamine ingestion.

July 1996

In July 1996, Patient 1 was evaluated by another physician for severe symptomatic tricuspid regurgitation. Echocardiography confirmed severe tricuspid regurgitation and thickening of the valve leaflets. These findings were similar to those seen in patients with carcinoid or ergotamine-induced valve disease. A history was obtained indicating fenfluramine–phentermine use for 25 months until 1 month before mitral-valve surgery. A 24-hour urinary 5-hydroxyindoleacetic acid value was normal.

January 1997

In January 1997, a woman (Patient 7) with pulmonary hypertension was evaluated at the Mayo Clinic, and echocardiography demonstrated thickened aortic-valve leaflets and aortic regurgitation. An echocardiogram obtained two years previously revealed no abnormalities. The patient had taken fenfluramine–phentermine for one year before the more recent echocardiographic examination.

Also in January 1997, a physician from MeritCare Medical Center (Fargo, N.D.) contacted the Mayo Clinic and inquired whether there was a recognized association between diet medications and valvular heart disease. The inquiry was precipitated by the physician's awareness that his echocardiographic sonographers had identified a cohort of 12 patients (Patients 2, 3, 6, and 10 through 18) with valvular heart disease who had a peculiar valvular morphology. A further review of the patients' records revealed that all 12 patients had taken fenfluramine–phentermine. The patients' records and echocardiograms were sent to the Mayo Clinic. The echocardiograms disclosed valve lesions very similar to those noted in Patients 1 and 7. Excised valve tissue was obtained from two patients (Patients 2 and 3), and slides prepared with elastic–van Gieson stain were reviewed by a cardiac pathologist. Histopathological examination revealed features identical to those of ergotamine-induced and carcinoid valve disease.

March 1997

In March 1997, a surgeon at the Mayo Clinic was contacted by one of his patients (Patient 4) who had undergone mitral-valve repair in 1996. The patient informed him that she had aortic regurgitation and pulmonary hypertension. A review of the surgical records showed that the appearance of the valve was distinctly unusual and not consistent with a history of rheumatic heart disease. Further inquiry revealed that the patient had taken fenfluramine–phentermine for 12 months before mitral-valve surgery.

Also in March 1997, valve tissue from a cardiac surgical patient (Patient 5) operated on at another institution was received by the Mayo Clinic for a pathological opinion. The morphologic features of the explanted valve (Fig. 1) were identical to those of valves from Patients 1 and 4 at the time of surgical inspection. Gross pathological features included thickening of the leaflets and chordae and a glistening white appearance. The histopathological features were identical to those in Patients 2 and 3. Patient 5 had been treated with fenfluramine–phentermine for 11 months.

April 1997

In April 1997, a patient (Patient 8) with a six-month history of fenfluramine–phentermine use was evaluated for dyspnea by a Mayo Clinic cardiologist consulting in another city. Multivalvular heart disease and pulmonary hypertension were identified. The cardiologist, unaware of the previous cases, asked a colleague whether he knew of an association between fenfluramine–phentermine therapy and valvular heart disease. Echocardiography revealed valvular morphology similar to that noted in the other patients.

Seven other patients (Patients 9 and 19 through 24) with similar clinical histories and echocardiographic findings were identified during clinical evaluations at MeritCare Medical Center from January through April 1997.

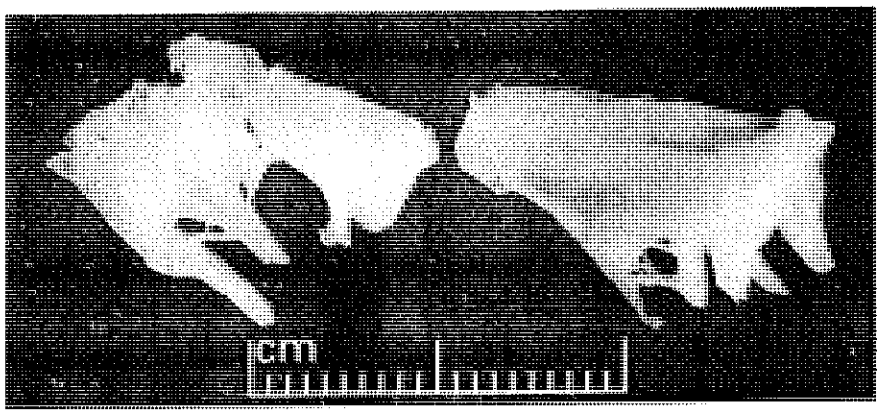

Figure 1. Explanted Mitral Valve from Patient 5, Demonstrating Glistening White Leaflets and Chordae with Mild-to-Moderate Irregular but Diffuse Thickening.

CASE REPORTS

Patient 1

Patient 1 was a 41-year-old woman (body-mass index [the weight in kilograms divided by the square of the height in meters] before treatment with appetite suppressants, 39.7) who was referred to the Mayo Clinic for mitral-valve surgery three months after a systolic murmur was first noted. She had taken fenfluramine–phentermine (fenfluramine, 40 mg three times per day, and phentermine hydrochloride, 16 mg three times per day) for 25 months. Therapy had been discontinued one month before cardiac surgery because of the reported potentially catastrophic catecholamine-depleting effect of fenfluramine.[11] Echocardiography and cardiac catheterization confirmed the presence of severe mitral regurgitation.

During mitral-valve repair, unusual morphologic features were noted: the posterior and anterior leaflets were tethered, and the chordae were shortened. The valve was glistening white, had no rheumatic calcification or yellowish discoloration, and resembled valves affected by ergot alkaloid derivatives.[8] The patient had not used ergot preparations. Intraoperative transesophageal echocardiography demonstrated severe mitral regurgitation (Fig. 2) and mild tricuspid regurgitation.

After hospital discharge, symptomatic tricuspid valve regurgitation developed. Echocardiography demonstrated that the mitral-valve repair was intact without regurgitation. The tricuspid valve was thickened and failed to coapt; tricuspid regurgitation was severe. With medical management, symptoms of right ventricular failure improved despite the persistence of severe tricuspid regurgitation.

Patient 2

Patient 2 was a 44-year-old woman (pretreatment body-mass index, 35.5) who was treated with fenfluramine–phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day) for one year before dyspnea and a heart murmur were noted. Echocardiography demonstrated thickened aortic, mitral, and tricuspid valves with regurgitation. Because of progressive symptoms, mitral-valve and aortic-valve replacement and tricuspid-valve repair were performed at MeritCare Medical Center six months after fenfluramine–phentermine therapy was stopped. Histopathological examination of the resected mitral valve demonstrated intact valve architecture, with a plaque-like process that extended along the leaflet surfaces and encased the chordae tendineae (Fig. 3). Lesions on the aortic valve were similar but less extensive.

Patient 3

Patient 3 was a 48-year-old woman (pretreatment body-mass index, 34.5) with no previous cardiac disease who was treated with fenfluramine–phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day) for nine months. Therapy was discontinued when a murmur was noted, and symptoms of edema and breathlessness were reported. At echocardiography, the mitral valve was thickened and severely regurgitant. Three months later, the patient underwent mitral-valve replacement at MeritCare Medical Center for symptomatic mitral regurgitation. Histopathological examination demonstrated intact valve architecture and plaque-like lesions of apparent myofibroblasts in an abundant extracellular matrix of glycosaminoglycans and collagen (Fig. 4).

Patient 6

Patient 6 was a 51-year-old woman (pretreatment body-mass index, 56.8) with normal findings on cardiac examination who was treated with fenfluramine–phentermine (fenfluramine, 20 mg three times daily, and phentermine, 30 mg per day in divided doses). Seven months after this treatment was initiated, dyspnea and edema developed and a new murmur was noted. Transthoracic and transesophageal echocardiography at MeritCare Medical Center demonstrated thickened valves with severe mitral regurgitation and moderate aortic-valve and tricuspid-valve regurgitation. Fenfluramine–phentermine therapy was discontinued, and medical therapy for heart failure was instituted. Echocardiography performed three months later demonstrated minimal improvement in the valvular disease. The patient continues to be observed medically and has persistent symptoms of dyspnea.

Patient 7

Patient 7 was a 44-year-old woman who began receiving fenfluramine–phentermine for a pretreatment body-mass index of 30.5. Two years earlier, echocardiography had revealed normal valves. The initial dose was 60 mg of fenfluramine per day in divided doses and 30 mg of phentermine per day. Under medical

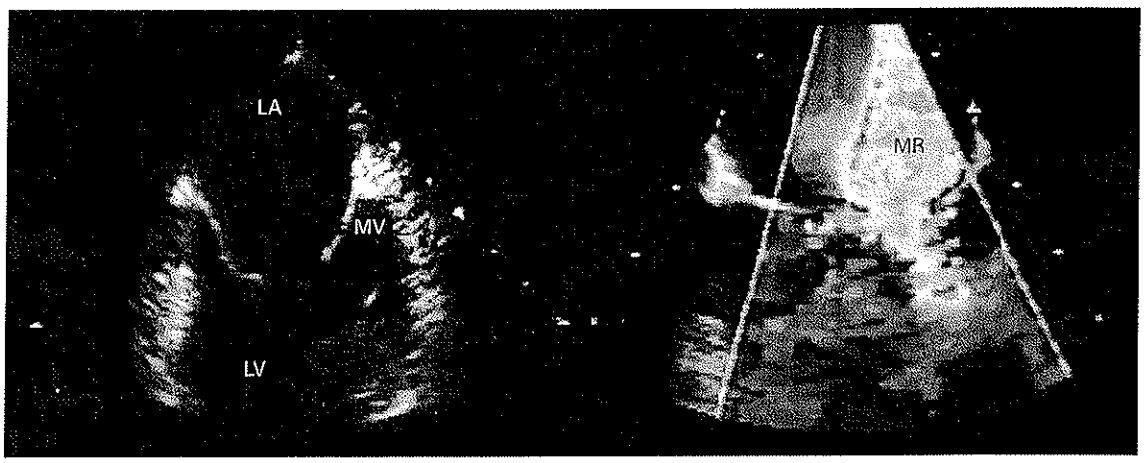

Figure 2. Intraoperative Transesophageal Echocardiograms in Patient 1.
The image on the left shows a thickened mitral valve (MV) during diastole. With the addition of color flow, the image on the right demonstrates severe mitral regurgitation (MR) during systole. LA denotes left atrium, and LV left ventricle.

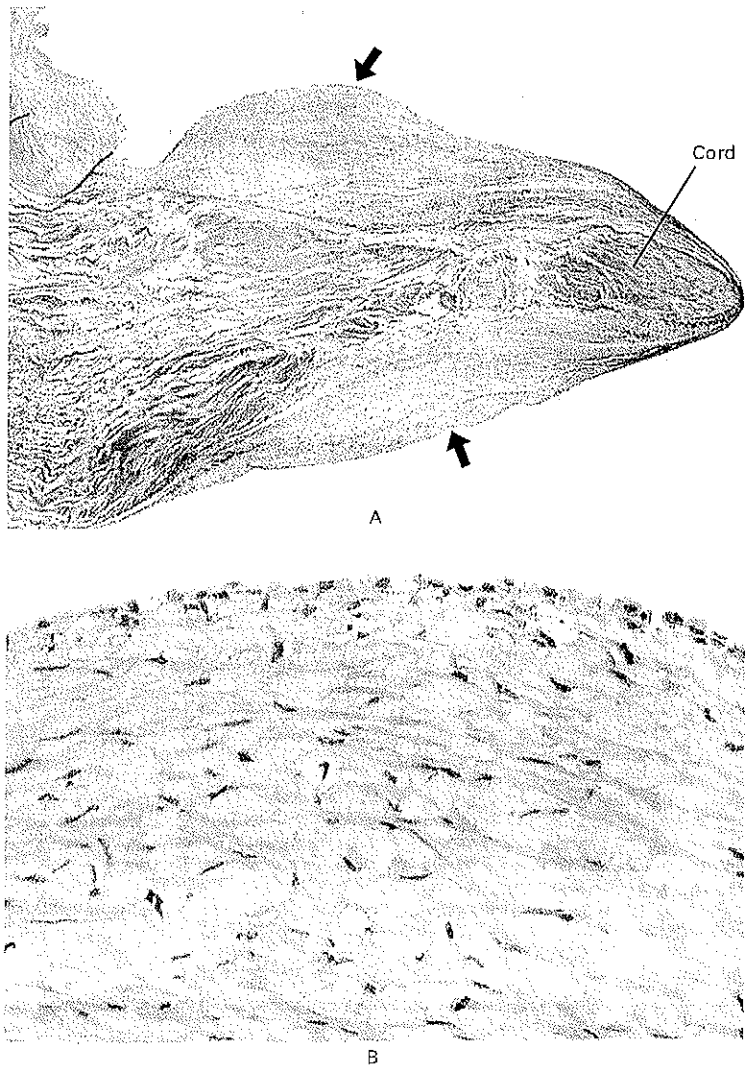

Figure 3. Photomicrographs of Resected Mitral Valve from Patient 2.

In Panel A, a low-power view (elastic–van Gieson stain, ×36) shows intact valve architecture with "stuck-on" plaques (arrows). In Panel B, a high-power view (hematoxylin and eosin, ×360) shows proliferative myofibroblasts in an abundant extracellular matrix.

direction, the daily doses were gradually increased to 220 mg of fenfluramine and 60 mg of phentermine.

Twelve months after fenfluramine–phentermine treatment was initiated, dyspnea developed on exertion. Echocardiography demonstrated a thickened trileaflet aortic valve with moderate regurgitation. Pulmonary-artery systolic pressure measured by cardiac catheterization was 75 mm Hg. Treatment with fenfluramine–phentermine was discontinued.

RESULTS

Table 1 summarizes the clinical features of the patients. Except for systemic hypertension, all of the patients were thought to be free of cardiovascular disease at the onset of weight-reduction therapy. The physicians who prescribed the anorectic agents for the patients were not the ones who evaluated the cardiovascular changes. The patients were evaluated a mean (±SD) of 12.3±7.1 months after the initiation of fenfluramine–phentermine treatment. The actual durations of drug therapy are shown in Table 1. Twenty patients presented with cardiovascular symptoms, and four patients had only a new murmur.

All patients underwent comprehensive two-dimen-

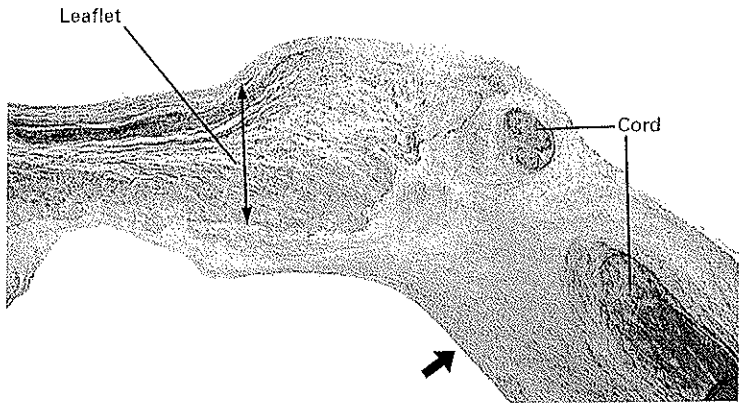

Figure 4. Photomicrograph of Resected Mitral Valve from Patient 3.
A low-power view (elastic–van Gieson stain, ×36) shows intact leaflet and tendinous cord, with encasement by proliferative plaque (arrow).

sional echocardiography, pulsed- and continuous-wave Doppler imaging, and color-flow examination according to previously described techniques.[12,13] Valve morphology was noted by two examiners to be atypical for rheumatic, congenital, or degenerative lesions. The mitral and aortic valves exhibited echocardiographic features similar to those seen in patients with chronic rheumatic involvement; however, there was no evidence of valve obstruction. Thickening and diastolic doming of the anterior mitral leaflet, with preserved mobility and thickening, and immobility of the posterior leaflet were typical findings (Fig. 2). Subvalvular involvement was characterized by thickening and shortening of the chordae tendineae, causing tethering of the posterior leaflet. The combination of abnormalities resulted in malcoaptation and central regurgitation. The aortic valve was characterized by thickening and mild retraction of the leaflets. With tricuspid-valve involvement, the septal leaflet was thickened and variably fixed to the septum. The anterior leaflet appeared thickened and exhibited decreased mobility, diastolic doming, and loss of coaptation visible on two-dimensional imaging. Color-flow imaging demonstrated variable degrees of regurgitation in all patients. The echocardiographic appearance of the valves was similar in the medically treated and the surgically treated patients.

Eight patients had Doppler echocardiographic or catheter evidence of pulmonary hypertension (right ventricular systolic pressure, >50 mm Hg; range, 52 to 93) that had not been documented previously. Tricuspid regurgitation of moderate or greater severity was present in five of the eight patients with pulmonary hypertension.

DISCUSSION

Fenfluramine is a sympathomimetic amine that has an anorectic action mediated through the activation of serotonergic pathways in the brain. Fenfluramine promotes the rapid release of serotonin, inhibits its reuptake, and may have receptor-agonist activity,[14] thus making serotonin more susceptible to metabolism and breakdown. The *d*-isomer of fenfluramine, dexfenfluramine, appears to be relatively selective for the central serotonergic system. Phentermine is a noradrenergic agent. Commonly used doses of these medications are 20 to 120 mg of fenfluramine per day and 18.75 to 37.5 mg of phentermine resin per day or 15 to 30 mg of phentermine hydrochloride per day.

Patients with malignant carcinoid syndrome have high levels of circulating serotonin. Associated cardiac disease is characterized by fibroplasia that involves primarily the valvular endocardium on the right side of the heart.[10,15] The mechanism of valve injury in patients with carcinoid syndrome has not been determined but is believed to be serotonin-mediated, because such patients have higher circulating levels of serotonin than do their counterparts without cardiac involvement.[10] The predilection for right-sided valve disease in carcinoid syndrome is most likely related to the serotonin-rich blood that enters the right atrium directly from the liver and the subsequent partial pulmonary degradation of serotonin. In our patients both left-sided and right-sided valvular lesions were seen, and multiple valves were often involved in individual patients.

The pathophysiologic mechanism in patients with ergot-alkaloid–induced valve disease has not been established, but the similar chemical structures of se-

rotonin, methysergide, and ergotamine may provide a clue.[16] Ergotamine-induced and carcinoid valve disease are microscopically identical, with fibrotic endocardial changes.[8] The pathological, surgical, and echocardiographic features of carcinoid and ergotamine-induced valve disease are indistinguishable from the features noted in our patients.

Fenfluramine alters serotonin metabolism in the brain.[14] Phentermine interferes with the pulmonary clearance of serotonin, which may explain its association with primary pulmonary hypertension.[17] Although serotonin levels were not measured in our patients, we postulate that the combination of fenfluramine and phentermine may potentiate the effect or concentration of circulating serotonin and result in valvular injury similar to that seen in patients with carcinoid syndrome or in those taking ergot preparations. However, the precise process by which this might occur is not known. No studies examining the effect of the combination of fenfluramine and phentermine in animals have been reported. Five of the 24 patients included in this series were taking either sertraline or fluoxetine while receiving fenfluramine–phentermine.

This description of patients is limited by the absence of pathological confirmation in the majority of cases. Many of the patients continue to be treated medically and have not undergone invasive or interventional procedures. Consequently, neither direct inspection nor histopathological evaluation has been carried out in most of the patients. Because no patient had symptomatic or clinical evidence of cardiovascular disease before the initiation of therapy with appetite suppressants, no routine pretreatment echocardiographic base-line studies were obtained. Only one patient had had an incidental echocardiographic study two years before treatment, and it showed no abnormalities. In the aggregate, however, these patients and those who underwent operative intervention had similar clinical and echocardiographic features. The mean age at the initiation of treatment, body-mass index, and duration of treatment before symptoms developed were similar in the medically and surgically treated groups.

In the absence of a control group or a case–control study, definitive statements about a true association of valvular disease with fenfluramine–phentermine therapy cannot be made. However, the appearance of clinically significant left-sided regurgitant valvular heart disease in a population less than 50 years old is rare.[18] Thus, the association of valvular regurgitation with fenfluramine–phentermine treatment is not likely to be due to chance. Moreover, the unusual echocardiographic morphology of the lesions further diminishes the likelihood of a coincidental observation.

These cases should arouse concern that this combination of appetite suppressants has important implications regarding valvular heart disease. Prospective studies of this association will be required to validate the possibility that this combination of medications may cause valvular heart disease. The mechanism of valve injury and the frequency of the association have yet to be determined. Candidates for fenfluramine–phentermine therapy should be informed about serious potential adverse effects, including pulmonary hypertension and valvular heart disease.

We are indebted to Pam Ruff, B.S., R.D.C.S., for identification of the patients, to Jeanne Beare, R.N., for data acquisition, and to Julie Klemmensen and Ann McCullough, M.D., for assistance in the preparation of the manuscript.

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The New England Journal of Medicine

Brief Report

Fatal Pulmonary Hypertension Associated with Short-Term Use of Fenfluramine and Phentermine

Eugene J. Mark, M.D., Eva D. Patalas, M.D., Howard T. Chang, M.D., Ph.D., Richard J. Evans, M.D., and Stanton C. Kessler, M.D.

THE dangers inherent in marked obesity have prompted physicians to advocate more aggressive strategies for weight reduction. One current strategy is the prescription of fenfluramine,[1,2] either alone or in combination with phentermine, with the knowledge that the risks of the drugs must be balanced against the risks of continued obesity.

Pulmonary hypertension in adults has several causes that can be identified pathologically. In the case of pulmonary hypertension that develops with hypoxia during the course of chronic obstructive or interstitial fibrosing disease of the lung, the pulmonary vessels are characterized by intimal and medial hyperplasia and luminal stenosis. Thromboembolic pulmonary hypertension results from the occlusion of large and small vessels by organizing blood clot with ingrowth of fibroblasts. Pulmonary venous hypertension due to cardiac failure or pulmonary veno-occlusive disease leads to secondary arterial hypertension as well as hemosiderosis. Collagen vascular disease, particularly scleroderma, can cause exuberant intimal proliferation described as onionskin change. Finally, plexogenic arteriopathy, a pathologically distinctive form of arterial remodeling, typically develops in patients with primary pulmonary hypertension.

Most patients with primary pulmonary hypertension are young women with a relatively rapid progression of disease.[3,4] Although most cases have no apparent cause, some can be traced to specific medical conditions or drugs. Particularly well established causes are cirrhosis[5,6] and human immunodeficiency virus infection.[7,8] Drugs used to suppress appetite can also cause pulmonary hypertension.

A small epidemic of pulmonary hypertension with fatalities in Switzerland, Germany, and Austria in the late 1960s and early 1970s was due to the use of aminorex for weight reduction.[9-13] Plexogenic arteriopathy characterized the pulmonary abnormalities.[10,14,15] Fenfluramine and dexfenfluramine, anorectic drugs currently in use, are also known to cause pulmonary hypertension.[16,17] We document on the basis of autopsy findings that plexogenic pulmonary hypertension was the cause of death in a woman who took fenfluramine and phentermine to lose weight. She died approximately 8 months after taking this off-label combination of drugs for only 23 days.

CASE REPORT

Clinical Findings

A 29-year-old woman sought medical help for obesity. She was otherwise healthy and did not smoke cigarettes. There was no family history of pulmonary hypertension. She weighed 88 kg (193 lb) and was 1.65 m (65 in.) tall. Her body-mass index (the weight in kilograms divided by the square of the height in meters) was 32. Combination therapy with fenfluramine (Pondimin) at a dose of 10 mg taken orally three times per day and phentermine (Ionamin) at a dose of 15 mg taken orally every morning was prescribed. The medications were discontinued after 23 days. The patient lost 4.5 kg (10 lb) during treatment. The patient subsequently reported an increased heart rate and shortness of breath with moderate exercise. These symptoms resolved over the next several weeks.

She felt well until five months later, when she noticed shortness of breath and pedal edema during an upper respiratory tract infection. Soon thereafter she had two episodes of syncope. Laboratory investigation showed mild polycythemia and respiratory alkalosis. Chest radiographs showed mild prominence of the right ventricular outflow tract and the left pulmonary artery. An electrocardiogram showed right-axis deviation and right ventricular hypertrophy. Cardiac catheterization showed severe pulmonary hypertension and markedly elevated pulmonary vascular resistance. The right ventricular pressure was 100/20 mm Hg; the pulmonary-artery pressure was 100/45 mm Hg, with a mean of 60 mm Hg; the pulmonary-capillary wedge pressure was 6 to 8 mm Hg; and the pulmonary vascular resistance was 20 to 24 Wood units (normal, <2). Ventilation–perfusion scanning showed a very low probability of acute pulmonary embolism, with no segmental perfusion defects. Pulmonary angiography showed vascular pruning and low flow consistent with the presence of high pulmonary vascular resistance and low cardiac output.

Other studies were performed to rule out various causes of pulmonary hypertension. Liver-function studies showed a mild elevation of alanine aminotransferase and lactate dehydrogenase in the serum. Abdominal ultrasonography revealed no liver abnormalities. Tests for antinuclear antibodies were negative. Administration of oxygen improved the patient's condition, but treatment with nitric oxide did not. A continuous intravenous infusion of epoprostenol was administered through an indwelling catheter two months after her syncopal episodes. The initial dose was 2 μg per kilogram of body weight per minute and was subsequently increased to 4 μg per kilogram per minute and then to 5 μg per kilogram per minute.

The patient was in stable condition and reasonably functional at home for six weeks before a fever developed and she was hospitalized. Cultures for bacteria were negative. Her condition improved with antibiotics, and she was discharged, only to be re-

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admitted two days later with more fever and pleuritic chest pain. An additional antibiotic was given, and she was again sent home. Two days later she died suddenly and unexpectedly in cardiac arrest.

Pathological Findings

An autopsy was performed at the Massachusetts General Hospital under the auspices of the Office of the Chief Medical Examiner of the Commonwealth of Massachusetts. There were no restrictions to the autopsy. A standard dissection protocol was followed. The lungs were inflated with formalin and cut 24 hours later into slabs 1 cm thick. Ten blocks of tissue were examined from each lung. The sections were stained with hematoxylin and eosin, Prussian blue for iron, elastic–van Gieson for elastic tissue, Mallory's trichrome for collagen, and Wilder's stain for reticulin.

At autopsy the body weighed 91 kg (200 lb). The right lung weighed 777 g and the left lung 630 g, approximately twice the normal weights. The lungs were congested but otherwise macroscopically unremarkable. The heart weighed 399 g, which is slightly heavier than normal. There was marked right ventricular hypertrophy. The lateral wall of the right ventricle was 0.6 cm thick (normal, 0.3 cm or less) when measured 1 cm below the tricuspid valve. The circumference of the pulmonary trunk was 6 cm, and the ascending aorta was 5 cm in circumference (Fig. 1), whereas normally the circumference of the ascending aorta is greater than that of the pulmonary trunk in an adult. Neither the aorta nor the main pulmonary arteries had atherosclerosis.

Histopathological examination of the lungs revealed congestion, extensive alveolar and interstitial edema, and evidence of marked pulmonary hypertension. Medial and intimal proliferation (Fig. 2) involved the majority of the muscular pulmonary arteries and arterioles. These findings correspond to a pathological grade of 3 on a 5-point scale in which 0 represents normal findings, 1 medial hypertrophy, 2 intimal hyperplasia, 3 occlusive intimal fibroelastosis, and 4 plexogenic arteriopathy.[18] Plexiform arteriopathy[14,15,18] (Fig. 3) was present in every slide and involved an average of three arteries per slide. Lesions manifested by dilatation, which are typically found distal to plexogenic lesions, were numerous as well (Fig. 4). Necrotizing arteritis (Fig. 5) with fibrinoid necrosis of the vascular wall, nuclear dust, and regional acute hemorrhage was present in a few slides. The findings are characteristic of plexogenic pulmonary hypertension and correspond to a pathological grade of 4.[18] The pulmonary veins were normal. A few aggregates of clear oval cells representing neuroendocrine cells were present in the basal layer of bronchiolar epithelium. There was no bronchiolitis, bronchopneumonia, or hemosiderosis. No acute or organizing thromboemboli were present. Polarization microscopy showed no birefringent material in blood vessels.

All other organs, including the brain, were macroscopically and microscopically normal. There was no coronary artery disease, hepatic fibrosis, or venous thrombosis.

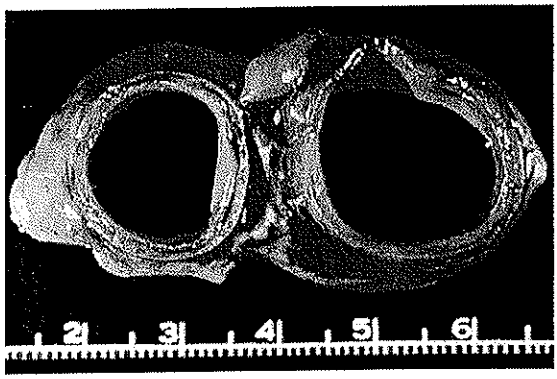

Figure 1. Cross Section of the Ascending Aorta (on the Left) and the Pulmonary Trunk (on the Right).
The pulmonary trunk is larger than the aorta, which is an abnormal finding indicative of pulmonary hypertension.

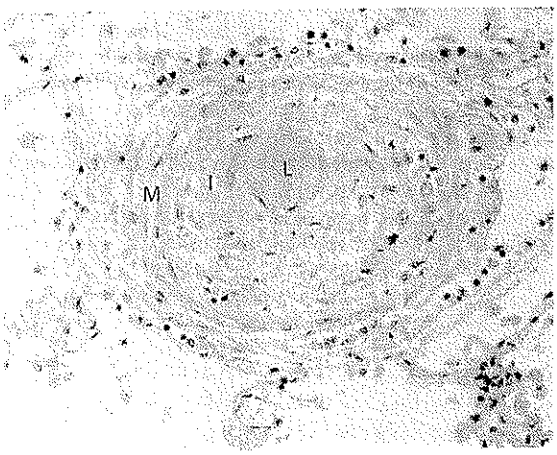

Figure 2. Pulmonary Hypertension with Marked Intimal (I) and Medial (M) Hyperplasia in a Muscular Pulmonary Artery (Hematoxylin and Eosin, ×20).
The lumen (L) is one fourth the normal diameter.

DISCUSSION

Plexogenic arteriopathy is the usual and most distinctive anatomical finding in primary pulmonary hypertension[14,15] and was present in European patients who had taken aminorex as an appetite suppressant in the 1960s and 1970s.[10] The morphology of plexogenic and angiomatoid lesions in these patients distinguished their form of the disease from common forms of pulmonary hypertension. Plexogenic lesions are preceded by exuberant proliferation of medial and intimal cells, which constitute lesser degrees of pulmonary hypertension. Necrosis of the arterial wall with repair and local vascular remodeling culminates in a racemose collection of abnormal channels outside the original artery. The proliferating cells are myofibroblasts[19] and endothelial cells with increased expression of endothelin-1.[20] Shunts develop between the pulmonary and bronchial arterial systems.[21,22] Vascular scarring leads to post-stenotically dilated blood vessels with thinned walls. All phases of plexogenic arteriopathy were observed in patients who took aminorex and in our patient, who took fenfluramine and phentermine.

The risk of pulmonary hypertension after treatment with aminorex was estimated to be only 2 in 1000,[11] but this figure was still 20 times the risk in the general population.[14] The latent period between drug therapy with aminorex and the development of the disease may have been related to the dose, but

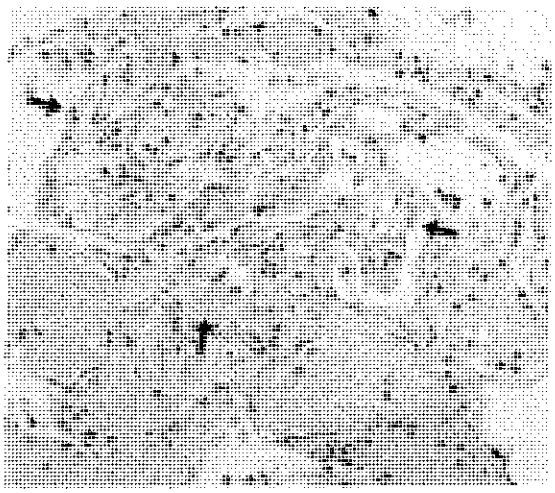

Figure 3. Plexogenic Arteriopathy (Hematoxylin and Eosin, ×20).
Interwoven vessels, which have the diameter of capillaries, form a plexus (arrows).

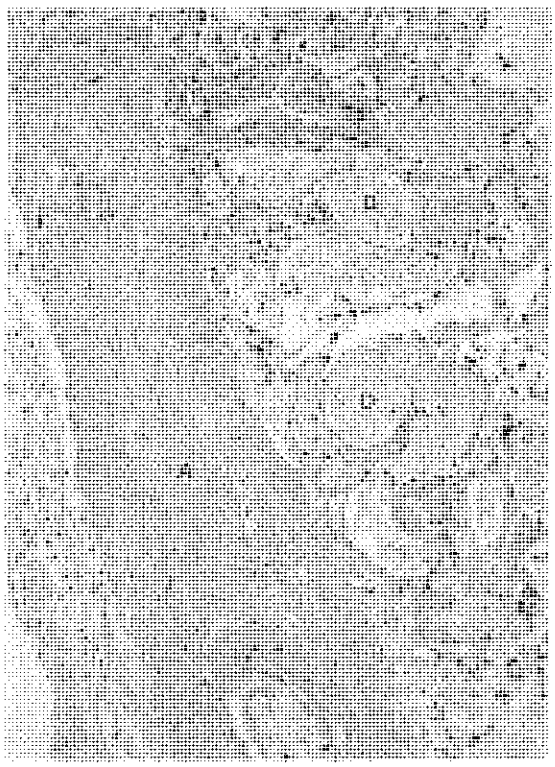

Figure 4. Dilated Blood Vessels with Thin Walls ("Dilatation Lesions," D) (Hematoxylin and Eosin, ×10).
Abnormal ectatic blood-filled vessels with thin walls lie adjacent to an artery occluded by intimal fibrosis (A).

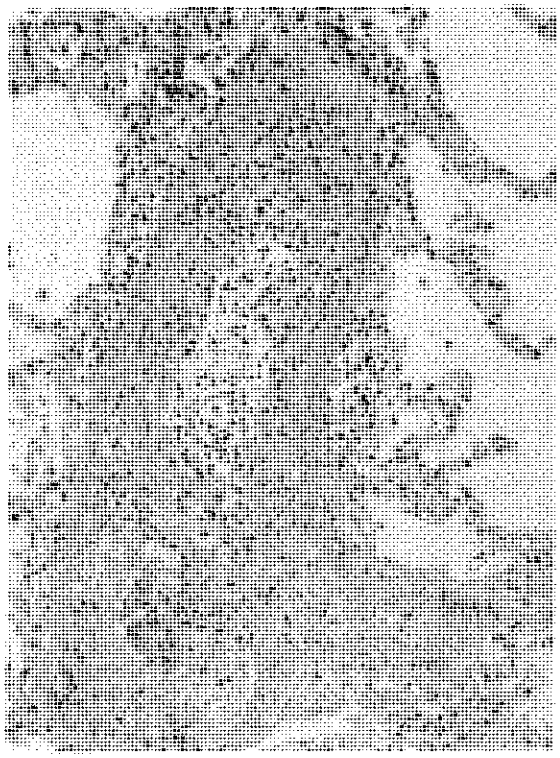

Figure 5. Necrotizing Arteritis (Hematoxylin and Eosin, ×10).
Neutrophils and nuclear dust (asterisks) infiltrate all layers of small elastic artery. Fibrinoid necrosis (F) is present. A glomeruloid (G) proliferation of endothelial cells protrudes into a curious aneurysmal structure.

the dose was sometimes small and often bore little relation to the degree of elevation in pressure.[14] Primary pulmonary hypertension has a familial basis in some instances.[23] In one case during the aminorex epidemic, pulmonary hypertension developed in a mother and daughter who were both taking the drug.[12] In one study of 32 patients in Switzerland in whom pulmonary hypertension developed during or after therapy with aminorex, 1 patient took the drug for only three weeks, another 3 took it for one month, and 23 took it for three months or longer.[12] Disease developed in 18 patients during treatment, in 4 within three months after therapy, in 2 between three and six months after therapy, and in 1 more than a year after therapy.[12] Since our patient took fenfluramine and phentermine for 23 days and died of pulmonary hypertension 8 months later, the time course of her disease falls within previously documented time frames for aminorex-associated pulmonary hypertension. The relative risk of pulmonary hypertension after treatment with dexfenfluramine for more than three months is approximately 30,[17] which is similar to that associated with aminorex.

How reversible is the pulmonary hypertension due to anorectic agents? Intimal and medial proliferations are believed to be potentially reversible. The necrotizing arteritis and ensuing plexogenic arteriopathy are probably permanent, but only a minority of the arteries generally show this change. In adults with idiopathic forms of plexogenic arteriopathy and in children in whom plexogenic arteriopathy develops as a result of congenital heart disease with left-to-right shunts, plexogenic lesions are believed to be irreversible and a bad prognostic sign.[13,15,24] However, the pulmonary hypertension caused by aminorex was sometimes reversible. The drug was sold in Europe from 1965 to 1968 and then withdrawn from the market. The epidemic of pulmonary hypertension had subsided by 1972. Ten years later, half the patients who had had signs and symptoms of pulmonary hypertension had died, the majority of right-sided heart failure. The average survival of those who died was 3½ years after the initial clinical diagnosis. Pulmonary vascular obstruction regressed in half the survivors.[13]

Fenfluramine and phentermine are chemical congeners of amphetamine[1] and are structurally similar to aminorex (Fig. 6). Fenfluramine differs from most derivatives of amphetamine by depressing rather than stimulating the central nervous system. It may suppress appetite by stimulating the ventromedial nucleus of the hypothalamus, possibly by promoting the release of serotonin and blocking its neuronal reuptake.[1] Since fenfluramine affects the cellular processing of serotonin and since intimal proliferation and fibrosis may develop in the veins and endocardium of patients with carcinoid syndrome and circulating serotonin or its metabolites,[25,26] drug-related hyperplasia of vascular myofibroblasts and endothelial cells is not entirely a surprise. The numbers of pulmonary endocrine cells, especially those containing gastrin-releasing peptide, are increased in plexogenic arteriopathy and not in other varieties of pulmonary hypertension.[27]

The histopathological findings related to pulmonary hypertension in our patient had four attributes with clinical correlates: it was partly irreversible, because there were plexogenic lesions in addition to intimal and medial proliferation; it was severe, present in every slide of lung tissue, whereas in some cases of idiopathic pulmonary hypertension the pathologist finds a plexogenic lesion in only every 5th or even every 10th block of tissue; it was in part established and ongoing, correlating with an onset months previously; and it was in part acute and necrotizing, correlating with rapid clinical deterioration terminally. The right ventricular hypertrophy and cor pulmonale attest to the severity of the pulmonary hypertension.

In summary, classic and severe plexogenic pulmonary arteriopathy developed in a patient who had taken anorectic agents for only 23 days. Although we cannot rule out preexisting disease, the histologic age of the lesions was consistent with the time elapsed since ingestion of the drugs. The patient died abruptly with cor pulmonale and necrotizing arteritis in the lungs. Pulmonary edema was a terminal event.

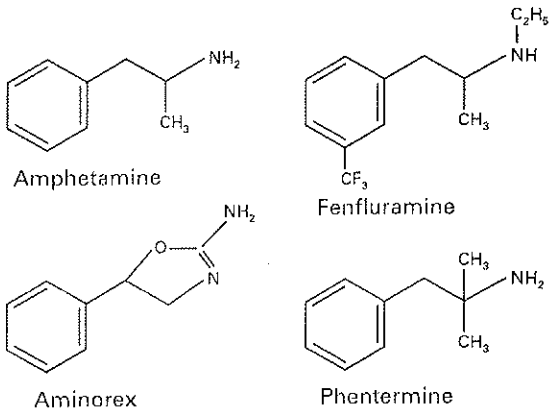

Figure 6. Chemical Structures of Amphetamine, Fenfluramine, Aminorex, and Phentermine.

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Annexe 2-13.1

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Neuilly, le 29 Novembre 1973

Monsieur le Ministre
de la Santé Publique et
de la Sécurité Sociale
Service Central de la Pharmacie
et des Médicaments
9, avenue Lowendal
75007 PARIS

A l'attention du 6ème Bureau

Monsieur le Ministre,

Conformément au décret n° 72-1062 du 21 Novembre 1972, nous avons l'honneur de solliciter une Autorisation de Mise sur le Marché pour notre médicament

MEDIATOR
comprimés dragéifiés

qui a été expérimenté sous le n° 780 SE.

Fabricant demandeur :	Les Laboratoires SERVIER 45 - GIDY-ORLEANS
Pharmacien signataire :	Docteur Jacques SERVIER 45 - GIDY-ORLEANS Président Directeur Général Inscrit à la Section B de l'Ordre des Pharmaciens sous le n° 21 921
Dénomination spéciale :	MEDIATOR
Forme pharmaceutique :	Comprimés dragéifiés
Contenances des modèles-vente:	10, 20, 24, 30, 60 et 100

.../...

22, rue Garnier 758 12-60
XXXXXXXXXXXXXX
17, Avenue Charles de Gaulle - 92 201 - Neuilly-sur-Seine • B.P. 110 • Tél. XXXXXXX + • Télex 62642 NLLSN
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LES LABORATOIRES SERVIER

Composition intégrale :

Principe actif :

Benzoate de {[méthyl-1 (trifluorométhyl-3 phényl)-2 éthyl] amino}-2 éthyle, chlorhydrate(*) ..... 0,150 g

Excipients :

Amidon de maïs,
Carboxyméthylcellulose sodique,
Cire blanche,
Ethylcellulose,
Magnésium (stéarate de),
Monooléate de glycérol,
Polysorbate,
Polyvidone excipient,
Silice colloïdale,
Sucre blanc officinal,
Talc,
Titane (oxyde de)

q. s. pour un comprimé dragéifié terminé à ..... 0,700 g

Formule de préparation pour un lot de 150 000 comprimés dragéifiés :

Benzoate de {[méthyl-1 (trifluorométhyl-3 phényl)-2 éthyl] amino}-2 éthyle, chlorhydrate		22,500 kg
Amidon de maïs	environ(+)	9,000 kg
Carboxyméthylcellulose sodique	"	0,105 kg
Ethylcellulose	"	0,125 kg
Magnésium (stéarate de)	"	0,750 kg
Monooléate de glycérol	"	0,062 kg
Polysorbate	"	0,038 kg
Polyvidone excipient	"	3,120 kg
Silice colloïdale	"	0,075 kg
Sucre blanc officinal	"	60,015 kg
Talc	"	8,760 kg
Titane (oxyde de)	"	0,450 kg
		105,000 kg

Cire blanche	q. s.	pour cirer
Eau purifiée		q. s.
Alcool éthylique industriel pharmaceutique :	environ	2 litres
Trichlorofluorométhane	"	1 litre

(+) Le terme "environ" couvre les variations quantitatives éventuelles à tolérer par rapport à la quantité théorique d'excipient indiquée, pour permettre un déroulement régulier de la fabrication tout en respectant le poids final désiré.

(*) Dénomination chimique selon les normes de nomenclature de la Pharmacopée Française

.../...

LES LABORATOIRES SERVIER

Nature du récipient :	Pilulier aluminium
Voie d'administration :	Orale
Indications thérapeutiques :	Troubles métaboliques glucido-lipidiques athérogènes. Troubles du métabolisme des lipides. Troubles du métabolisme des glucides.
Contre-indications :	Aucune contre-indication n'a été signalée au cours des essais.
Effets secondaires :	Aucun effet secondaire n'a été signalé au cours des essais.
Posologie usuelle :	1 à 4 comprimés dragéifiés par jour
Durée de conservation proposée :	4 ans
Tableau des substances vénéneuses :	C
Lieux de fabrication et de contrôle :	25, rue Eugène Vignat 45 - ORLEANS
Lieu de conditionnement :	326, rue Marcellin Berthelot 45 - FLEURY-les-AUBRAIS
Date prévue pour le début d'exploitation de la spécialité :	Octobre 1974
Exploitation prévue à l'étranger :	Dans tous les pays où un brevet a été délivré
Expérimentation à l'étranger :	Australie - Belgique - Brésil - Canada - Etats Unis - Grande Bretagne - Italie - République d'Afrique du Sud.
Brevets délivrés :	Allemagne - Angleterre - Australie - Autriche - Belgique - Canada - Danemark - Espagne - Etats Unis - Finlande - Grèce - Hollande - Irlande - Japon - Mexique - Norvège - Nouvelle Zélande - Philippines - Portugal - République Africaine Malgache - Suède - Suisse - Union Sud Africaine - U. R. S. S.

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Texte du projet d'étiquetage : Joint en annexe

Projet de fiche signalétique : Joint en annexe

Nous joignons à la présente demande :

- en quatre exemplaires, les documents suivants :

1/ un dossier réunissant

. la description du mode et des conditions de fabrication du médicament

. la description des techniques de contrôle des matières premières et de la spécialité prête à l'emploi
ainsi que l'indication des résultats obtenus par application de ces techniques

. le brevet

2/ l'expertise analytique de M. Christian EGNELL, Expert Analyste, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 2. 7. 72)

- en deux exemplaires, les documents suivants :

1/ l'expertise pharmacologique de M. le Docteur J. CHARPENTIER, Expert Pharmacologue-Toxicologue agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70)

2/ l'expertise toxicologique de M. le Docteur J. CHARPENTIER

3/ l'expertise tératologique de M. le Docteur J. CHARPENTIER

4/ les expertises cliniques suivantes :

- Démonstration de l'activité du Médiator dans le traitement des hyperlipoprotéinémies primitives

. Expertise de

M. le Professeur J. LOEPER, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70).

. Expertise de

M. le Professeur J. ROUFFY, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 15. 11. 72).

.../...

- Etude en double aveugle de l'activité du Médiator sur la mobilisation des acides gras libres plasmatiques, sur la balance azotée et sur les dépenses énergétiques basale et post-prandiale

. Expertise de

M. le Professeur Agrégé M. APFELBAUM, Expert Clinicien en Endocrinologie-Nutrition, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 2. 7. 72).

- Etude de l'activité du Médiator dans les troubles métaboliques athérogènes glucido-lipidiques observés au cours du diabète clinique ou latent, avec notamment une étude en double aveugle

. Expertise de

M. le Docteur R. DEUIL, Expert Clinicien en Endocrinologie-Nutrition, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70)

M. le Professeur M. PLAUCHU, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70)

et de M. le Professeur H. WAREMBOURG, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70).

- Etude comparative en double aveugle contre phenformine de l'activité du Médiator dans les troubles métaboliques athérogènes glucido-lipidiques au cours du diabète chimique ou clinique

. Expertise de

M. le Professeur J. MIROUZE, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70)

- Etude d'activité et d'acceptabilité du Médiator dans l'athérosclérose avec notamment une étude en double aveugle

. Expertise de

M. le Professeur P. Y. HATT, Expert Clinicien en Cardiologie, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 30. 3. 71)

M. le Docteur C. ELBAZ, Expert Clinicien en Chirurgie, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 30. 3. 71)

et M. le Docteur J. FREYRIA, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70).

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LES LABORATOIRES SERVIER

- Etude de l'acceptabilité clinique et biologique du Mediator lors de traitements à moyen terme

. Expertise de

M. le Professeur G. CABANEL, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70)

M. le Docteur A. CREFF, Expert Clinicien en Endocrinologie-Nutrition, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 2. 7. 72)

M. le Professeur M. PLAUCHU, Expert Clinicien en Médecine Interne, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70)

et M. le Docteur M. ZARA, Expert Clinicien en Endocrinologie-Nutrition, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 30. 3. 71).

- Etude de l'acceptabilité clinique et biologique du Mediator lors de traitements au long cours

. Expertise de

M. le Professeur Agrégé J. GUYOTAT, Expert Clinicien en Neuro-Psychiatrie, agréé par le Ministère de la Santé Publique et de la Sécurité Sociale (J. O. du 10. 5. 70).

Enfin, nous joignons un chèque bancaire de 2 500 F. - (deux mille cinq cents francs) établi à l'ordre du Trésor Public.

Nous vous prions de croire, Monsieur le Ministre, à l'assurance de notre très haute considération.

Docteur Jacques SERVIER

Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

Sommaire :

- **Préambule : p. 1 à 2**
- **Périodes de transposition en droit interne des directives / 1967- 1994 : p. 2 à 7**
- **Période 1995 – 2001 : p. 7 à 9**
- **Révision du droit communautaire en 2004 : p. 9 à 12**

Périodes	AMM	Contenu du dossier de demande	Modification d'AMM	Renouvellement d'AMM	Suspension/retrait	Instruction de la demande d'AMM
Préambule						
Lois de 1941 et 1946 : le visa ministériel	Article L. 601 1/Institution d'une autorisation obligatoire préalable à l'exploitation de toute spécialité pharmaceutique, mettant fin au régime antérieur de liberté 2/ Nouveaux critères : intérêt thérapeutique du médicament qui ne doit pas présenter de danger pour la santé morale et physique de la population 3/ accordé pour une période de 6 ans	–	–	–	–	–
Ordonnance du 4 février 1959 Décret du 5 avril 1960		Dossier d'expérimentation avec intervention d'experts agréés.				
Directive 65/65/CE du 26 janvier 1965 relative au rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques	Pose les définitions et principes de : - la spécialité pharmaceutique, - l'autorisation préalable à la mise sur le marché (AMM), - la composition du dossier devant accompagner la demande d'AMM,			Validité de l'AMM de 5 ans. Renouvellement quinquennal	Suspension ou retrait d'AMM quand : - la spécialité nocive dans les conditions normales d'emploi, - effet thérapeutique fait défaut	AMM refusée si : - spécialité est nocive dans les conditions normales d'emploi, - effet thérapeutique fait défaut ou est insuffisamment justifié par le demandeur,

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	- dossier devant démontrer que le médicament répond aux 3 critères suivants : qualité pharmaceutique, sécurité dans les conditions normales d'emploi et effet thérapeutique				- la spécialité n'a pas la composition qualitative et quantitative déclarée, - renseignements fournis à l'occasion de la demande sont erronés ou n'ont pas été modifiés, - contrôle du produit fini non effectués -	- spécialité n'a pas la composition qualitative et quantitative déclarée, - la documentation et renseignements présentés ne sont pas conformes aux prescriptions de la directive Durée maximale pour l'octroi de l'AMM de 210 jours
Périodes de transposition en droit interne des directives : 1967- 1994						
Ordonnance du 23 septembre 1967 L. 601	- Définition de la spécialité pharmaceutique, - AMM préalable à la commercialisation - Accordée par le Ministère des Affaires sociales - Validité de 5 ans	Obligations du fabricant : - vérification de l'innocuité du médicament dans les conditions normales d'emploi et de son intérêt thérapeutique, - analyse qualitative et quantitative, - disposer d'une méthode de fabrication et de procédés de contrôle de nature à garantir la qualité du produit au stade de la fabrication en série.		Renouvellement quinquennal	AMM peut être suspendue ou supprimée par le Ministre des Affaires sociales	
Décret d'application du 21 novembre 1972	**Art. R. 5128** Mentions de la demande d'AMM (fabricant et pharmacien signataire de la demande, dénomination spéciale du médicament, forme pharmaceutique, composition intégrale, dénomination internationale des composants si recommandée par OMS, formule de préparation du médicament, nature ou composition du récipient, modes et voies	**Art. R. 5129** Composition du dossier accompagnant la demande : - Description du mode et des conditions de fabrication, - Description des techniques de contrôle des matières premières et de la spécialité prête à l'emploi,	**Art. R.5138** Possibilité de changement de titulaire.	**Art. R. 5137** AMM renouvelée si le fabricant atteste qu'aucune modification intervenue dans les éléments produits à l'appui de la demande d'AMM ; AMM non renouvelée si effet thérapeutique fait défaut.	**Art. R. 5139** Suspension d'AMM pour une durée limitée à 1 an ou retrait d'AMM. Possibilité dans ces cas, d'interdiction de distribution si les conditions prévues notamment aux art. R. 5128 à R. 5133 ne sont pas ou ne sont plus remplies.	**Art. R. 5134** Possibilité donnée au ministre notamment de faire procéder à toute enquête relative à la fabrication du médicament, de consulter les experts agréés, choisis par le demandeur d'AMM pour participer à la constitution du dossier, de recueillir l'avis d'experts désignés par lui (cf. art. L. 605), de désigner des rapporteurs s'assurant de la

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	d'administration, indications thérapeutiques, contre-indications, effets secondaires, posologie, durée de conservation, lieux de fabrication, de contrôle et de conditionnement, tous renseignements relatifs à l'exploitation du médicament ou d'un principe actif de ce médicament dans un autre pays, texte du projet d'étiquetage)	- Brevets de médicament et de procédé de fabrication, - Compte rendus des expertises analytiques, pharmaco-toxicologiques et cliniques (détaillés à l'art. R. 5130). **Art. R. 5131** Les compte rendus des experts pharmacologues et toxicologues indiquent les méthodes utilisées et comportent une évaluation de la toxicité et de l'activité pharmacologique du médicament sur l'animal **Art. R. 5132** Compte rendus des expertises cliniques comprenant le relevé de chaque observation et les conclusions relatives notamment aux : - indications et aux effets thérapeutiques, - à l'innocuité dans les conditions normales d'emploi, - à l'évaluation de l'efficacité du dosage, - aux contre-indications et aux effets secondaires, - aux conditions normales et particulières de prescription, de délivrance et d'emploi.		Demande de renouvellement à présenter 90 jours avant date d'expiration.	Quand une AMM est retirée ou suspendue, le titulaire doit prendre toute disposition utile pour faire cesser la distribution de la spécialité en cause	régularité des demandes par rapport aux dispositions réglementaires ; **Art R. 5135** AMM accordée par le ministre en charge de la santé, - Délai d'instruction de 120 jours à partir réception d'un dossier complet. **Art R. 5136 :** Motifs de refus d'AMM - documentation et renseignements fournis non conformes aux dispositions réglementaires, - spécialité nocive dans les conditions normales d'emploi, - intérêt thérapeutique fait défaut ou insuffisamment justifié par le demandeur, - spécialité n'a pas la composition qualitative et quantitative déclarée **Art. R. 5141** Tout recours gracieux à l'encontre des décisions d'AMM, de refus, de renouvellement, de retrait ou de suspension d'AMM est soumis pour avis à une commission dont les membres sont désignés par le ministre chargé de la santé publique (composition détaillée dans le même art.)

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Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

Directive 75/318/CEE relative au rapprochement des législations des Etats membres concernant les normes et protocoles analytiques, toxico-pharmacologiques et cliniques en matière d'essais de spécialités		Son annexe définit l'architecture du dossier standard de demande d'AMM.				Un « considérant » de la directive 75/318 introduit la n écessité d'examiner les notions de nocivité et d'effet thérapeutique qu'en relation réciproque ; les documents qui doivent être joints à la demande d'AMM doivent faire ressortir l'aspect favorable de la balance entre l'efficacité et les risques potentiels.
Décret du 9 février 1978						Modification de l'art. R. 5140 Les décisions d'octroi, de refus, de renouvellement, de transfert de titulaire, de retrait (sont exclues les suspensions) sont prises par le ministre chargé de la santé après avis de la commission constituée à cet effet ; R. 5141 : composition de cette commission.
Transposition en droit interne : Décret du 20 septembre 1978 Arrêtés ministériels fixant les protocoles applicables aux essais	–	–	–	–	Ajout à l'art. R. 5139 : Suspension ou retrait d'AMM quand : - la spécialité nocive dans les conditions normales d'emploi, - effet thérapeutique fait défaut - la spécialité n'a pas la composition qualitative et quantitative déclarée,	

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					- renseignements fournis à l'occasion de la demande sont erronés, - conditions réglementaires ne sont pas ou plus remplies - les contrôles n'ont pas été effectués.	
Transposition en droit interne : Décret du 30 octobre 1985	Modification de l'article R. 5128 : La demande d'AMM doit proposer un « Résumé des Caractéristique du Produit » (RCP) Art. R. 5128-1 : Description des informations prévues par le RCP	–	Ajout de l'art. R. 5135-1 : Le titulaire de l'AMM doit après la délivrance de l'AMM, modifier les méthodes de contrôle en fonction des progrès de la science et de l'évolution des techniques, de façon que la spécialité soit contrôlée suivant les méthodes scientifiques généralement acceptées ; Il soumet ces modifications de méthodes de contrôle à l'approbation du ministre chargé de la santé.	Modification de l'art. R. 5137 : Si aucune décision n'est notifiée ou si aucune demande complémentaire n'est adressée au demandeur à la date d'expiration de l'AMM, l'AMM est considérée comme renouvelée à cette date.	–	Modification de l'art. R. 5135 : L'AMM est accompagnée du RCP tel qu'il est approuvé par le ministre chargé de la santé.

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Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

Directive 75/319/CEE concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques	Procédure de validation des spécialités pharmaceutiques : **article 39 (point 2) de la directive 75/319CEE** Les Etats membres doivent dans un délai de 15 ans appliquer les dispositions de la directive 75/319 **Aux termes des notes de la DPhM des 30 janvier et 22 mai 1985 :** Les industriels doivent mettre à jour les dossiers de fabrication et du contrôle de qualité des produits ainsi que procéder à une réévaluation en fonction de la progression des connaissances toxicologiques, pharmacologiques et cliniques des différents médicaments et de l'apport de connaissances médicales nouvelles. Un médicament sera maintenu sur le marché si son efficacité est démontrée ou suffisamment justifiée, et lorsque son rapport bénéfice/risque est positif. La validation pourra conduire au retrait du marché lorsque notamment la sécurité ne sera pas assurée au regard des connaissances actuelles (...). L'efficacité et la sécurité, dans les conditions normales d'emploi et dans les indications revendiquées seront appréciées indication par indication compte tenu : - des données et connaissances disponibles sur la base des travaux expérimentaux : dans ce cadre, la présentation des éléments bibliographiques est importante ; - et/ou de l'expérience acquise à leur sujet. Dans cette optique, les travaux de réflexion et de révision de la Commission de Révision des dictionnaires de spécialités pharmaceutiques seront très largement pris en compte. **Aux termes des avis aux fabricants de spécialités pharmaceutiques, relatif à l'application de l'article 39 précité, publiés aux JO du 20 décembre 1984, du 4 juin 1985 et du 5 juillet 1985.** L'opération dite « de validation » ou de réévaluation des spécialités pharmaceutiques impose aux titulaires d'autorisation (visa ou AMM délivrées antérieurement au 1er décembre 1976) d'effectuer auprès de la DPhM une demande de transformation de visa en AMM ou une demande de validation d'AMM ou à indiquer qu'ils ne souhaitent pas cette transformation ou cette validation. Les dossiers doivent être soumis en 1985 selon un calendrier par tranche défini par la classe pharmacothérapeutique dont relève la spécialité pharmaceutique. Le dossier de demande de validation comporte notamment un document de synthèse dans lequel doivent figurer en particulier : - le résumé des caractéristiques du produit ; - le niveau des ventes ; - les pays dans lesquels l'AMM a été donnée ; - le bilan des effets indésirables signalés à la firme après mise sur le marché ; données de pharmacovigilance et de consommation globale du produit ; utilisation dans d'autres pays.					
Directive 92/26/CEE concernant la classification en matière de délivrance des médicaments	Définition de sous-catégories de médicaments soumis à prescription médicale, assorties de critères de classification spécifique					
Transposition en droit interne : -Décret du 7 septembre 1992,	Codifient les différentes catégories de médicaments de prescription restreinte	–	–	–	–	–

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Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

-Décret du 2 décembre 1994	Modification de l'art. R. 5135 : L'AMM indique le cas échéant, le classement du médicament dans l'une des catégories suivantes : - soumis à prescription médicale du fait de l'inscription du médicament sur les listes des substances vénéneuses, - soumis à prescription spéciale du fait de son classement comme stupéfiant, - soumis à prescription restreinte.					
Période 1995 - 2001						
Règlement 541/95/CE relatif aux modifications d'AMM délivrée par l'autorité compétente d'un Etat membre (reconnaissance mutuelle)			Définition de modifications - de type mineur (Type I) figurant en annexe du Règlement - de type majeur (Type II « par défaut ») impliquant un changement fondamental du point de vue de la qualité, de la l'efficacité ou de la sécurité du médicament			
Loi n°93-5 du 4 janvier 1993 relative à la sécurité en matière de sécurité en matière de transfusion sanguine et n°96-452 du 2 mai 1996 Décret n° 93-982 du 5 août 1993	R. 5128 Demande d'AMM adressée au directeur général de l'Agence du médicament					Art. L. 567-1 : Création de l'Agence du Médicament. Transfert de compétence en matière d'AMM à l'Agence du médicament. Maintien de la Commission d'AMM en tant qu'instance consultative compétente en matière d'AMM

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Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

Loi du 28 mai 1996 Article L. 601			Toute modification des éléments d'une AMM délivrée par l'agence du médicament, quelle que soit son importance, doit être préalablement autorisée. L'autorisation peut être modifiée, suspendue ou retirée par l'Agence du médicament.			641
Loi n° 98-535 du 1er juillet 1998 relative au renforcement de la veille sanitaire et du contrôle de la sécurité sanitaire des produits destinés à l'homme						Abrogation de l'art. L.567-1 et ajout art. L. 793-1 et suivants : Agence du Médicament devient l'Agence français de sécurité sanitaire des produits de santé (Afssaps)
Ordonnance du 15 juin 2000 Refonte du code de la santé publique pour ce qui concerne la partie législative Décret n°2004-802 du 29 juillet 2004 relatif aux dispositions réglementaires	A droit constant L. 601 devient L. 5121-8 R. 5128 devient R. 5121-21	Art. R. 5129 devient R. 5121- 25		Art. R. 5137 devient R. 5121-45	Art. R. 5139 devient R. 5121-47	R.5135 devient R.5121-36 R.5136 devient R.5121-42 R.5140 devient R.5121-50 Annexe 2-2

Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

Directive 2001/83/CE du 6 novembre 2003 instituant un code communautaire relatif aux médicaments à usage humain	Codification à droit constant					
Révision du droit communautaire en 2004						
Directive 2004/27/CE		Modification de l'annexe I définissant un nouveau format de dossier d'AMM : l'European Common Technical Document (EU-CTD)	Obligation pour le titulaire de communiquer immédiatement à l'autorité compétente toute information nouvelle qui pourrait entraîner une modification des informations fournies lors de la demande d'AMM	- Principe de l'AMM illimitée après un premier renouvellement quinquennal sur la base d'une évaluation du rapport bénéfice/risque ; - Dossier consolidé concernant la qualité, la sécurité et l'efficacité et comprenant l'ensemble des modifications intervenues depuis la délivrance de l'AMM - Principe de caducité de l'AMM en l'absence de commercialisation de la spécialité concernée pendant une période de 3 ans consécutifs	Refus et retrait/suspension : Remplacement de la condition de la nocivité dans les conditions normales d'emploi par la condition du rapport bénéfice/risque défavorable.	Afin que le rapport bénéfice/risque puisse être évalué en permanence, l'autorité compétente peut à tout moment demander au titulaire de l'AMM de transmettre des données démontrant que le rapport bénéfice/risque demeure favorable

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Transposition en droit interne : Arrêté du 23 avril 2004 fixant les normes et protocoles applicables aux essais analytiques, toxicologiques et pharmacologiques ainsi qu'à la documentation clinique auxquels sont soumises les spécialités		Arrêté du 23 avril 2004				
Règlement n° 1084/2003 du 3 juin 2003 concernant l'examen des modifications des termes des AMM délivrée par une autorité compétente d'un Etat membre (issues des procédures de reconnaissance mutuelle et décentralisée			Abroge le Règlement 541/95/CE			643
Transposition en droit interne : Décret n°2005-156 du 18 février 2005 relatif aux modifications des AMM de médicaments à usage humain Arrêté du 7 mars 2005			Art. R. 5121-41-1 et suivants : - Définition des modifications de type IA et IB (administratives et/ou techniques) et de type II par défaut - Modalités de soumission et délais d'examen Art. R. 5121-41-7 :			Annexe 2-2

Synthèse de la réglementation applicable à l'autorisation de mise sur le marché d'un médicament, selon une procédure nationale, de 1970 à 2010

			Principe de la modification d'office d'une AMM à l'initiative de l'Afssaps, dans l'intérêt des malades ou pour tout autre motif de santé publique et ce, lorsqu'il est nécessaire de la mettre à jour en fonction des connaissances scientifiques.			
Transposition en droit interne de la directive 2004/27/CE : Loi n°2007-248 du 26 février 2007 et Décret n°2008-435 du 6 mai 2008		R.5121-25 : possibilité de demander un Plan de Gestion des Risques (PGR) / Décision Afssaps sur contenu du PGR. R.5121-37-2 : Possibilité de demander mise en place d'un PGR à tout moment, après la délivrance de l'AMM. L.5311-1 /R.5121-35 : Principe du rapport d'évaluation rédigé par l'Agence, mise à jour dès que de nouvelles informations importantes pour l'évaluation de la qualité, de la sécurité, de l'efficacité sont disponibles. R.5121-138 et R.5121-148 : modification de certaines sections de l'étiquetage et de la notice / tests de lisibilité des notices		L.5121-8 / R. 5121-45 : Renouvellement de l'AMM (AMM délivrée pour 5 ans puis illimitée suite à un seul renouvellement, sauf problème de pharmacovigilance nécessitant un 2nd renouvellement / demande de renouvellement accompagnée d'un dossier dit « consolidé ». L.5121-8 / R.5131-36-1 : Principe de caducité de l'AMM dès lors que le médicament n'est pas commercialisé pendant 3 années consécutives et dérogations possibles à la caducité	L.5121-9 : introduction de la notion de rapport bénéfice / risque dans les critères de refus d'AMM, modification d'office, suspension, retrait d'AMM. R.5121-21-2, R.5121-37-1 et R.5121-45-1 :Obligations d'information renforcée à la charge de l'industriel : transmission sans délai de toute donnée nouvelle pouvant avoir une incidence sur le rapport bénéfice / risque, notamment tous les résultats de recherche biomédicales + afin de pouvoir évaluer en permanence le rapport B/R , l'agence peut à tout	Modification de l'art. R. 5121-35 : 210 jours pour se prononcer sur une demande d'AMM. R.5121-50 : suppression des interdictions de délivrance limitées à certains lots (R.5121-48) et des décisions prises suite aux procédures d'arbitrages communautaires (R.5121-47 3°) parmi les décisions devant faire l'objet d'un avis préalable de la commission d'AMM.

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					moment demander au titulaire de transmettre des données démontrant que ce rapport reste favorable + possibilité de demander toute information relative au volume des ventes et des prescriptions et à l'état des stocks.	

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NUMÉRO DU DOSSIER :

NL 10008

DOSSIER DE PRÉSENTATION

Nom du produit : MEDIATOR

Forme : Comprimés Dragéifiés

Nom du Laboratoire : LABO. SERVIER

Rapporteur : M.r le Professeur Guignard

Désigné le 20 DEC 1973

Délai : 15 Jours

Signature :

RAPPORT TOXICO-PHARMACO-CLINIQUE

La présente demande concerne des comprimés dragéifiés appelés MEDIATOR renfermant par unité de prise 150 mg de benzoate de ((méthyl-1 (trifluorométhyl-3 phényl)- 2 éthyl) amino)- 2 éthyle, chlorhydrate.

A raison de 1 à 4 comprimés par jour le produit est indiqué dans les troubles métaboliques glucido-lipidiques athérogène.

L'expertise toxico-pharmacologique est due au Dr J. CHAUPENTIER. L'expert a étudié : - 1°) la toxicité aigüe du principe actif chez la souris (per os, I.P.) et le rat (idem), - 2) la toxicité sub-chronique pendant deux mois chez la souris, - 3) la toxicité chronique chez le rat durant 3 mois et 6 mois, - 4) un essai d'innocuité chez la souris, - 4) la toxicité chronique (essai complémentaire) chez le chien durant 6 mois, - 5) l'action sur le métabolisme lipidique (action sur les acides gras libres, le glycérol et les triglycérides chez le rat ; activité sur les lipides plasmatiques, les acides gras libres, le glycogène et les lipides hépatiques du rat avec un régime normal et avec un régime hyperlipidique ; activité sur la lipase pancréatique et sur la phosphatidate phosphohydrolase), - 6) l'action sur le métabolisme glucidique (rat) : activité sur le glycogène hépatique au cours du jeune ; glycémie et glycogène hépatique

Annexe 2-3

lors de traitements répétés, - 7) l'effet sédatif et anxiolytique chez le rat, - 8) l'action sur l'appareil cardio-vasculaire chez le chien et le rat, - 9) les effets latéraux sur les appareils gastro-intestinal, respiratoire et nerveux autonome.

L'expert conclut notamment que le MEDIATOR s'oppose à la déplétion glycogénique au cours du jeune, diminue l'activité de la lipase pancréatique favorisant la consommation des triglycérides plutôt que leur stokage dans les adipocytes, s'oppose à la surcharge lipidique lors des régimes hyperlipidiques par action directe sur la phosphatidate phosphohydrolase, inhibe, à des concentrations très faibles, la réponse pressive à la noradrénaline d'un vaisseau isolé, présente une action sédative et anxiolytique.

L'expert a en outre recherché l'éventuel effet tératogène du MEDIATOR chez le rat, la souris et le lapin.

L'expertise clinique a été réalisée par les Prs LOEPER, ROUFFY, APFELBAUM, le Dr DEUIL, les Prs PLAUCHU, WAREMBOURG MIROUZE, HATT, ELBAZ, FREYRIA, CABANEL, GUYOTAT, les Drs CREFF et ZARA.

(expertise pharmaco-clinique)

Le Pr APFELDBAUM a étudié en double aveugle : 1) chez 10 patients la libération des acides gras plasmatiques après l'administration d'une dose unique de MEDIATOR, - 2) chez 30 autres sujets l'action sur la balance azotée et les dépenses énergétiques basales et post-prandiales, montrant que le MEDIATOR ne détériore pas le capital protidique de l'organisme et entraine une diminution significative de la dépense d'énergie post-prandiale, énergie perdue qui ne pourra être utilisée ni pour un travail mécanique, ni pour un travail de synthèse chimique.

Les Prs LOEPER et ROUFFY ont étudié le MEDIATOR dans le traitement des hyperlipoprotéinémies primitives chez 56 malades ; le Pr LOEPER a observé une baisse du cholestérol de 13 % (15 % dans les formes II) et une baisse plus modérée de 10 à 15 % des triglycérides ; le Pr ROUFFY a pour sa part noté une baisse de 6,4 % de la cholestérolémie dans le groupe II et de 8 % dans les hyperlipidémies mixtes.

Annexe 2-3

Les Prs PLAUCHU et WAREMBOURG ont étudié le MEDIATOR dans les corrections des troubles glucido-lipidiques observés au cours du diabete (54 malades dont 16 en double aveugle), et le Dr DEUIL dans les anomalies lipidiques du diabète clinique (55 observations). Les experts observent une amélioration de la tolérance hydrocarbonée, une diminution du poids ainsi qu'un abaissement des constituants lipidique sériques (réduction du cholestérol de 13,6 à 21,4 % et des triglycérides de 32,2 % à 37,9 %.

Le Pr MIROUZE a étudié comparativement en double aveugle le MEDIATOR et le PHENFORMINE chez 32 diabètiques, le premier produit se montrant statistiquement plus efficace (par exemple amélioration de la tolérance glucidique dans 1 cas sur 2 contre 1 cas sur 5 avec la PHENFORMINE.

Les Prs HATT, ELBAZ et RREYRIA rapportent 52 observation dont 11 conduites en double aveugle chez des malades atteints d'athéroscléroze. En particulier, sur 41 patients ayant un excés de poids,34 ont maigri sous traitement.

Les Prs CABANEL et PLAUCHU ainsique les Drs CREFF et ZARA ont étudié plus spécialement l'acceptabilité clinique et biologique du MEDIATOR lors de traitement à moyen terme (1 à 5 mois) chez 79 malades dont 34 surcharges pondérales, et le Pr GUYOTAT lors du traitement à long terme (6 à 15 mois) chez 45 malades atteints de troubles psychiatriques variés et présentant des anomalies lipidiques. Aucune action fâcheuse sur le foie, les reins ou les éléments figurés du sang, n'a été observée ; aucune interférence facheuse avec les médicaments associés n'est apparue.

En ce qui concerne les effets secondaires ces deux dernières expertises recoupent les observations des autres experts : bonne tolérance marquée surtout par quelques incidents digestifs (nausées, diarrhées, douleurs épigastriques. 29 cas rapportés par les Prs LOEPER, ROUFFY, PLAUCHU et HATT, - des vertiges (5 cas rapportés par les Prs LOEPER et PLAUCHU, - des prurits (4 observations dues au Pr PLAUCHU), - de la somnolence (4 cas mentionnés par les Prs PLAUCHU et HATT. Les arrêts de traitement ont été exceptionnels (Pr PLAUCHU, 4 arrêts, Pr ROUFFY deux arrêts)

Annexe 2-3

Au total le MEDIATOR apparait comme un médicament actif et bien toléré.

EN CONCLUSION la présente demande relative à un nouveau médicament de la famille de la fenfluramine ayant des propriétés métaboliques anti-athéromateuses ne parait recevable en ce qui concerne le plan toxico-pharmaco-clinique.

PARIS, le 30 janvier 1974

-5 FEV. 1974 SAISINE DE LA COMMISSION

22 mars 1974

Avis de la Commission

Mesure d'instruction

Le dossier de demande d'Autorisation de Mise sur le Marché devra être complété :

1°) par une étude métabolique de la molécule étant donné ses liens de parenté chimique avec la fenfluramine.

2°) par une exploration plus approfondie de la tolérance biologique et clinique à long terme, cette spécialité étant en effet réservé à des traitements au long cours.

9-4-74

NOTIFICATION DE LA DECISION AU FABRICANT

1) L'étude métabolique réalisée par le Dr Jean CHARPENTIER chez le chien et chez l'homme permet de conclure que : - 1, le MEDIATOR est rapidement et totalement absorbé par le tractus digestif. Son élimination s'effectue exclusivement par les reins. Cette élimination est rapide évitant le risque d'une accumulation, - 2 la voie principale du métabolisme passe par la débenzoylation puis la sulfo- et la glycuroconjugaison - 3 que la voie secondaire est plus complexe : une séquence de débenzoylation, désalkylation, désamination oxydative et conjugaison à la glycine conduit à l'acide m-trifluorométhylhippurique, terme ultime du métabolisme hépatique.

Le métabolisme du MEDIATOR ne passe donc pas par le stade fenfluramine.

2) Une synthèse avec évaluation statistique, portant sur l'acceptabilité clinique et biologique, a été réalisé sur 151

NUMÉRO DU DOSSIER :

NL 10008

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DOSSIER DE PRÉSENTATION

patients traités durant 3 à 18 mois et dont les observations figurent dans le dossier d'Autorisation de Mise sur le Marché. Cette synthèse, confirmant notre rapport, montre que l'acceptabilité du Médiator s'avère satisfaisante : 1) sur le plan clinique, seules six observations font état de troubles mineurs, qui n'ont en aucun cas fait envisager la nécessité d'interrompre le traitement, - 2) sur le plan biologique, même aux plus fortes doses totales de MEDIATOR reçues par chaque patient, les contrôles portant sur le foie, le rein et le sang n'ont montré aucune modification, - 3) il n'est apparu aucune interaction de quelque sorte que ce soit au cours des 94 associations réalisées entre MEDIATOR et d'autres médicaments.

En conséquence, j'estime les compléments versés au dossier par le fabricant recevables

Paris, le 11 juin 1974

27 JUIN 1974 SAISINE DE LA COMMISSION

Avis de la Commission : Favorable

12.7.74

Décision du Chef de Service

Octroi d'A.M.M. + T. C

CB/DC

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MINISTERE DE LA SANTE PUBLIQUE
ET DE LA SECURITE SOCIALE

Service Central de la Pharmacie
et des Médicaments

PH. 11

PARIS, le 1 AVRIL 1974

Dossier n° : NL 10006 C 557

Monsieur,

Vous m'avez adressé une demande tendant à obtenir l'autorisation de mise sur le marché pour la spécialité dénommée :

MEDIATOR, comprimés dragéifiés.

Il ressort de l'examen du dossier :

que compte-tenu des liens de parenté chimique de la molécule avec la fenfluramine il devra être procédé à une étude métabolique.

En outre il s'avère nécessaire d'approfondir l'exploration de la tolérance clinique et biologique de ce produit destiné à des traitements au long cours.

En conséquence, j'ai l'honneur de vous faire connaître qu'une mesure d'instruction a été décidé (e) à l'encontre de votre demande et qu'un délai de 3 mois vous est accordé pour me fournir vos justifications.

Veuillez agréer, Monsieur, l'assurance de ma considération distinguée.

Pour le Ministre et par délégation
Le Chef du Service Central de la Pharmacie et des Médicaments

Henri NARGEOLET

Monsieur le Pharmacien responsable
des Laboratoires SERVIER,
92, rue Garnier
92200 - NEUILLY-SUR-SEINE

CB/DC

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MINISTÈRE
DE LA SANTÉ PUBLIQUE

SERVICE CENTRAL
DE LA PHARMACIE
ET DES MÉDICAMENTS

PH. 6

RÉPUBLIQUE FRANÇAISE

Paris, le 16 JUIL. 1974

Dossier n° : 10 008

LE MINISTRE DE LA SANTÉ PUBLIQUE

Vu le livre V du Code de la Santé Publique (partie législative et partie réglementaire et notamment l'article L 601)

DÉCIDE :

ARTICLE 1er - L'autorisation de mise sur le marché prévue à l'article L 601 du Code de la Santé Publique est accordée en vue de son débit à titre gratuit ou onéreux à la spécialité :
MEDIATOR, comprimés dragéifiés.
des Laboratoires

SERVIER, 45 - GIDY-ORLEANS

ARTICLE 2 - Ladite spécialité répond à la composition suivante :

Principe actif :

Benzoate de {[méthyl-1 (trifluorométhyl-3 phényl)-2 éthyl] amino}-2 éthyle, chlorhydrate ..... 0,150 g

Excipients :

Amidon de maïs,
Carboxyméthylcellulose sodique,
Cire blanche,
Ethylcellulose,
Magnésium (stéarate de),
Monooléate de glycérol,
Polysorbate,
Polyvidone excipient,
Silice colloïdale,
Sucre blanc officinal,
Talc,
Titane (oxyde de)
q.s. pour un comprimé dragéifié terminé à ..... 0,700 g

AUTORISATION DE MISE SUR LE MARCHÉ :

- 317 225.3 : 10 comprimés dragéifiés.
- 317 226.6 : 20 comprimés dragéifiés.
- 317 227.2 : 24 comprimés dragéifiés.
- 317 227.9 : 30 comprimés dragéifiés.
- 317 228.5 : 60 comprimés dragéifiés.
- 317 229.1 : 100 comprimés dragéifiés.

Annexe 2-5

ARTICLE 3 - Le fabricant devra respecter les conditions prévues dans sa demande d'autorisation de mise sur le marché en ce qui concerne la fabrication et le contrôle de ce produit.

ARTICLE 4 - La durée de conservation prévisible dans l'état actuel du dossier est de... 4 ans.

ARTICLE 5 - La validité de cette autorisation est limitée à cinq ans à partir de la date de la présente décision.

ARTICLE 6 - Les indications thérapeutiques sont limitées à :

. Troubles métaboliques glucido-lipidiques athérogènes.
. Troubles du métabolisme des lipides.
. Troubles du métabolisme des glucides.

ARTICLE 7 - Dans la publicité auprès du corps médical et auprès du public, le fabricant mentionnera :

. Qu'en fonction de susceptibilités individuelles et plus particulièrement aux posologies supérieures à 3 comprimés par jour, les effets secondaires suivants ont été observés :

- digestifs (nausées, vomissements, gastralgies, diarrhée),
- asthénie,
- somnolence ou état vertigineux.

ARTICLE 8 - Le Chef du Service Central de la Pharmacie et des Médicaments est chargé de notifier cette décision aux intéressés.

NOTIFIÉ le

Fait à Paris, le 16 JUIL. 1974

LE MINISTRE DE LA SANTÉ PUBLIQUE

Pour le Ministre et par délégation
Le Chef du Service Central de la Pharmacie et des Médicaments

Henri NARGEOLET

Pour Ampliation
Le Chef du 11e Bureau,

C. BARRAU

3 251 483 0

ervice Central de la Pharmacie
et des Médicaments

PH.11

Dossier n° : NL 10 008

16 JUIL. 1974

Monsieur le Professeur,

J'ai l'honneur de vous faire connaître qu'une Autorisation de Mise sur le Marché vient d'être accordée à la spécialité :

- MEDIATOR, comprimés dragéifiés -

présentée par les Laboratoires SERVIER.

S'agissant d'une molécule nouvelle, dont vous trouverez ci-joint une notice de renseignements, il m'a paru nécessaire de vous demander si vous ne jugez pas opportun que ce produit fasse l'objet d'une surveillance au titre de la Pharmaco-vigilanc

Avec mes remerciements anticipés, Veuillez agréer, Monsieur le Professeur, l'assurance de ma considération distinguée.

Pour le Ministre et par délégation
Le Chef du Service Central de la Pharmacie et des Médicaments

P.J : 1 notice de renseignements.

Henri NARGEOLET

Monsieur le Professeur QUERAUVILLIER
Faculté de Pharmacie

4, avenue de l'Observatoire

PARIS

CB/DC

Annexe 2-7

Service Central de la Pharmacie
et des Médicaments

PH.11

16 JUIL. 1974

Dossier n° : NL 10 008

Monsieur,

J'ai l'honneur de vous faire connaître que conformément à la réglementation des Substances Vénéneuses, la spécialité dénommée :

- MEDIATOR, comprimés dragéifiés -

sera soumise au régime du Tableau C.

Veuillez agréer, Monsieur, l'assurance de ma considération distinguée.

Pour le Ministre et par délégation
Le Chef du Service Central de la Pharmacie et des Médicaments

Henri NARGEOLET

Monsieur le Pharmacien responsable
des Laboratoires SERVIER

45 - GIDY-ORLEANS

Annexe 2-8

MINISTERE DE LA SANTE

REPUBLIQUE FRANCAISE

Service Central de la Pharmacie
et des Médicaments
PH. 11

PARIS, le

Dossier n° NL 10 008

LE MINISTRE DE LA SANTE

VU le Code de la Santé Publique et notamment l'article L 601,

D E C I D E :

L'autorisation de mise sur le marché accordée à la spécialité dénommée : MEDIATOR, comprimés dragéifiés

par décision en date du : 16 juillet 1974.
est rectifiée comme suit :

AU LIEU DE :	LIRE :
Principe actif :	Principe actif :
Benzoate de { [méthyl-1 (trifluoro-méthyl-3 phényl)-2 éthyl] amino } -2 éthyle, chlorhydrate..... 0,150g	Benzoate de { [méthyl-1 (trifluoro-méthyl-3 phényl)-2 éthyl] amino } -2 éthyle, chlorhydrate, BENFLUOREX..0,150

Pour Ampliation
Le Chef du 11e Bureau,

C. BARRAU

Pour le Ministre et par délégation
Le Chef du Service Central de la Pharmacie et des Médicaments

Henri NARGEOLET

Monsieur le Pharmacien responsable
des Laboratoires SERVIER

45 GIDY-ORLEANS

NOTIFIÉ le

Fait à PARIS, le 23 SEPT 1974

POUR LE MINISTRE DE LA SANTE

Annexe 2-9

MINISTERE DE LA SANTE
ET DE LA SECURITE SOCIALE

DIRECTION DE LA PHARMACIE
ET DU MEDICAMENT

RECTIFICATIF

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REPUBLIQUE FRANCAISE

PARIS, le 29 OCTOBRE 19 79

1 Place Fontenoy - 75007 PARIS
Tél. : 567.55.44

Madame, Monsieur le Pharmacien Responsable
des Laboratoires
SERVIER
22 rue Garnier
92201 NEUILLY SUR SEINE CEDEX BP 110

Madame, Monsieur,

La monographie de votre spécialité :

M E D I A T O R

a fait l'objet d'une étude approfondie par la Commission de Contrôle des Dictionnaires de Spécialités Pharmaceutiques, en application du décret du 24 août 1976.

A l'issu du travail commun entre les experts de la Commission et les spécialistes au sein de votre Etablissement Pharmaceutique, un texte a été rédigé, que vous avez approuvé par lettre adressée le 25 OCTOBRE 1979 au Président de la Commission. La copie de ce texte est jointe à la présente lettre.

Je donne mon accord à cette rédaction, qui sera désormais la seule à pouvoir paraître dans les prochaines éditions du dictionnaire VIDAL, et des recueils de même nature. Cet accord, bien entendu, est donné dans l'état actuel des connaissances.

Je vous engage à rendre l'information que porte la Fiche Signalétique remise par le visiteur médical, conforme au présent texte dès sa prochaine édition.

Je me félicite du résultat de cet effort commun, qui a permis de contribuer à l'amélioration de l'information médicale et pharmaceutique.

Veuillez agréer, Madame, Monsieur, l'assurance de ma considération distinguée.

Pour le Ministre et par délégation

Le Pharmacien Inspecteur
Divisionnaire de la Santé

Jacques CORDONNIER

Neuilly, le 25 octobre 1979

Annexe 2-9

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Direction de Recherche et Développement

MONOGRAPHIE DESTINEE AUX DICTIONNAIRES DES SPECIALITES PHARMACEUTIQUES

M E D I A T O R

DENOMINATION SPECIALE : MEDIATOR

FORME PHARMACEUTIQUE : Comprimés dragéifiés

PRESENTATION ET COMPOSITION :

Présentation : Pilulier de 30 comprimés dragéifiés

Composition :

	dose par unité de prise	dose par conditionnement
Benzoate de {[méthyl-1 (trifluoro-méthyl-3 phényl)-2 éthyl] amino}-2 éthyle, chlorhydrate ou benfluorex chlorhydrate	0,150 g	4,5 g

Excipients :

Amidon de maïs, carboxyméthylcellulose sodique, cire blanche, éthylcellulose, stéarate de magnésium, mono-oléate de glycérol, polysorbate, polyvidone - excipient, silice colloïdale, sucre blanc officinal, talc, oxyde de titane.

q.s. pour un comprimé dragéifié terminé à 0,700 g

SORT DU MEDICAMENT :

- Absorption gastro-intestinale rapide et totale avec un pic maximal survenant entre 1 et 2 heures après l'administration.
- Elimination rapide et totale par voie urinaire : en 8 heures, une excrétion moyenne d'environ 74 % de la dose administrée est constatée.

L'élimination se fait en 2 phases :

- une première phase rapide (60 % en 3 ou 4 heures)
- une deuxième phase lente, se terminant en 36 heures environ.

.../...

22, rue Garnier - 92201 Neuilly-sur-Seine-Cedex • B.P. 110 • Tél. : 758.12.60 • Télex : 620542 NLLSN • R.C. Paris B 085 480 796
Siège Social : 45-Gidy - France • Société anonyme au capital de 2 220 000 F • R.C. Orléans B 085 480 796

PROPRIETES :

Hypolipémiant

Il agit ainsi sur plusieurs facteurs fondamentaux liés au risque athérogène.

1. Actions de MEDIATOR sur le métabolisme lipidique

   - MEDIATOR diminue l'absorption intestinale des triglycérides (rat) Cet effet, confirmé chez l'homme en pharmacologie clinique, repose sur la diminution d'activité de la lipase pancréatique
   - Il réduit la synthèse hépatique des triglycérides et du cholestérol in vitro et in vivo (rat)
   - Il diminue la stéatose hépatique induite par des régimes riches en lipides, en glucides chez le rat obèse et au cours du diabète expérimental (ra
   - Il limite l'incorporation du cholestérol dans la paroi artérielle (lapin).

   Ce mode d'action est susceptible d'expliquer la diminution du cholestérol et des triglycérides chez l'homme.

2. Actions de MEDIATOR sur le métabolisme glucidique :

   - Il facilite la pénétration et l'utilisation cellulaire du glucose (rat)
   - Il diminue l'hyperglycémie du rat diabétique (insulinoprive ou non) et l'aire d'H.P.O. chez le lapin
   - Dans le diabète asymptomatique chez les patients obèses, il entraîne une baisse de la glycémie post-prandiale et une amélioration de la courbe d'H.P.O. supérieure à celle qu'on obtient avec un régime identique associé à un placébo.

   MEDIATOR n'ayant pas d'action sur l'insulinosécrétion ne peut pas provoquer d'hypoglycémie.

3. Effet complémentaire de MEDIATOR :

   Chez des patients obèses traités par MEDIATOR et régime, une baisse de l'uricémie d'environ 14 % a été observée.

   hyperuricémiant.

Aucune interférence indésirable de MEDIATOR avec les traitements associés au cours des études n'a été constatée.

MEDIATOR :
- ne potentialise pas les anticoagulants,
- ne provoque pas d'hypoglycémie,
- n'interfère pas avec la fonction thyroïdienne.

.../...

INDICATIONS :

Proposé dans le traitement des :

1. Hypercholestérolémies et hypertriglycéridémies endogènes de l'adulte, isolées ou associées,
   - lorsqu'un REGIME ADAPTE ET ASSIDU s'est avéré insuffisant,
   - lorsque la cholestérolémie après régime reste élevée et/ou qu'il existe des facteurs de risque associés.
     La poursuite du régime est toujours indispensable.
2. Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Remarque :
L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

CONTRE-INDICATIONS :

- les pancréatites chroniques avérées,
- la grossesse, par mesure de prudence.

MISE EN GARDE :

Les troubles métaboliques relevant d'un traitement par MEDIATOR sont essentiellement observés chez l'adulte. La prescription de MEDIATOR n'est donc pas justifiée chez l'enfant.

PRECAUTIONS D'EMPLOI :

Si après une période d'administration de quelques mois (3 à 6 mois), une réduction satisfaisante des concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

EFFETS INDESIRABLES :

Les effets secondaires suivants ont été observés : digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.

En raison de la nouveauté de ce produit, les effets indésirables à long terme n'ont pu encore être appréciés par des études contrôlées.

MODE D'EMPLOI ET POSOLOGIE :

- 3 comprimés dragéifiés par jour.

Coût de traitement journalier : 0,98 à 2,94 F.
Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

- 1 comprimé la première semaine au dîner,
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner,
- 3 comprimés à partir de la troisième semaine, 1 au petit-déjeuner, 1 au déjeuner, 1 au dîner.

.../...

Par la suite, la posologie peut être ramenée à 2 parfois 1 comprimé par jour, en fonction des résultats biologiques.

Durée du traitement :

En association avec le régime, MEDIATOR constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

SURDOSAGE :

Conduite à tenir en cas d'absorption massive :

Le traitement sera purement symptomatique : lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la tension artérielle, de l'état de conscience, des fonctions respiratoire et cardiaque.

MENTION IMPOSEE :

Durée de conservation : 4 ans.

CLASSEMENT DES SPECIALITES AU REGARD DU REGIME DES SUBSTANCES VENENEUSES

Tableau A.

RENSEIGNEMENTS ADMINISTRATIFS :

A.M.M. n° 317.557.9 du 16 juillet 1974.

Année de la première mise sur le marché : 1976.

PRIX DE VENTE AU PUBLIC :

Pilulier de 30 comprimés dragéifiés : 29,05 F. + 0,35 SHP.

Remboursement de la Sécurité Sociale : 70 %.

Admis aux Collectivités : 70 %.

RESPONSABLE DE LA MISE SUR LE MARCHE :

Les Laboratoires SERVIER
45520 GIDY.

Information médicale :

22, rue Garnier
92200 NEUILLY S/SEINE
Tél. 758.12.60.

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afssaps

Agence française de sécurité sanitaire des produits de santé

Direction de l'évaluation des médicaments et des produits biologiques
DARP / Unité des Affaires réglementaires
France Rousselle
Dossier suivi par Julie Cavalier / Carole Fosset
Tél. +33 (0)1 55 87 32 88 / 32 86
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Saint-Denis, le 27 DEC. 2010

Note

à l'attention de
la mission de l'Inspection Générale des Affaires Sociales sur le retrait du benfluorex

Objet : Procédure de validation des spécialités autorisées avant le 1 décembre 1976
Réf. : Message électronique de M. Etienne Marie du 24 décembre 2010

Dans le cadre de l'enquête en cours relative au retrait du benfluorex, vous avez souhaité disposer des références juridiques et les modalités de mise en application de la procédure dite de « validation » des spécialités pharmaceutiques autorisées avant le 1er décembre 1976 et de celle de l'AMM de la spécialité MEDIATOR en particulier.

A cet égard, je vous prie de trouver ci-après les éléments de réponse que je suis en mesure de vous apporter à ce jour.

1. sur les textes de référence de la procédure dite « de validation »

La directive 65/65/CEE du Conseil du 26 janvier 1965 concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques indiquait que ses dispositions seraient progressivement appliquées aux spécialités autorisées en vertu des dispositions antérieures, dans le délai de cinq ans à compter de sa notification. L'ordonnance n° 67-827 du 23 septembre 1967, qui transpose la directive 65/65/CEE, a donc prévu en son article 5 que la nouvelle législation relative à l'AMM serait progressivement appliquée aux spécialités autorisées avant le 28 septembre 1967. En application de cet article, le décret n° 68-964 du 4 novembre 1968 a organisé une procédure de validation.

Est ensuite intervenue la directive 75/319/CEE du Conseil du 20 mai 1975 concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques (J.O. n° L 47 du 09/06/1975) (P.J. n°1), qui a de nouveau modifié la réglementation et a par conséquent enjoint les Etats-membres à procéder à la mise en conformité des AMM délivrées avant le 1er décembre 1976 et ce, dans un délai de 15 ans à compter de sa notification, soit avant juin 1990 (article 39, point 2).

A cette fin, en France, plusieurs avis aux fabricants de spécialités pharmaceutiques, relatifs à l'application de l'article 39 précité, ont été publiés au J.O. ou au B.O.S.P, et des notes de la Direction de la pharmacie et du médicament (DPhM) du Ministère chargé de la santé ont été diffusées.

Annexe 2-10

2. sur les modalités générales de mise en œuvre de la procédure de validation

L'avis aux demandeurs publié au J.O. du 20 décembre 1984 (P.J. n°2) précisait aux titulaires d'autorisation (visa ou AMM délivrées antérieurement au 1er décembre 1976) d'effectuer auprès de la DPhM :

- soit une demande de transformation de visa en AMM ;
- soit une demande de validation d'AMM ;
- soit une déclaration indiquant qu'ils ne souhaitaient pas cette transformation ou validation des autorisations précédemment délivrées.

Le contenu du dossier de demande était précisé. Ce dossier devait inclure :

- une lettre de demande comportant certaines informations définies ;
- une proposition de résumé des caractéristiques du produit (RCP) ;
- une proposition de libellé de l'information pour le public ;
- un dossier incluant notamment un document de synthèse comprenant des renseignements pharmaceutiques, toxicologiques, pharmacologiques et cliniques. Ce document devait mentionner les éléments du dossier primitif et des informations complémentaires, dont « les noms des experts, le lieu et la date des études effectuées et toutes les informations permettant d'apprécier, pour le médicament dont il s'agit, son niveau d'efficacité et de sécurité dans des conditions normales d'emploi pour les indications revendiquées, compte tenu des données et des connaissances disponibles sur la base des travaux expérimentaux et/ou de l'expérience acquise à leur sujet (notamment données de pharmacovigilance, de consommation globale du produit, utilisation dans d'autres pays,...) » ;
- un dossier pharmaceutique actualisé.

L'opération générale de validation devait s'effectuer par classes pharmacothérapeutiques, réparties en 9 tranches. Le contenu de chaque tranche et le calendrier de dépôt des dossiers afférents étaient précisés dans l'avis aux demandeurs du 20 décembre 1984 précité et dans les avis aux demandeurs publiés aux J. O. du 4 juin 1985 (P.J. n°3) et du 5 juillet 1985 (P.J. n°4).
Le calendrier global prévisionnel s'étalait de 1985 à 1990.
Il était notamment indiqué que la validation portait sur les indications thérapeutiques et qu'en conséquence, les spécialités revendiquant plusieurs indications appartenant à différentes classes pharmacothérapeutiques seraient étudiées avec chacune des classes concernées (et donc selon le calendrier envisagé pour chacune des classes concernées).

Le contenu de chaque « tranche » et les dates de dépôt correspondantes étaient les suivants (voir les avis aux demandeurs précités pour le détail sur les groupes de médicaments concernés dans chaque classe pharmacothérapeutique) :

- 1ère tranche : les premiers dossiers, appartenant aux classes suivantes, devaient être déposés entre le 1er janvier 1985 et le 30 juin 1985 : antivitamines K, héparines injectables, antiangoreux, antiarythmiques, antihypertenseurs, bêta-bloquants, hypolipémiants, glucosides, cardiotoniques, diurétiques, sédatifs cardiaques, cardio-accélérateurs (antibradycardisants), analeptiques cardiovasculaires ; médicaments ophtalmologiques antiglaucomateux et mydriatiques.

- 2ème tranche : les dossiers appartenant aux classes pharmacothérapeutiques suivantes devaient être déposés entre le 1er juillet 1985 et le 31 décembre 1985 : médicaments de neurologie et de psychiatrie.

- 3ème tranche : janvier à juin 1986 : médicaments utilisés en médecine cardio-vasculaire et non appelés au cours de la 1ère tranche, potassium et antihyperkaliémiques, hémostase, anorexigènes.

- 4ème tranche : juillet à décembre 1986 : gastro-entérologie, hépatologie.

- 5ème tranche : janvier à juin 1987 : ophtalmologie, glucorticoïdes oraux et injectables et ACTH, infections.

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- 6ème tranche : sauf exception, jusqu'au 30 juin 1988: gastro-entérologie (laxatifs), pneumologie, rhinologie, ophtalmologie, otologie, stomatologie, allergologie, produits dentaires.

- 7ème tranche : mars 1989 : pneumologie, dermatologie, spécialités à base de principes actifs d'origine végétale revendiquant une indication thérapeutique liée à leur utilisation traditionnelle.

- 8ème tranche : décembre 1989 : rhumatologie, douleurs, anesthésiologie, antipyrétiques, gynécologie, endocrinologie, uronéphrologie.

- 9ème tranche : 10 juin 1990 : parasitologie, hématologie, cancérologie, ophtalmologie, métabolisme-nutrition-vitamines, alimentation parentérale, toxicologie, produits de diagnostic, diététique pharmaceutique, produits dentaires.

Les principes généraux et la procédure de validation ont été détaillés par une note de la DPhM du 30 janvier 1985 (P.J. n°5). Il s'agissait d'une « mise à jour des dossiers de fabrication et du contrôle de la qualité des produits ainsi que d'une réévaluation en fonction de la progression des connaissances toxicologiques, pharmacologiques, cliniques des différents médicaments et de l'apport de connaissances médicales nouvelles ». L'issue de cette réévaluation devait aboutir au maintien sur le marché des médicaments « à efficacité démontrée » ou « suffisamment justifiée » **et « ayant un rapport bénéfice/risque positif »**. A cette fin, il est à noter que des modifications qualitatives ou quantitatives de formule pouvaient être demandées et acceptées.

Les modalités précises d'examen des dossiers par la DPhM n'étaient pas décrites dans les textes précités. Concernant l'examen du dossier clinique (efficacité, intérêt thérapeutique), il était toutefois précisé dans la note précitée que « les travaux de réflexion et de révision de la Commission de révision des Dictionnaires de Spécialités Pharmaceutiques » seraient « très largement pris en compte ». En outre, la Commission d'AMM ayant été créée en 1978, il est probable que son avis ait été sollicité pour l'examen de ces demandes.

L'examen des dossiers débutait par les données cliniques qui correspondaient au « critère premier déterminant de la validation ou de la non validation ». Il était effectué par le Ministère de la Santé (DPhM) dans un délai de 6 mois et conduisait à la validation, au refus, à une demande de compléments préalables ou à un accord pour une modification de formule (et sur le dossier complémentaire à fournir) :

- après accord sur le dossier clinique, l'examen des données pharmaceutiques et toxicologiques pouvait s'effectuer dans un second temps ;

- dans les cas de demande de compléments préalables ou d'accord pour une modification de formule, les demandeurs disposaient de 18 mois pour apporter les compléments ; la DPhM statuait ensuite dans les 3 mois en validant ou refusant la spécialité ;

- enfin, pour les médicaments non validés, « un délai de 18 mois à compter de l'issue de la période du 1er examen du groupe de médicaments appelés » était « accordé pour permettre aux fabricants une éventuelle reconversion (par exemple modification de formule) » ; à l'issue de cette période, le retrait devait être le cas échéant prononcé. Pendant cette période intermédiaire, les conditions dans lesquelles les médicaments non validés pouvaient rester sur le marché étaient « déterminées pour chaque cas particulier ». L'information des utilisateurs de cette absence de validation était prévue « afin de faciliter les changements d'habitude ».

Par note de la DPhM du 22 mai 1985 (lettre au SNIP) (P.J. n°6), les modalités de constitution du dossier pharmaceutique ont été précisées.

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Dans un nouvel avis aux fabricants publié le 3 juin 1986 (B.O.S.P. 86/19) (P.J. n°7), le format et le contenu du dossier complet de demande de validation étaient reprécisés et davantage détaillés. Ces nouvelles dispositions étaient applicables aux dossiers correspondants à la 3ème tranche et aux tranches suivantes. Deux types de dossiers étaient décrits : ceux correspondant à un « premier dépôt » et ceux correspondants à un « dépôt ultérieur » (pour les produits ayant déjà fait l'objet d'un dépôt antérieur pour d'autres indications dans une tranche précédemment appelée).

3. sur l'achèvement de la procédure générale de validation

La procédure de validation n'a pas été finalisée à la date initialement annoncée et imposée par la directive 75/319/CEE (1990). Il semble que la DPhM a notamment rencontré au début des années 90 d'importantes difficultés à traiter tant les demandes de validation que les nouvelles demandes d'AMM. Des retards importants se sont donc accumulés à cette période.

A partir de 1993, la procédure de validation s'est naturellement poursuivie et achevée sous la responsabilité de l'Agence du Médicament (ADM) ; une cellule spécifique a été chargée de cette mission au sein de la Direction de l'évaluation (DEV).
Des avis aux demandeurs ont repoussé certains délais correspondants aux tranches non finalisés, jusqu'au 31 janvier 1996 au plus tard.
Il est à noter que l'ADM a soumis tous les dossiers de validation à l'avis de la Commission d'AMM.

Mi-1996, un nouvel objectif d'achèvement complet de la procédure fin 1996 a été sollicité par le Ministère. L'Afssaps a alors alloué des moyens et du personnel supplémentaires pour cette activité.

Selon une note de D. Tabuteau, directeur général de l'ADM, à P. Bas, directeur de cabinet du Ministre du travail et des affaires sociales, du 31 décembre 1996, la procédure de validation aurait concerné au total près de 6000 dossiers. A la création de l'ADM en 1993, 4500 dossiers étaient encore à traiter.

L'évaluation de l'ensemble des dossiers a pu être achevée fin 1996 ; toutefois, les notifications des AMM correspondantes, des réponses aux firmes ayant sollicité des délais supplémentaires ou le traitement des recours déposés par les firmes ont été achevés à la fin de l'année 1997.

4. sur le processus de validation de l'AMM de MEDIATOR

Vous trouverez ci-aprés l'historique de la validation de la spécialité MEDIATOR, tiré des documents archivés dans les feuilles de garde de cette spécialité :

- 16 juillet 1974 : octroi de l'AMM dans les indications :
  - troubles métaboliques glucido-lipidiques athérogènes ;
  - troubles du métabolisme des lipides ;
  - troubles du métabolisme des glucides ;

- 29 octobre 1979 : accord sur la monographie étoilée par la Commission de Contrôle des Dictionnaires de Spécialités Pharmaceutiques. Les indications retenues sont :
  - Hypercholestérolémies et hypertriglycéridémies endogènes de l'adulte, isolées ou associées, lorsqu' régime adapté et assidu s'est avéré insuffisant ; lorsque la cholestérolémie aprés régime reste élevée et/ou qu'il existe des facteurs de risque associés. La poursuite du régime est toujours indispensable.
  - Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

- 26 juin 1985 : demande de Servier de validation de l'AMM (correspondant à la 1ère tranche de validation, classe « hypolipémiants »)

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- 22 avril 1987 : validation de l'AMM (1ère tranche / hypolipémiants). La seule indication retenue est : « adjuvant du régime adapté dans les hypertriglycéridémies » ; à noter toutefois le maintien de l'action sur le métabolisme glucidique dans la rubrique « propriétés pharmacologiques » du RCP.

- 29 juillet 1987 : lettre de Servier sollicitant le maintien de l'indication « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale » dans les annexes de l'AMM validée, dans l'attente de la validation de cette indication lors de l'appel de la 8ème tranche prévu en 1989 (classe « endocrinologie ») ;

- 1er septembre 1987 : lettre de réponse de la DPhM précisant que l'indication « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale » a été examinée mais n'a pas été retenue, et donc n'a donc pas été reprise dans les annexes de l'AMM. Il est proposé au laboratoire de déposer une demande pour cette indication lors de l'appel de la 8ème tranche (classe « endocrinologie ») ;

- 19 janvier 1990 : demande de Servier de validation de l'indication relative à la 8ème tranche (« endocrinologie ») ;

- 26 juillet 1994 : demande de modification de la rubrique « propriétés pharmacologiques » du RCP afin de renforcer les propriétés sur le métabolisme glucidique ;

- 16 mars 1995 : avis défavorable de l'ADM à cette demande de modification du libellé pour les raisons suivantes : « L'indication soumise à la validation n'est pas justifiée par les données fournies » ; « aucune mention de propriétés pharmacologiques en relation avec cette indication ne peut être acceptée » ;

- 22 septembre 1995 : réunion de concertation relative à l'indication non validée « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale » dont les conclusions sont : « Le benfluorex pourrait avoir une place dans la stratégie thérapeutique du diabète (ie. intolérance à la metformine) mais celle-ci reste entièrement à démontrer. Dans l'intervalle, l'indication chez le diabétique n'est pas maintenue. » ;

- 5 décembre 1995 : examen de l'indication « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale » par le groupe de travail interne (GTI) n°53. Avis du GTI : projet de rejet de la validation de cette indication (« (...) L'insuffisance de données d'efficacité ne permet donc pas de définir un bénéfice clinique pertinent chez les patients diabétiques en surcharge pondérale. ») ;

- 16 avril 1997 : décision de modification de l'AMM confirmant la validation de l'indication « hypertriglycéridémies » ; en revanche, démonstration d'efficacité insuffisante pour l'indication « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale ». Par ailleurs, suppression des propriétés sur le métabolisme glucidique de la rubrique « propriétés pharmacologiques » ;

- 28 avril 1997 : observations de l'Agence du médicament sur le projet de notice/étiquetage déposé en janvier 1997 dans le cadre général de la mise en conformité des textes relatifs à la notice et à l'étiquetage des spécialités[1] : suppression de toute mention relative à l'indication « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale » ;

- 4 août 1997 : lettre de l'ADM à Servier indiquant que suite à un « entretien » de Servier avec Arielle North (responsable de la « Coordination des Affaires réglementaires » de la DEV), les mentions concernant l'indication « adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale » peuvent être maintenues. Les nouvelles observations de l'ADM sur le projet de notice/étiquetage sont jointes au courrier ; l'indication précitée n'y est plus supprimée ;

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[1] *Directive 92/27/CEE du 31 mars 1992 concernant l'étiquetage et la notice des médicaments à usage humain (transposée par le décret 94-19 du 5 janvier 1994)*

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- 29 mai 1998 : demande de Servier d'extension de l'AMM dans l'indication « Diabète de type II, en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique » ;

- Avis de la Commission d'AMM n° 273 du 2 octobre 1998 : sursis à statuer « en l'attente d'une réévaluation du dossier au plan méthodologique, notamment afin de situer l'efficacité du benfluorex vis à vis de la metformine » ;

- Avis de la Commission d'AMM n° 289 du 8 juillet 1999 : sursis à statuer « en l'attente des conclusions de l'inspection sur la qualité de l'essai ; de l'évaluation des données disponibles de pharmacovigilance ; de l'avis de l'expert méthodologiste » ;

- Avis de la Commission d'AMM n° 296 du 9 décembre 1999 : avis défavorable à l'indication proposée ;

- 25 avril 2000 : décision de refus de modification de l'AMM.

- 29 juin 2000 : demande de recours gracieux de Servier à l'encontre du projet de rejet de sa demande

- Avis du GT « endocrinologie, gynécologie, rhumatologie, antalgie, pneumologie, ORL et ophtalmologie » (PTC2) n°1 du 20 septembre 2000, validé par la Commission d'AMM n° 311 du 16 novembre 2000 : « Maintien de l'avis défavorable à l'indication proposée par la firme. (...). En conséquence, le libellé de l'indication thérapeutique retenu est le suivant : « adjuvant du régime adapté dans les hypertriglycéridémies ; adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale (...)» ;

- 12 juin 2001 : décision de modification de l'AMM intégrant notamment ce libellé d'indications au sein des annexes de l'AMM.

Au vu de ce qui précède, l'indication du traitement adjuvant du diabète n'a pas été retenue dans le cadre de la validation, tant lors de son examen dans le cadre de la 1ère tranche que lors d'un nouvel examen dans le cadre de la 8ème tranche.
En revanche, pour des raisons non précisées dans les échanges, cette indication a été acceptée en 1997 dans le cadre de la procédure de mise en conformité des textes relatifs à la notice à l'étiquetage.
Elle a ensuite été reprise telle que validée en 1997 dans la notice à l'occasion de la notification d'une modification de l'AMM initialement demandée par Servier pour l'ajout du traitement du diabète de type II.

Mes services se tiennent à votre disposition pour toute précision que vous jugeriez utile.

Le Directeur Général

Jean MARIMBERT

31975L0319

Deuxième directive 75/319/CEE du Conseil, du 20 mai 1975, concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques

Journal officiel n° L 147 du 09/06/1975 p. 0013 - 0022
édition spéciale finnoise: chapitre 13 tome 4 p. 0098
édition spéciale grecque: chapitre 13 tome 3 p. 0066
édition spéciale suédoise: chapitre 13 tome 4 p. 0098
édition spéciale espagnole: chapitre 13 tome 4 p. 0092
édition spéciale portugaise: chapitre 13 tome 4 p. 0092

DEUXIÈME DIRECTIVE DU CONSEIL du 20 mai 1975 concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques (75/319/CEE)

LE CONSEIL DES COMMUNAUTÉS EUROPÉENNES,

vu le traité instituant la Communauté économique européenne, et notamment son article 100,

vu la proposition de la Commission,

vu l'avis de l'Assemblée (1),

vu l'avis du Comité économique et social (2),

considérant qu'il importe, d'une part, de poursuivre le rapprochement amorcé par la directive 65/65/CEE du Conseil, du 26 janvier 1965, concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques (3), et, d'autre part, d'assurer une application des principes posés par cette directive;

considérant que, en vue de réduire les disparités qui subsistent, il importe, d'une part, de déterminer les règles relatives au contrôle des spécialités pharmaceutiques et, d'autre part, de préciser les tâches qui incombent aux autorités compétentes des États membres en vue d'assurer le respect des prescriptions légales;

considérant qu'il convient, en vue de réaliser progressivement la libre circulation des spécialités pharmaceutiques, de faciliter la délivrance d'autorisations de mise sur le marché dans plusieurs États membres pour une même spécialité pharmaceutique;

considérant que, à cette fin, il convient d'instituer un comité des spécialités pharmaceutiques composé des représentants des États membres et de la Commission et chargé d'émettre un avis sur la conformité d'une spécialité pharmaceutique aux conditions prévues par la directive 65/65/CEE;

considérant que la présente directive ne constitue qu'une étape dans la réalisation de l'objectif de la libre circulation des spécialités pharmaceutiques ; que, à cet effet, de nouvelles mesures s'avéreront nécessaires, compte tenu de l'expérience acquise, notamment au sein dudit comité, en vue d'éliminer les obstacles à la libre circulation qui subsistent encore;

considérant que, afin de faciliter la circulation des spécialités pharmaceutiques et d'éviter que les contrôles effectués dans un État membre ne soient refaits dans un autre État membre, il y a lieu de déterminer les conditions minimales de fabrication et d'importation en provenance de pays tiers et l'octroi de l'autorisation y relative;

considérant qu'il importe que, dans les États membres, la surveillance et le contrôle de la fabrication des spécialités pharmaceutiques soient assurés par une personne répondant à des conditions minimales de qualification;

considérant, en outre, que les dispositions de la présente directive et de la directive 65/65/CEE qui concernent les spécialités pharmaceutiques ne sont pas suffisantes, encore qu'appropriées, pour les vaccins, toxines ou sérums, les spécialités à base de sang humain ou

de composants de sang ou d'isotopes radioactifs et les spécialités homéopathiques ; qu'il convient dès lors de ne pas en imposer actuellement l'application à ces spécialités;

considérant que certaines règles de la présente directive rendent nécessaire une adaptation de différentes dispositions de la directive 65/65/CEE,

A ARRÊTÉ LA PRÉSENTE DIRECTIVE:

CHAPITRE Ier Demande d'autorisation de mise sur le marché

Article premier

Les États membres prennent toutes les dispositions utiles pour que les documents et renseignements (1)JO nº 96 du 2.6.1965, p. 1677/65. (2)JO nº 107 du 19.6.1965, p. 1825/65. (3)JO nº 22 du 9.2.1965, p. 369/65.

énumérés à l'article 4 deuxième alinéa points 7 et 8 de la directive 65/65/CEE soient établis par des experts possédant les qualifications techniques ou professionnelles nécessaires, avant d'être présentés aux autorités compétentes. Ces documents et renseignements sont signés par ces experts.

Article 2

Selon leurs qualifications, le rôle des experts est: a) de procéder aux travaux relevant de leur discipline (analyse, pharmacologie et sciences expérimentales analogues, clinique) et de décrire objectivement les résultats obtenus (qualitatifs et quantitatifs);

b) de décrire les constatations qu'ils ont faites conformément à la directive 75/318/CEE du Conseil, du 20 mai 1975, relative au rapprochement des législations des États membres concernant les normes et protocoles analytiques, toxicopharmacologiques et cliniques en matière d'essais des spécialités pharmaceutiques (1), et de dire notamment: - pour l'analyste, si le produit est conforme à la composition déclarée en fournissant toute justification sur les méthodes de contrôle qui seront utilisées par le fabricant,

- pour le pharmacologue ou le spécialiste ayant une compétence expérimentale analogue, quelle est la toxicité du produit et quelles sont les propriétés pharmacologiques constatées,

- pour le clinicien, s'il a pu retrouver sur les personnes traitées avec le produit les effets correspondant aux renseignements donnés par le demandeur en application de l'article 4 de la directive 65/65/CEE, si le produit est bien toléré, quelle posologie il conseille et quels sont les éventuels contre-indications et effets secondaires;

c) de justifier le recours éventuel à la documentation bibliographique visée à l'article 4 deuxième alinéa point 8 sous a) et b) de la directive 65/65/CEE, dans les conditions prévues par la directive 75/318/CEE.

Les rapports détaillés des experts font partie du dossier que le demandeur présente aux autorités compétentes.

Article 3

En cas de non-respect de l'article 2 de la présente directive, l'article 5 deuxième alinéa de la directive 65/65/CEE est applicable.

CHAPITRE II Instruction de la demande d'autorisation de mise sur le marché

Article 4

Pour instruire la demande présentée en vertu de l'article 4 de la directive 65/65/CEE, les autorités compétentes des États membres: a) doivent vérifier la conformité à l'article 4 précité du dossier présenté et examiner si les conditions de délivrance de l'autorisation de mise sur le marché sont remplies;

b) peuvent soumettre la spécialité au contrôle d'un laboratoire d'État ou d'un laboratoire désigné à cet effet, pour s'assurer que les méthodes de contrôle utilisées par le fabricant et décrites dans le dossier, conformément à l'article 4 deuxième alinéa point 7 de la directive 65/65/CEE, sont satisfaisantes;

c) peuvent, le cas échéant, exiger du demandeur qu'il complète le dossier en ce qui concerne les éléments visés à l'article 4 deuxième alinéa de la directive 65/65/CEE. Lorsque les autorités compétentes se prévalent de cette faculté, les délais prévus à l'article 7 de ladite directive sont suspendus jusqu'à ce que les données complémentaires requises aient été fournies. De même, ces délais sont suspendus du temps laissé, le cas échéant, au demandeur pour s'expliquer oralement ou par écrit.

Article 5

Les États membres prennent toutes les dispositions utiles afin que: a) les autorités compétentes vérifient que les fabricants et les importateurs de spécialités pharmaceutiques en provenance de pays tiers sont en mesure de réaliser la fabrication dans le respect des indications fournies en application de l'article 4 deuxième alinéa point 4 de la directive 65/65/CEE et/ou d'effectuer les contrôles suivant les méthodes décrites dans le dossier conformément à l'article 4 deuxième alinéa point 7 de ladite directive; (1)Voir page 1 du présent Journal officiel.

b) les autorités compétentes puissent autoriser les fabricants et les importateurs de spécialités pharmaceutiques en provenance de pays tiers, dans des cas exceptionnels et justifiés, à faire effectuer par des tiers certaines phases de la fabrication et/ou certains des contrôles prévus sous a) ; dans ce cas, les vérifications des autorités compétentes s'effectuent également dans l'établissement désigné.

Article 6

Lorsqu'une notice est jointe au conditionnement d'une spécialité pharmaceutique, les États membres prennent toutes les mesures utiles pour que la notice ne concerne que cette spécialité.

Toutes les indications figurant dans la notice doivent être conformes aux renseignements et documents fournis en vertu de l'article 4 de la directive 65/65/CEE et être approuvées par les autorités compétentes.

La notice doit comporter au moins les indications suivantes: a) nom et domicile ou raison sociale et domicile ou siège social du responsable de la mise sur le marché et, le cas échéant, du fabricant;

b) dénomination et composition qualitative et quantitative de la spécialité pharmaceutique en principes actifs.

Les dénominations communes internationales recommandées par l'Organisation mondiale de la santé doivent être employées chaque fois que ces dénominations existent;

c) sauf décision contraire des autorités compétentes: - indications thérapeutiques,

- contre-indications, effets secondaires et précautions particulières d'emploi.

Les indications et décisions prévues aux premier et deuxième tirets doivent tenir compte des résultats des essais cliniques et pharmacologiques prévus à l'article 4 deuxième alinéa point 8 de la directive 65/65/CEE ainsi que, pour les indications visées au deuxième tiret, de l'expérience acquise lors de l'emploi de la spécialité pharmaceutique après la commercialisation;

d) toute indication relative à l'utilisation de la spécialité pharmaceutique (mode et voie d'administration, durée du traitement lorsqu'elle doit être limitée, posologie usuelle);

e) précautions particulières de conservation s'il y a lieu.

Les autres indications doivent être nettement séparées des indications visées ci-dessus.

Les États membres peuvent exiger qu'une notice soit jointe au conditionnement de la spécialité pharmaceutique.

Article 7

Sans préjudice du chapitre IV et de l'article 21 de la directive 65/65/CEE, les États membres peuvent exiger qu'il soit porté sur le récipient et/ou sur l'emballage extérieur et/ou sur la notice de la spécialité pharmaceutique d'autres mentions essentielles pour la sécurité ou pour la protection de la santé publique, y compris les précautions particulières d'emploi et d'autres avertissements résultant des essais cliniques et pharmacologiques prévus à l'article 4 deuxième alinéa point 8 de la directive 65/65/CEE ou qui, après la commercialisation, résultent de l'expérience acquise lors de l'emploi de la spécialité pharmaceutique.

CHAPITRE III Comité des spécialités pharmaceutiques

Article 8

1. En vue de faciliter l'adoption d'une attitude commune par les États membres relative aux autorisations de mise sur le marché, il est institué un comité des spécialités pharmaceutiques, ci-après dénommé «comité», qui est composé de représentants des États membres et de la Commission.

2. Le comité, sur saisine d'un État membre, est chargé d'examiner, conformément aux articles 9 à 14, les questions relatives à l'application des articles 5, 11 ou 20 de la directive

65/65/CEE.

3. Le comité établit son règlement intérieur.

Article 9

1. Lorsqu'un État membre a accordé une autorisation de mise sur le marché, il transmet au comité un dossier comprenant une copie de cette autorisation ainsi que les renseignements et documents énumérés à l'article 4 deuxième alinéa de la directive 65/65/ CEE si le responsable de la mise sur le marché a demandé cette transmission à cinq autres États membres au moins.

2. Le comité transmet sans délai ce dossier aux autorités compétentes des États membres désignés.

3. Cette transmission vaut introduction, au sens de l'article 4 de la directive 65/65/CEE, d'une demande d'autorisation de mise sur le marché auprès desdites autorités.

Article 10

1. Si, dans un délai de 120 jours à compter de la date de transmission visée à l'article 9 paragraphe 2, aucune opposition n'a été formulée auprès du comité par les autorités compétentes des États membres désignés, ce comité, après constat, en informe immédiatement les États membres concernés.

2. Lorsqu'un État membre estime ne pas pouvoir envisager d'accorder l'autorisation de mise sur le marché, il transmet, dans ce délai de 120 jours, son opposition motivée sur la base de l'article 5 de la directive 65/65/CEE.

Article 11

1. Dans les cas visés à l'article 10 paragraphe 2, le comité délibère et émet un avis motivé dans un délai de 60 jours à compter de l'expiration du délai visé à l'article 10.

2. L'avis du comité porte sur la conformité de la spécialité pharmaceutique aux conditions prévues à l'article 5 de la directive 65/65/CEE.

Le comité informe immédiatement les États membres concernés de son avis, ou de ceux de ses membres en cas d'avis divergents.

3. Les États membres concernés se prononcent sur la demande d'autorisation de mise sur le marché dans un délai n'excédant pas 30 jours à compter de l'information visée à l'article 10 paragraphe 1 ou au paragraphe 2 du présent article. Ils informent immédiatement le comité de leur décision.

Article 12

1. Lorsqu'une même spécialité pharmaceutique à fait l'objet de plusieurs demandes d'autorisation de mise sur le marché, introduites conformément à l'article 4 de la directive 65/65/CEE et qu'un ou plusieurs États membres ont accordé l'autorisation alors qu'un ou plusieurs autres États membres l'ont refusée, un des États membres concernés peut saisir le comité.

Il en est de même lorsqu'un ou plusieurs États membres ont suspendu ou retiré une autorisation de mise sur le marché, alors qu'un ou plusieurs États membres n'ont pas procédé à cette suspension ou à ce retrait.

2. Le comité délibère et émet un avis motivé dans un délai maximal de 120 jours.

3. L'avis du comité ne porte que sur les motifs pour lesquels l'autorisation a été refusée, suspendue ou retirée.

Le comité informe immédiatement les États membres concernés de son avis, ou de ceux de ses membres en cas d'avis divergents.

4. Les États membres concernés font connaître, dans un délai de 30 jours, la suite qu'ils donnent à l'avis du comité.

Article 13

Le comité peut se fixer un délai pour un nouvel examen sur la base des données relatives aux conditions prévues aux articles 5, 11 ou 20 de la directive 65/65/CEE recueillies entre-temps par les États membres, notamment ceux qui autorisent la spécialité.

Article 14

Les autorités compétentes des États membres peuvent, dans des cas particuliers présentant un intérêt communautaire, saisir le comité avant qu'elles décident, sur une demande, une

suspension ou un retrait d'autorisation de mise sur le marché.

Article 15

1. La Commission fait rapport au Conseil, chaque année, sur le fonctionnement de la procédure prévue au présent chapitre et ses effets sur l'évolution des échanges intracommunautaires, et pour la première fois 2 ans après l'entrée en application de la présente directive.

2. En fonction de l'expérience acquise, et au plus tard 4 ans après l'entrée en application de la présente directive, la Commission soumet au Conseil une proposition comportant toutes mesures appropriées tendant à éliminer les obstacles à la libre circulation des spécialités pharmaceutiques qui subsistent encore. Le Conseil se prononce sur la proposition de la Commission au plus tard un an après en avoir été saisi.

CHAPITRE IV Fabrication et importation en provenance de pays tiers

Article 16

1. Les États membres prennent toutes les dispositions utiles pour que la fabrication des spécialités pharmaceutiques soit soumise à la possession d'une autorisation.

2. L'autorisation visée au paragraphe 1 est exigée tant pour la fabrication totale ou partielle que pour les opérations de division, de conditionnement ou de présentation.

Toutefois, cette autorisation n'est pas exigée pour les préparations, divisions, changements de conditionnement ou présentation, dans la mesure où ces opérations sont exécutées, uniquement en vue de la dispensation au détail, par des pharmaciens dans une officine ou par d'autres personnes légalement autorisées dans les États membres à effectuer lesdites opérations.

3. L'autorisation visée au paragraphe 1 est exigée également pour les importations en provenance de pays tiers dans un État membre ; à cette fin, le présent chapitre et l'article 29 s'appliquent à de telles importations de la même manière qu'ils s'appliquent à la fabrication.

Article 17

Pour obtenir l'autorisation visée à l'article 16, le demandeur doit satisfaire au moins aux exigences suivantes: a) spécifier les spécialités et les formes pharmaceutiques à fabriquer ou à importer ainsi que l'endroit de leur fabrication et/ou de leur contrôle;

b) disposer, pour leur fabrication ou leur importation, des locaux, de l'équipement technique et des possibilités de contrôle appropriés et suffisants répondant aux exigences légales que l'État membre concerné prévoit, tant du point de vue de la fabrication et du contrôle que de la conservation des produits, dans le respect des dispositions de l'article 5 sous a);

c) disposer d'au moins une personne qualifiée au sens de l'article 21.

Le demandeur doit fournir, dans sa demande, les renseignements justificatifs.

Article 18

1. L'autorité compétente de l'État membre ne délivre l'autorisation visée à l'article 16 qu'après s'être assurée, par une enquête réalisée par ses agents, que les renseignements fournis en application de l'article 17 sont exacts.

2. L'autorisation peut être assortie, pour garantir le respect des conditions prévues à l'article 17, de certaines obligations imposées soit à l'occasion de son octroi, soit postérieurement à sa délivrance.

3. L'autorisation ne s'applique qu'aux locaux indiqués dans la demande ainsi qu'aux spécialités et aux formes pharmaceutiques indiquées dans cette même demande.

Article 19

Le titulaire de l'autorisation visée à l'article 16 est tenu au moins: a) de disposer du personnel répondant aux exigences légales prévues par l'État membre concerné tant du point de vue de la fabrication que des contrôles;

b) de ne céder les spécialités autorisées qu'en conformité avec la législation des États membres concernés;

c) d'informer préalablement l'autorité compétente de toute modification qu'il désirerait apporter à l'un des renseignements fournis en application de l'article 17 ; toutefois, l'autorité compétente est informée sans délai en cas de remplacement imprévu de la personne qualifiée visée à l'article 21;

d) de rendre ses locaux, en tout temps, accessibles aux agents de l'autorité compétente de

l'État membre concerné;

e) de mettre la personne qualifiée visée à l'article 21 en mesure d'accomplir sa mission, notamment en mettant à sa disposition tous les moyens nécessaires.

Article 20

1. Les États membres prennent toutes les dispositions utiles pour que la durée de la procédure pour l'octroi de l'autorisation visée à l'article 16 n'excède pas un délai de 90 jours à compter de la date de la réception de la demande par l'autorité compétente.

2. En cas de demande de modification par le titulaire de l'autorisation de l'un des éléments visés à l'article 17 sous a) et b), la durée de la procédure concernant cette demande ne dépasse pas 30 jours. Dans les cas exceptionnels, ce délai peut être prorogé jusqu'à 90 jours.

3. Les États membres peuvent exiger du demandeur des compléments d'information en ce qui concerne les renseignements fournis en application de l'article 17 ainsi qu'en ce qui concerne la personne qualifiée visée à l'article 21 ; lorsque l'autorité compétente se prévaut de cette faculté, les délais prévus aux paragraphes 1 et 2 sont suspendus jusqu'à ce que les données complémentaires requises aient été fournies.

Article 21

1. Les États membres prennent toutes les dispositions utiles pour que le titulaire de l'autorisation visée à l'article 16 dispose d'une façon permanente et continue d'au moins une personne qualifiée répondant aux conditions prévues à l'article 23, responsable notamment de l'exécution des obligations spécifiées à l'article 22.

2. S'il répond personnellement aux conditions prévues à l'article 23, le titulaire de l'autorisation peut assumer lui-même la responsabilité visée au paragraphe 1.

Article 22

1. Les États membres prennent toutes les dispositions utiles pour que la personne qualifiée visée à l'article 21, sans préjudice de ses relations avec le titulaire de l'autorisation visée à l'article 16, ait la responsabilité, dans le cadre des procédures visées à l'article 25, de veiller que: a) dans le cas de spécialités fabriquées dans l'État membre concerné, chaque lot de spécialités pharmaceutiques a été fabriqué et contrôlé conformément à la législation en vigueur dans cet État membre et dans le respect des exigences retenues pour l'autorisation de mise sur le marché;

b) dans le cas de spécialités en provenance de pays tiers, chaque lot de fabrication importé a fait l'objet, dans le pays importateur, d'une analyse qualitative complète, d'une analyse quantitative d'au moins tous les principes actifs et de tous les autres essais ou vérifications nécessaires pour assurer la qualité des spécialités pharmaceutiques dans le respect des exigences retenues pour l'autorisation de mise sur le marché.

Les lots de spécialités ainsi contrôlés dans un État membre sont dispensés des contrôles précités lorsqu'ils sont importés dans un autre État membre, accompagnés des comptes rendus de contrôle signés par la personne qualifiée.

Un État membre peut exempter la personne qualifiée de la responsabilité des contrôles prévus sous b) pour les spécialités importées et destinées à rester dans cet État membre lorsque des arrangements appropriés sont intervenus avec le pays exportateur assurant que ces contrôles ont été effectués dans ce pays. Lorsque ces spécialités sont importées conditionnées pour la vente au détail, les États membres peuvent prévoir des exceptions aux exigences prévues à l'article 17.

2. Dans tous les cas, et notamment lorsque les spécialités pharmaceutiques sont livrées à la vente, la personne qualifiée doit attester que chaque lot de fabrication répond aux dispositions du présent article, sur un registre ou document équivalent prévu à cet effet ; ledit registre ou document équivalent doit être tenu à jour au fur et à mesure des opérations effectuées et mis à la disposition des agents de l'autorité compétente pendant une période respectant les dispositions de l'État membre concerné et au moins pendant une période de 5 ans.

Article 23

Les États membres assurent que la personne qualifiée visée à l'article 21 répond aux conditions minimales de qualification suivantes: a) Possession d'un diplôme, certificat ou autre titre sanctionnant un cycle de formation universitaire - ou un cycle de formation reconnu équivalent par l'État membre intéressé - s'étendant sur une durée minimale de 4 années d'enseignement théorique et pratique dans l'une des disciplines scientifiques suivantes :

pharmacie, médecine, médecine vétérinaire, chimie, chimie et technologie pharmaceutiques, biologie. Toutefois: - la durée minimale du cycle de formation universitaire peut être de 3 ans et demi lorsque le cycle de formation est suivi d'une période de formation théorique et pratique d'une durée minimale d'un an et comportant un stage d'au moins six mois dans une officine ouverte au public, sanctionnée par un examen de niveau universitaire;

- lorsque, dans un État membre, coexistent deux cycles de formation universitaire ou reconnus équivalents par cet État dont l'un s'étend sur 4 années et l'autre sur 3 années, le diplôme, certificat ou autre titre sanctionnant le cycle de formation universitaire - ou reconnu équivalent - de trois ans est considéré comme remplissant la condition de durée visée sous a) pour autant que les diplômes, certificats ou autres titres sanctionnant les deux cycles de formation soient reconnus équivalents par cet État.

Le cycle de formation comporte un enseignement théorique et pratique portant au moins sur les matières de base suivantes: - physique expérimentale,

- chimie générale et inorganique,

- chimie organique,

- chimie analytique,

- chimie pharmaceutique, y compris l'analyse des médicaments,

- biochimie générale et appliquée (médicale),

- physiologie,

- microbiologie,

- pharmacologie,

- technologie pharmaceutique,

- toxicologie,

- pharmacognosie (matière médicale) (étude de la composition et des effets des principes actifs de substances naturelles d'origine végétale ou animale).

L'enseignement de ces matières doit être dosé de façon à permettre à l'intéressé d'assumer les obligations spécifiées à l'article 22.

Dans la mesure où certains diplômes, certificats ou autres titres énumérés sous a) ne respectent pas les critères fixés ci-dessus, l'autorité compétente de l'État membre s'assure que l'intéressé fait la preuve de connaissances satisfaisantes dans les matières en cause.

b) Exercice pendant au moins 2 ans, dans une ou plusieurs entreprises ayant obtenu une autorisation de fabrication, des activités d'analyse qualitative des médicaments, d'analyse quantitative des principes actifs ainsi que d'essais et vérifications nécessaires pour assurer la qualité des spécialités.

La durée de l'expérience pratique peut être diminuée d'une année lorsque le cycle de formation universitaire s'étend sur une durée d'au moins 5 ans et d'un an et demi lorsque ce cycle de formation s'étend sur une durée d'au moins 6 ans.

Article 24

1. Une personne exerçant dans un État membre les activités de la personne visée à l'article 21 au moment de la mise en application de la présente directive dans cet État, sans répondre aux dispositions de l'article 23, est qualifiée pour continuer à exercer ces activités dans cet État.

2. Le titulaire d'un diplôme, certificat ou autre titre, sanctionnant un cycle de formation universitaire - ou un cycle de formation reconnu équivalent par l'État membre intéressé - dans une discipline scientifique qui l'habilite à exercer les activités de la personne visée à l'article 21, conformément à la législation de cet État, peut - lorsqu'il a commencé sa formation avant la notification de la présente directive - être considéré comme qualifié pour assumer dans cet État la charge de la personne visée à l'article 21 à condition d'avoir au préalable exercé, avant la fin de la dixième année suivant la notification de la présente directive, pendant au moins 2 ans, dans une ou plusieurs entreprises ayant obtenu une autorisation visée à l'article 16, des activités de surveillance de production et/ou des activités d'analyse qualitative, d'analyse quantitative des principes actifs ainsi que d'essais et vérifications nécessaires pour assurer la qualité des spécialités sous l'autorité directe d'une personne visée à l'article 21.

Lorsque l'intéressé a acquis l'expérience pratique visée au premier alinéa plus de 10 ans avant la notification de la présente directive, il est exigé une année supplémentaire d'expérience

pratique répondant aux conditions visées au premier alinéa et effectuée immédiatement avant l'exercice de ces activités.

3. Une personne qui, au moment de la mise en application de la présente directive, exerce en collaboration directe avec une personne visée à l'article 21, des activités de surveillance de production et/ou des activités d'analyse qualitative, d'analyse quantitative des principes actifs ainsi que d'essais et vérifications nécessaires pour assurer la qualité des spécialités, peut - pendant une période de cinq ans après la mise en application de la présente directive - être considérée comme qualifiée pour assumer dans cet État la charge de la personne visée à l'article 21, à condition que l'État membre s'assure que la personne fait la preuve de connaissances théoriques et pratiques satisfaisantes et qu'elle a exercé lesdites activités pendant 5 ans au moins.

Article 25

Les États membres assurent le respect des obligations de la personne qualifiée visée à l'article 21 par des mesures administratives appropriées, ou par la soumission à une discipline professionnelle.

Les États membres peuvent prévoir la suspension temporaire de cette personne dès l'ouverture d'une procédure administrative ou disciplinaire à son encontre pour manquement à ses obligations.

CHAPITRE V Surveillance et sanctions

Article 26

L'autorité compétente de l'État membre concerné s'assure, par des inspections, que les prescriptions légales concernant les spécialités pharmaceutiques sont respectées.

Ces inspections sont effectuées par des agents de l'autorité compétente qui doivent être habilités à: a) procéder à des inspections des établissements de fabrication et de commerce ainsi que des laboratoires chargés, par le titulaire de l'autorisation visée à l'article 16, d'effectuer des contrôles en vertu de l'article 5 sous b);

b) prélever des échantillons;

c) prendre connaissance de tous les documents se rapportant à l'objet des inspections, sous réserve des dispositions en vigueur dans les États membres au moment de la notification de la présente directive, qui limitent cette faculté en ce qui concerne la description du mode de préparation.

Article 27

Les États membres prennent toutes les dispositions utiles pour que le responsable de la mise sur le marché et, le cas échéant, le titulaire de l'autorisation visée à l'article 16 justifient de l'exécution des contrôles pratiqués sur le produit fini et/ou sur les composants et les produits intermédiaires de la fabrication, selon les méthodes retenues pour l'autorisation de mise sur le marché.

Article 28

1. Sans préjudice des mesures prévues à l'article 11 de la directive 65/65/CEE, les États membres prennent toutes les dispositions utiles pour que la délivrance de la spécialité pharmaceutique soit interdite et que cette spécialité soit retirée du marché lorsque: a) il apparaît que la spécialité est nocive dans les conditions normales d'emploi;

b) l'effet thérapeutique de la spécialité fait défaut;

c) la spécialité n'a pas la composition qualitative et quantitative déclarée;

d) les contrôles sur le produit fini et/ou sur les composants et les produits intermédiaires de la fabrication n'ont pas été effectués ou lorsqu'une autre exigence ou obligation relative à l'octroi de l'autorisation prévue à l'article 16 n'a pas été respectée.

2. L'autorité compétente peut limiter l'interdiction de délivrance et le retrait du marché aux seuls lots de fabrication faisant l'objet d'une contestation.

Article 29

1. L'autorité compétente d'un État membre suspend ou retire l'autorisation visée à l'article 16 pour une catégorie de préparations ou pour l'ensemble de celles-ci lorsqu'une des exigences prévues à l'article 17 n'est plus respectée.

2. L'autorité compétente d'un État membre, outre les mesures prévues à l'article 28, peut soit suspendre la fabrication ou l'importation de spécialités pharmaceutiques en provenance de

pays tiers, soit suspendre ou retirer l'autorisation visée à l'article 16 pour une catégorie de préparations ou pour l'ensemble de celles-ci en cas de non-respect des articles 18, 19, 22 et 27.

CHAPITRE VI Dispositions diverses

Article 30

Les États membres prennent toutes les dispositions utiles pour que les autorités compétentes concernées se communiquent mutuellement les informations appropriées pour garantir le respect des exigences retenues pour l'autorisation visée à l'article 16 ou pour l'autorisation de mise sur le marché.

Article 31

Toute décision prise en vertu des articles 18, 28 et 29, ainsi que toute décision négative prise en application de l'article 5 sous b) et de l'article 11 paragraphe 3 doivent être motivées de façon précise. Elles sont notifiées à l'intéressé avec l'indication des moyens de recours prévus par la législation en vigueur et du délai dans lequel le recours peut être présenté.

Article 32

Toute décision de suspension de fabrication ou d'importation de spécialités pharmaceutiques en provenance de pays tiers, d'interdiction de délivrance et de retrait du marché d'une spécialité ne peut être prise que pour des raisons énumérées aux articles 28 et 29.

Article 33

Chaque État membre prend toutes les dispositions utiles pour que les décisions d'autorisation, de mise sur le marché, de refus ou de retrait d'autorisation de mise sur le marché, d'annulation de décision de refus ou de retrait d'autorisation de mise sur le marché, d'interdiction de délivrance, de retrait du marché et leurs motifs soient immédiatement portés à la connaissance du comité.

Article 34

La présente directive ne s'applique qu'aux spécialités pharmaceutiques à usage humain.

Les chapitres II à V de la directive 65/65/CEE et la présente directive ne sont pas applicables aux spécialités pharmaceutiques consistant en vaccins, toxines ou sérums, ni aux spécialités pharmaceutiques à base de sang humain ou de composants de sang ou d'isotopes radioactifs, ni aux spécialités homéopathiques. Une énumération indicative de ces vaccins, toxines ou sérums, figure en annexe.

Article 35

Le texte de l'article 4 deuxième alinéa point 7 de la directive 65/65/CEE est remplacé par le texte suivant:

«Description des méthodes de contrôle utilisées par le fabricant (analyse qualitative et quantitative des composants et du produit fini, essais particuliers, par exemple, essais de stérilité, essais pour la recherche des substances pyrogènes, recherche des métaux lourds, essais de stabilité, essais biologiques et de toxicité, contrôles sur les produits intermédiaires de la fabrication).»

Article 36

Le texte de l'article 11 deuxième alinéa de la directive 65/65/CEE est remplacé par le texte suivant:

«L'autorisation sera également suspendue ou retirée lorsqu'il sera reconnu que les renseignements figurant dans le dossier, en vertu de l'article 4, sont erronés ou lorsque les contrôles visés à l'article 8 de la présente directive ou à l'article 27 de la deuxième directive 75/319/CEE du Conseil, du 20 mai 1795, concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives aux spécialités pharmaceutiques (1), (La note suivante est ajoutée) : n'ont pas été effectués.»

Article 37

Le texte de l'article 24 de la directive 65/65/CEE est remplacé par le texte suivant:

«La réglementation prévue par la présente directive sera progressivement appliquée aux spécialités ayant reçu l'autorisation de mise sur le marché en vertu des dispositions antérieures, dans les délais et les conditions prévus à l'article 39 paragraphes 2 et 3 de la deuxième directive 75/319/CEE.»

CHAPITRE VII Dispositions d'application et mesures transitoires

Article 38

Les États membres mettent en vigueur les dispositions législatives, réglementaires et administratives nécessaires pour se conformer à la présente directive dans un délai de dix-huit mois à compter de sa notification et en informent immédiatement la Commission.

Les États membres communiquent à la Commission le texte des dispositions essentielles de droit interne qu'ils adoptent dans le domaine régi par la présente directive.

Article 39

1. Pour ce qui est des autorisations visées à l'article 16 et délivrées avant l'expiration du délai fixé à l'article 38, les États membres peuvent accorder aux entreprises intéressées un délai supplémentaire d'un an pour se conformer aux dispositions du chapitre IV.

2. Les autres dispositions de la présente directive sont progressivement appliquées aux spécialités pharmaceutiques mises sur le marché, en vertu des dispositions antérieures, dans un délai de 15 ans à compter de la notification visée à l'article 38.

3. Les États membres communiquent à la Commission, dans les 3 ans à compter de la notification de la présente directive, le nombre des spécialités pharmaceutiques qui relèvent du paragraphe 2 et, chaque année qui suit, le nombre de ces spécialités pour lesquelles l'autorisation de mise sur le marché visée à l'article 3 de la directive 65/65/CEE n'a pas encore été délivrée.

Article 40

Les États membres sont destinataires de la présente directive.

Fait à Bruxelles, le 20 mai 1975.

Par le Conseil

Le président

R. RYAN (1) JO nº L 147 du 9.6.1975, p. 13.»

ANNEXE

Les termes «vaccins, toxines ou sérums» figurant à l'article 34 recouvrent notamment: - les agents utilisés en vue de provoquer une immunité active

(tels que le vaccin anticholérique, le BCG, le vaccin antipoliomyélitique, le vaccin antivariolique),

- les agents utilisés en vue de diagnostiquer l'état d'immunité,

comprenant notamment la tuberculine ainsi que la tuberculine PPD, les toxines utilisées pour les tests de Schick et de Dick, la brucelline,

- les agents utilisés en vue de provoquer une immunité passive

(tels que l'antitoxine diphtérique, la globuline antivariolique, la globuline antilymphocytique).

R.J. n°2
(J.O. du 20/12/1984)

Annexe 2-10 2.

MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SOLIDARITÉ NATIONALE

Avis aux fabricants de spécialités pharmaceutiques relatif à l'application de l'article 39 (point 2) de la directive 75-319 C.E.E.

VALIDATION DES SPECIALITES PHARMACEUTIQUES

Cet avis remplace l'avis n° 22 690 publié au *Bulletin officiel* du ministère de la solidarité nationale SN-S 82-13.

Les titulaires d'autorisation (visa ou A.M.M. délivrés antérieurement au 1er décembre 1976) doivent effectuer la validation de leurs spécialités conformément à l'article 39 (point 2) de la directive 75-319 C.E.E. du 20 mai 1975 ; ils ont à fournir, auprès de la direction de la pharmacie et du médicament (secrétariat d'Etat chargé de la santé), 1, place Fontenoy, 75700 Paris, soit une demande de transformation de visa en A.M.M., soit une demande de validation d'A.M.M., selon le schéma défini ci-dessous, ou à indiquer qu'ils ne souhaitent pas cette transformation ou cette validation.

L'opération générale de validation des spécialités pharmaceutiques s'effectuera par classe pharmacothérapeutique à partir du 1er janvier 1985. Les délais de dépôt de dossier devront être expressément respectés, sous peine de forclusion.

Les premiers dossiers, appartenant aux classes suivantes, doivent être déposés entre le 1er janvier 1985 et le 30 juin 1985 :

- antivitamines K, héparines injectables, antiangoreux, antiarythmiques, antihypertenseurs, bétabloquants, hypolipémiants, glucosides cardiotoniques, diurétiques, sédatifs cardiaques, cardio-accélérateurs (antibradycardisants), analeptiques cardiovasculaires ;
- médicaments ophtalmologiques antiglaucomateux et mydriatiques.

Liste des documents à fournir

1. Lettre de demande

Elle devra indiquer notamment :

- numéro de dossier ;
- date d'octroi du visa et de ses rectificatifs ; date et numéro d'enregistrement définitif de la demande de transformation en autorisation de mise sur le marché,

ou,

- date d'octroi de l'autorisation de mise sur le marché, de ses rectificatifs et de ses renouvellements quinquennaux ;
- lieu de fabrication (1), de conditionnement, de contrôle ;
- composition intégrale qualitative et quantitative en principes actifs et en constituants de l'excipient.

2. Résumé des caractéristiques du produit

Il doit comprendre les informations suivantes :

- dénomination de la spécialité et forme pharmaceutique ; (s'il y a lieu, la dénomination commune internationale lorsqu'elle existe, ou celle de la pharmacopée française ou européenne ;
- nom ou raison sociale et domicile ou siège social du titulaire de l'autorisation de mise sur le marché ;
- composition qualitative et quantitative en principes actifs et en constituants de l'excipient dont la connaissance est nécessaire à une bonne administration du médicament ;
- nature et contenance du (des) récipient(s) destiné(s) à la vente (préciser le numéro attribué par le C.I.P.) ;
- condition de délivrance au public, réserve à l'usage hospitalier, à l'usage professionnel ;
- durée de stabilité, si nécessaire après reconstitution du produit, ou lorsque le récipient est ouvert pour la première fois ;
- précautions particulières de conservation ;
- incompatibilités majeures chimiques ou physiques ;
- propriétés pharmacologiques et, dans la mesure où ces renseignements sont utiles pour l'utilisation thérapeutique, éléments de pharmacocinétique ;
- indications thérapeutiques ;
- effets indésirables (fréquence et gravité) ;
- mises en garde spéciales ;
- contre-indications ;
- précautions particulières d'emploi, notamment en cas de grossesse et d'allaitement, d'utilisation par des enfants, des personnes âgées, et dans des circonstances pathologiques particulières et effets sur la capacité de conduire et l'usage des machines ;
- interactions médicamenteuses et autres ;
- posologie et mode d'administration ;
- surdosage (symptômes, conduite d'urgence, antidotes) ;
- date d'établissement du résumé des caractéristiques du produit.

3. Proposition du libellé de l'information au public

4. Dossier présenté à l'appui de la demande

Il doit comprendre :

- un chèque de 1 000 francs ;
- la photocopie des pièces administratives ;
- un document de synthèse en 20 exemplaires comprenant des renseignements pharmaceutiques, toxicologiques, pharmacologiques et cliniques. Ce document mentionne les éléments du dossier primitif et les informations complémentaires (2) dont dispose l'industriel pour chaque partie du dossier ; sont précisés les noms des experts, le lieu et la date des études effectuées et toutes les informations permettant d'apprécier, pour le médicament dont il s'agit, son niveau d'efficacité et de sécurité dans des conditions normales d'emploi pour les indications revendiquées, compte tenu des données et des connaissances disponibles sur la base des travaux expérimentaux et/ou de l'expérience acquise à leur sujet (notamment données de pharmacovigilance, de consommation globale du produit, utilisation dans d'autres pays...) ;
- un dossier pharmaceutique actualisé (3).

(1) Préciser le nom et l'adresse du fabricant si le titulaire ne fabrique pas la spécialité.

(2) Adresser comme il est prévu pour les dossiers d'autorisation de mise sur le marché à la direction de la pharmacie et du médicament deux exemplaires des éléments bibliographiques pertinents et des travaux expérimentaux.

(3) Le dossier pourra être remplacé :

a) En cas de mise à jour récente ayant reçu l'aval de la direction de la pharmacie et du médicament, par une note y faisant référence.

b) En cas de demande de modification de formule, par une demande de dispense motivée conforme à l'article R. 5133 *a* du code de la santé publique.

Dans les autres cas, adresser le dossier pharmaceutique comme il est prévu pour les dossiers d'autorisation de mise sur le marché :

- deux exemplaires à la direction de la pharmacie et du médicament ;
- un exemplaire au Laboratoire national de la santé, 25, boulevard Saint-Jacques, 75014 Paris ;
- un exemplaire au Laboratoire national de la santé, 14, rue de l'Ecole-de-la-Pharmacie, 34000 Montpellier ;
- un exemplaire à l'inspection régionale de la pharmacie du lieu de fabrication.

- **AVIS** aux fabricants de spécialités pharmaceutiques relatif à l'application de l'article 39 (point 2) de la directive 75/319/CEE - Validation des spécialités pharmaceutiques (J.O. du 4 juin 1985).

Cet avis fait suite à l'avis paru au
Journal Officiel du 20 décembre 1984.

Les titulaires d'autorisation (visa ou autorisation de mise sur le marché délivrés antérieurement au 1er décembre 1976) doivent effectuer la validation de leurs spécialités conformément à l'article 39 (point 2) de la directive 75/319/CEE du 20 mai 1975 ; ils ont à fournir, auprès de la direction de la pharmacie et du médicament (secrétariat d'Etat chargé de la santé), 1, place Fontenoy, 75007 Paris, soit une demande de transformation de visa en autorisation de mise sur le marché, soit une demande de validation d'autorisation de mise sur le marché, selon le schéma défini dans l'avis du 20 décembre 1984, ou à indiquer qu'ils ne souhaitent pas cette transformation ou cette validation.

Les dossiers appartenant aux classes pharmacothérapeutiques suivantes doivent être déposés entre le 1er juillet et le 31 décembre 1985 :

Les médicaments de neurologie et de psychiatrie

Avec en particulier : les antimigraineux, les antiparkinsoniens, les antiépileptiques, les antimyasthéniques, les sédatifs (barbituriques et autres), les hypnotiques (barbituriques et autres), les neuroleptiques, les anxiolytiques, les psycho-stimulants, les antidépresseurs et les normothymiques.

Sont exclus :

- les anesthésiques locaux et généraux ;
- les antalgiques ;
- parmi les psychostimulants : les médicaments à visée antiasthénique ;
- les médicaments vasodilatateurs et anti-ischémiques.

VALIDATION DES SPECIALITES PHARMACEUTIQUES

La validation des spécialités pharmaceutiques se fera selon le calendrier qui suit.

Il est rappelé que la validation porte sur les indications thérapeutiques ; donc une spécialité revendiquant plusieurs indications, appartenant à différentes classes pharmacothérapeutiques, sera étudiée avec chacune des classes concernées au plan des indications.

Troisième tranche : janvier à juin 1986

Les médicaments utilisés en médecine cardio-vasculaire (ceux non appelés au cours de la 1ère tranche), les médicaments de l'hémostase et les anorexigènes.

Cardiovasculaires :

Vasodilatateurs et antiischémiques, vasculoprotecteurs et veinotoniques, topiques en phlébologie et sclérosants veineux.

Potassium et antihyperkaliémiques.

Hémostase :

Hémostatiques généraux et locaux, thrombolytiques, antifibrinolytiques, antiagrégants plaquettaires, vitamines K et divers.

Anorexigènes.

Quatrième tranche : juillet à décembre 1986

Gastro-entérologie :

Antihistaminiques H_1, antiacides et protecteurs gastriques, antireflux gastro-oesophagien, antiulcéreux divers, anesthésiques de contact, adsorbants, antiflatulents et protecteurs intestinaux, antimétéoriques divers, antispasmodiques, antisécrétoires, épaississants antiémétisants, enzymes digestives, acidifiants gastriques et stimulants sécrétoires, péristaltigènes intestinaux, antidiarrhéiques, topiques en proctologie, divers.

Hépatologie :

Cholagogues et cholérétiques seuls ou associés, hépatotropes, antilithiasiques, divers.

Cinquième tranche : janvier à juin 1987

Ophtalmologie :

Anti-infectieux locaux seuls ou associés et corticoïdes locaux.
Antiseptiques (seuls ou associés) en ophtalmologie.

Glucocorticoïdes oraux et injectables et ACTH.

Infections :

Substances antibactériennes à usage général, anti-infectieux urinaires, antiseptiques (seuls ou associés) intestinaux et urinaires, antibiotiques et anticandidosiques intestinaux, associations d'antibiotiques, sulfamides généraux, antibactériens divers, antifongiques systémiques, anti-tuberculeux, antilépreux, antiviraux.

Sixième tranche : sauf exception, jusqu'au 30 juin 1988

Gastro-entérologie :

Laxatifs (reportée au 30 mars 1988).

Pneumologie :

Bronchodilatateurs et antiasthmatiques, analeptiques respiratoires, produits bronchopulmonaires, mucomodificateurs bronchiques, divers produits pour inhalations, produits à usage externe, immunothérapie.

Rhinologie :

Anticoryza par voie générale, produits locaux, immunothérapie, divers.

Ophtalmologie :

Anesthésiques locaux, produits pour le cristallin.

Otologie :

Céruménolytiques, autres produits locaux, produits généraux, antiémétiques, antinauséeux, antinaupathiques et antivertigineux.

Stomatologie :

Produits locaux gingivodentaires et buccopharyngés, produits bismuthés (angines), divers.

Allergologie :

- **AVIS aux fabricants** de spécialités pharmaceutiques relatif à l'application de l'article 39 (point 2) de la directive 75/319/CEE (J.O. du 5 juillet 1985)
  modifié par :
  - Avis aux fabricants (J.O. du 29 janvier 1986)
  - Avis aux fabricants (J.O. du 31 mai 1986)
  - Avis aux fabricants (J.O. du 20 novembre 1986)
  - Avis aux fabricants J.O. du 21 mars 1987)
  - Avis aux fabricants (J.O. du 22 mai 1987)
  - Avis aux fabricants (J.O. du 8 novembre 1987)
  - Avis aux fabricants (J.O. du 15 mars 1988)
  - Avis aux fabricants (J.O. du 3 août 1988)
  - Avis aux fabricants (J.O. du 22 décembre 1988)
  - Avis aux farications (J.O. du 2 mai 1989)
  - Avis aux fabricants (J.O. du10 août 1989).

Antihistaminiques, divers.

Produits dentaires : (reporté avec la 9e tranche - décembre 1989)

Septième tranche : mars 1989

Pneumologie :

Antitussifs.

Dermatologie :

Corticoïdes seuls ou associés, antibiotiques seuls ou associés, antifongiques seuls ou associés, antiherpétiques, antiviraux, antiséborrhéiques, antiacnéiques, antialopéciques, trophiques des ongles, antisénescents cutanés, réducteurs, kératolytiques, antiverrues, antimétabolites locaux, antihistaminiques, anesthésiques de surface seuls ou associés, antiprurigineux, anhidrotiques, enzymes protéolytiques, cicatrisants, antisclérodermiques, photosensibilisants, dépigmentant, antidyschromique, caroténoïdes, radioprotecteurs, antiérythrose, anticouperose, topiques divers, .

Spécialités à base de principes actifs d'origine végétale revendiquant une indication thérapeutique liée à leur utilisation traditionnelle.

Huitième tranche : décembre 1989

Rhumatologie :

Corticoïdes injectables intra-articulaires, anti-inflammatoires non stéroïdiens, antirhumatismaux divers, calcitonine, antipagétiques, vitamine D, myorelaxants, médications phospho-calciques, analgésiques et antirhumatismaux externes, enzymes anti-inflammatoires et antioedémateuses, antigoutteux, divers.

Douleurs :

Analgésiques généraux, analgésiques du tableau B et inhibiteurs.

Anesthésiologie :

Anesthésiques généraux, anesthésiques locaux et vaginaux, anesthésiques locaux à usage dentaire, analgésiques pour anesthésie, curarisants, divers.

Antipyrétiques.

Gynécologie :

Contraceptifs locaux, anti-infectieux locaux (non encore appelés) et généraux, antiseptiques (seuls ou associés), ocytociques et hémostatiques utérins, utérorelaxants, divers.

Endocrinologie :

Antidiabétiques et hyperglycémiants, anabolisants stéroïdiens, hormones hypothalamiques et hypophysaires, inducteurs de l'ovulation, modérateurs hypophysaires, antigonadotropes, antiprolactines, androgènes, antiandrogènes, oestrogènes, antioestrogènes, contraceptifs oraux, oestroprogestatifs, progestatifs, associations d'hormones sexuelles, minéralo-corticoïdes, anticortisolique, hormones thyroïdiennes, extraits thyroïdiens et produits iodés, antithyroïdiens, opothérapie.

Uronéphrologie :

Epuration extrarénale, acidifiants urinaires, alcalinisants urinaires, diurétiques osmotiques, diurétiques divers (non encore appelés), sédatifs urinaires pelviens, produits proposés dans l'adénome prostatique antiénurétiques, vasodilatateurs génitaux, divers.

Neuvième tranche : 10 juin 1990

Parasitologie :

Antiamibiens, antihelminthiques, antipaludéens, antileshmaniens, antitrypanosomes, antiparasitaires externes.

Hématologie :

Antianémiques, antileucopéniques.

Cancérologie :

Cytostatiques, immunostimulants, immunodépresseurs.

Ophtalmologie :

Larmes artificielles, produits locaux divers, produits généraux divers et tout autre produit d'ophtalmologie.

Métabolisme - nutrition - vitamines :

Psychostimulant à visée antiasthénique, antiobésité, et désinfiltrants, orexigènes, vitamines A, B1, B2, B5, B6, B12, B associées, C, E, H, H', PP, polyvitamines, associations diverses de vitamines, produits d'apports énergétiques, plastiques, minéraux, vitaminiques (sauf ceux concernant le métabolisme phosphocalcique).

Alimentation parentérale :

Solutés divers pour perfusions et succédanés du plasma.

Toxicologie :

Emétique, chélateurs et antidotes (sauf inhibiteurs de la morphine et de l'héparine), désintoxication alcoolique, désintoxication tabagique.

Produits de diagnostic :

Opacifiants iodés, opacifiants barytés, produits divers.

Diététique pharmaceutique :

Substituts du sucre et du sel, laits, divers.

Produits dentaires :

Produits pour la chirurgie orale et la parodontie, produits de prophylaxie des affections bucco-dentaires, produits pour l'endodontie et produits divers, anesthésiques locaux à usage dentaire.

Des précisions complémentaires seront apportées si besoin est au moment de l'appel de chaque tranche.

P.J. n°5

- **NOTE de la Direction de la Pharmacie et du Médicament**, du 30 janvier 1985.

Annexe 2-10

VALIDATION
PRINCIPES GENERAUX
ETABLISSEMENT DE LA PROCEDURE

L'opération dite "de validation" ou de réévaluation des spécialités pharmaceutiques mises sur le marché antérieurement aux directives européennes doit être effectuée.

C'est une obligation réglementaire prise en application de (point 2) nos engagements internationaux dans le cadre du Traité de Rome (Article 39 de la directive 75/319/CEE du 20 mai 1975).

I - L'OBJECTIF

L'obligation juridique rejoint celle qui s'impose à nous sur le plan de la santé publique : une mise à jour des dossiers de fabrication et du contrôle de qualité des produits ainsi que d'une réévaluation en fonction de la progression des connaissances toxicologiques, pharmacologiques, cliniques des différents médicaments et de l'apport de connaissances médicales nouvelles.

La validation apparaît comme une opération nationale de santé publique et de qualité du médicament français basée sur une réflexion et des arguments objectifs.

La validation ne doit pas être l'occasion d'une remise en cause du niveau scientifique et technique d'évaluation sur lequel est fondé l'octroi des nouvelles autorisations de mise sur le marché.

Elle doit au contraire être l'occasion d'un approfondissement de la réflexion sur les niveaux d'exigences requis, en fonction de chaque type de médicament.

Elle aura des conséquences sur la politique du médicament et la régularisation du marché.

Il sera maintenu sur le marché des médicaments :

- à efficacité démontrée ;
- à efficacité suffisamment justifiée (1) ;

et ayant un rapport bénéfice/risque positif (2).

En conséquence, trois niveaux d'indications thérapeutiques seront acceptés (voir plus loin).

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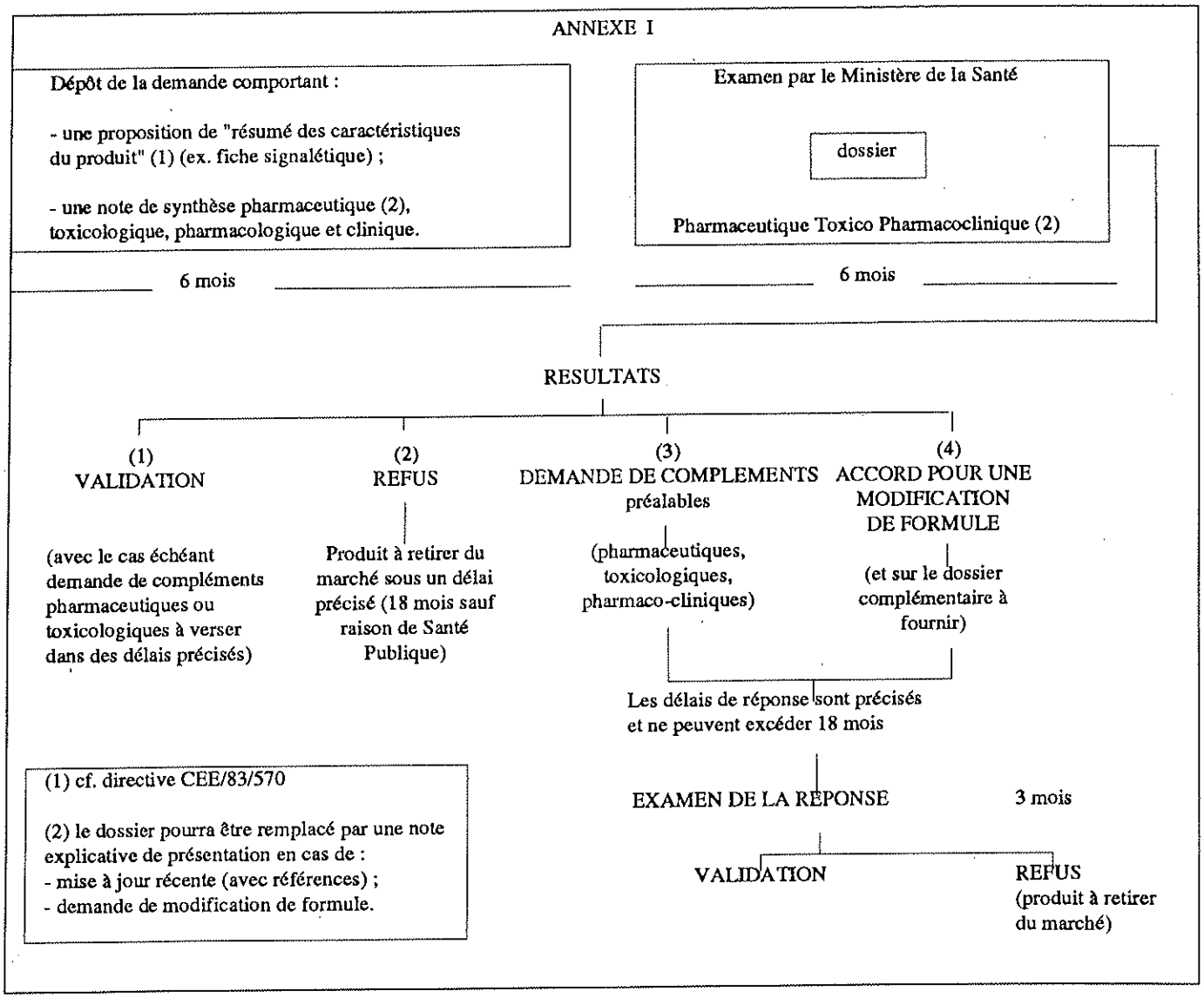
(1) Voir article 5 de la directive CEE/65/65 qui prévoit que l'autorisation de mise sur le marché est refusée ... "lorsque l'effet thérapeutique fait défaut ou est insuffisamment justifié".

(2) Voir directive CEE/75/318, 3e partie, chapitre III-I, modifié par la directive CEE/83/570.



Il sera aussi accepté ou demandé des modifications (qualitatives et quantitatives) de formules de certaines spécialités pour leur permettre de correspondre à la définition ci-dessus.

2 - LA VALIDATION DOIT ETRE REALISTE

Elle doit permettre d'offrir aux utilisateurs, les médicaments les mieux adaptés à leur intérêt et à leurs besoins, ceci sans coût indu pour les fabricants et pour la Communauté nationale.

Ceci conduit à estimer que des médicaments actuellement sur le marché seront validés sous réserve dans certains cas :

- d'une mise à jour si besoin du dossier pharmaceutique ;
- que les indications thérapeutiques et la posologie soient éventuellement précisées.

L'appréciation de l'innocuité sera effectuée en prenant en compte les éléments de toxicologie expérimentale prévus par les directives que la firme pharmaceutique aura apportés, ainsi que des observations de pharmacovigilance rendues disponibles.

Toutefois, certains médicaments actuellement sur le marché devront être retirés (sécurité non assurée au regard des connaissances actuelles, principes actifs mal définis, associations illogiques, dosages mal adaptés à la posologie ...) ; cependant dans certains des cas évoqués ci-dessus, des modifications de formule ou de présentation pourront être envisagées.

Les firmes seront donc appelées à déposer une note de synthèse pharmaceutique, toxicologique, pharmacologique et clinique constituant une sorte de carte d'identité de leurs produits (cf. avis aux fabricants de spécialités pharmaceutiques relatif à l'application de l'article 39 (point 2) de la directive 75-319/CEE publié au J.O. du 20 décembre 1984).

3 - LE CRITERE PREMIER DETERMINANT DE LA VALIDATION OU DE LA NON-VALIDATION SERA CLINIQUE

Pour éviter un gaspillage de temps et d'argent, notamment pour les spécialités dont la formule devra être modifiée, l'examen des dossiers complets pourra être effectué en étapes successives (voir schéma en annexe I) :

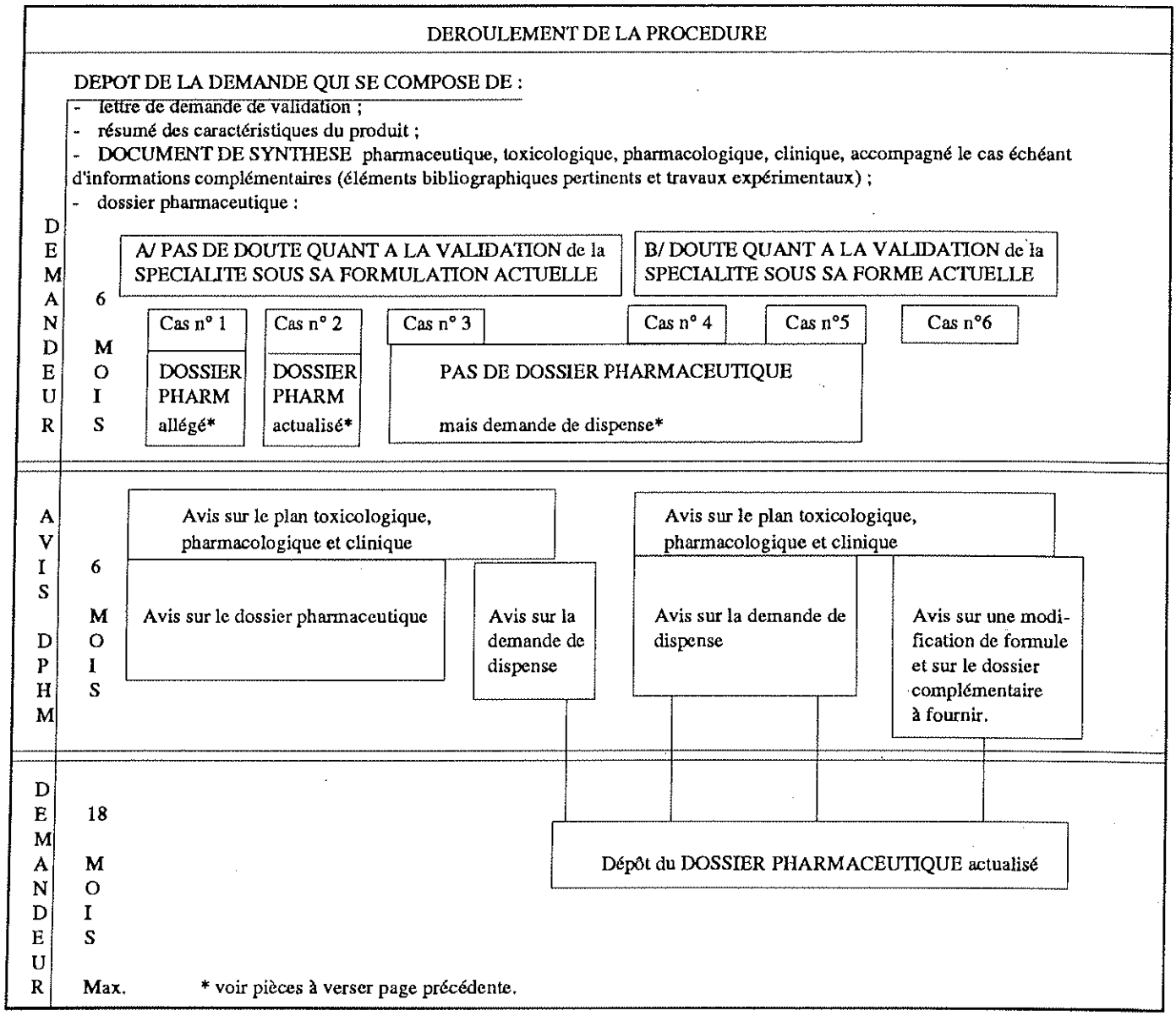
3.1. Prise de position sur le dossier clinique (efficacité, intérêt thérapeutique)

3.1.1. - Bases de travail

L'efficacité et la sécurité, dans les conditions normales d'emploi et dans les indications revendiquées seront appréciées indication par indication compte tenu :

- des données et connaissances disponibles sur la base des travaux expérimentaux : dans ce cadre, la présentation des éléments bilbliographiques est importante ;
- et/ou de l'expérience acquise à leur sujet.

Dans cette optique, les travaux de réflexion et de révision de la



Commission de Révision des Dictionnaires de Spécialités Pharmaceutiques seront très largement pris en compte.

Toutefois, ils ont été menés dans un but différent de celui d'une validation et quelques aménagements devront être envisagés, dans des cas ponctuels, au coup par coup ; en outre, certaines mises à jour des monographies étoilées pourront s'avérer nécessaires en fonction de connaissances nouvelles et dans des cas particuliers, lorsque cela sera utile, certaines études pharmacocinétiques ou cliniques pourront être demandées.

3.1.2. Types d'indications accessibles

Les indications se situeront aux niveaux suivants :

- indications pleinement reconnues : elles sont portées directement lorsque l'efficacité est démontrée par une méthodologie approuvée ;
- indications suffisamment justifiées : lorsque le médicament a une utilité thérapeutique et que la démonstration de l'efficacité ne peut être apportée de façon plus probante en l'état actuel de la science :
  - elles sont précédées de la mention "proposé dans" lorsque le dossier montre un rapport efficacité/tolérance favorable ;
  - elles sont précédées de la mention "appartient à la classe des ... traditionnellement utilisé dans ..." pour les classes ainsi identifiées comme, par exemple, certains médicaments de phytothérapie (voir 4-3).

Il faut remarqner que les rubriques "proposé dans ..." et "utilisé comme" se retrouvent dans les monographies actuelles des dictionnaires de spécialités, et correspondent à des situations qui peuvent mériter un réexamen pouvant entraîner dans certains cas une modification de formule et/ou un changement de niveau d'indications.

3.1.3. Règles de la validation clinique

Dans une même classe pharmacothérapeutique et pour une même indication, et en tenant compte de la nature et de la gravité de la pathologie traitée, seul le niveau d'indication le plus élevé déjà atteint sera retenu.

3.2. Prise de position sur le dossier toxicologique et le dossier pharmaceutique

Elle pourra s'effectuer dans un second temps (voir schéma) après accord sur le dossier clinique et éventuellement adaptation de la formule ; un délai de 6 mois à 18 mois sera donné si besoin, pour fournir les éléments complémentaires.

3.2.1. Sur le plan toxicologique

Une note bibliographique, accompagnée le cas échéant d'études complémentaires effectuées par le laboratoire et non déposées au Ministère, devra être établie pour chaque principe actif et/ou spécialité. Elle devra comprendre une analyse critique situant notamment le dossier par rapport aux directives européennes.

Compte tenu des connaissances actuelles apportées par l'utilisation prolongée dans l'espèce humaine de ces médicaments anciens, il est observé qu'une garantie supplémentaire dans la sécurité d'emploi peut être en particulier apportée par les études de reproduction (notamment segment II) et par les études de mutagénèse. Ces études relativement aisées à conduire sont sources d'informations que l'on ne peut pas retirer d'une utilisation prolongée chez l'homme.

3.2.2. Sur le plan galénique et analytique

Un dossier établi sur la formule finalement retenue devra être garant du haut niveau de qualité de la fabrication (conforme aux B.P.F.) et du contrôle ; l'attention sera portée sur l'adéquation des conditionnements aux usages et posologies prévues.

4 - LES CONSEQUENCES DE LA VALIDATION

4.1. - Les produits qui ne seront pas validés : quand devront-ils être retirés du marché ?

Un délai de 18 mois (à compter de l'issue de la période du premier examen du groupe *de médicaments appelés) sera accordé pour permettre aux fabricants* une éventuelle reconversion (par exemple modification de formule) ; à l'issue de cette période de retrait sera, s'il y a lieu, prononcé (voir annexe I).

Pendant cette période intermédiaire, les conditions dans lesquelles les médicaments qui ne seront pas validés pourront rester sur le marché, seront déterminées pour chaque cas particulier. L'information que le produit ne sera pas validé sera portée à la connaissance des utilisateurs afin de faciliter les changements d'habitude.

4.2. - Les produits dont l'autorisation de mise sur le marché a été octroyée postérieurement au 30 Novembre 1976,

date à laquelle la directive 75/319/CEE a été théoriquement mise en application.

Leur information devrait être révisée si besoin est, et alignée sur celle de la classe pharmacothérapeutique à laquelle ils appartiennent, lorsque cette dernière fera l'objet d'une validation.

4.3. - Les octrois de nouvelles autorisations de mise sur le marché

Différents niveaux d'indications pourront-ils être envisagés pour de nouvelles autorisations de mise sur le marché ? A ce jour, la Commission d'Autorisation des Médicaments reconnaît l'intérêt que peuvent présenter certains produits "traditionnellement utilisés dans" ; ainsi a été actuellement reconnue la classe des médicaments de phytothérapie présentés sous forme de mélanges de plantes pour tisanes ; d'autres travaux sont en cours.

En ce qui concerne le niveau "proposé dans", une difficulté existe à accepter ce niveau d'indication pour de nouveaux médicaments ; en effet cette reconnaissance risquerait d'avoir un effet négatif sur l'effort de recherche et de conduire à une attitude trop souvent laxiste.

Toutefois, la Commission d'Autorisation des Médicaments pourra discuter cette éventualité, classe par classe, à l'occasion des travaux de validation.

Cette éventualité ne paraît cependant acceptable :

1/ qu'en l'absence de produits à activité démontrée dans cette indication, et aussi longtemps qu'il n'en apparaît pas avec une activité très nettement supérieure, en tenant compte de la nature et de la gravité de la pathologie traitée ;

2/ que si les dossiers comportent des études établies sur la base des critères scientifiques actuellement en vigueur.

Ces dossiers devront faire l'objet d'actualisations régulières en fonction de l'évolution scientifique.

L'étude de tels médicaments s'adressant à des pathologies majeures doit obligatoirement se poursuivre afin d'apporter à la collectivité scientifique d'une part, nationale voire internationale d'autre part, la réponse aux problèmes de santé posés. Les firmes bénéficiaires de telles autorisations devront donc s'engager à continuer leurs études et à en soumettre périodiquement les résultats au Ministère de la Santé.

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* Sont également concernées les autorisations de mise sur le marché résultant d'une transformation de visa octroyé antérieurement au 1er décembre 1976.

P.J. n° 6

Annexe 2-10

- **NOTE de la Direction de la Pharmacie et du Médicament du 22 mai 1985 (Lettre au S.N.I.P.).**

L'avis aux fabricants de spécialités pharmaceutiques, publié au Journal Officiel du 20 décembre 1984, a annoncé la mise en place de l'opération de validation des spécialités pour lesquelles une autorisation (visa ou A.M.M.*) a été délivrée antérieurement au 1er décembre 1976, en application de l'article 39 (point 2) de la directive 75/319/CEE.

Les principes généraux ainsi que la procédure de cette opération de validation ont été définis dans le document du 30 janvier 1985.

Le présent document a pour objet de préciser les modalités de constitution du dossier pharmaceutique.

Afin de faciliter le travail des demandeurs et de l'administration, et compte tenu du fait que le critère premier déterminant la validation ou la non validation sera d'ordre clinique, il convient d'envisager à quel moment devra être déposé le dossier pharmaceutique.

Pour être validée, une spécialité doit répondre simultanément aux conditions suivantes :

- le médicament a une efficacité démontrée ou une efficacité suffisamment justifiée, et le rapport bénéfice/risque est jugé positif ;
- pour une association fixe, l'intérêt est démontré au regard des critères actuels et/ou la composition repose sur des bases rationnelles.

Sur cette base de réflexion, il appartient au demandeur de situer sa spécialité dans un des six cas définis ci-après.

A - Le demandeur n'a pas de doute quant à la validation de la spécialité sous sa formulation actuelle.

Trois cas sont possibles :

- Cas 1 : le dossier pharmaceutique (fabrication - contrôle - étude de stabilité) a fait l'objet d'une actualisation récente qui a reçu l'aval de la Direction de la Pharmacie et du Médicament ;
- Cas 2 : le dossier pharmaceutique nécessite une actualisation **;
- Cas 3 : le demandeur envisage une modification de la formule portant exclusivement sur les excipients.

B - Le demandeur désire la validation et a un doute quant à la possibilité de validation de la spécialité sous sa formulation actuelle, - et/ou il souhaite une modification de la formulation (principe actif et/ou excipient) de la spécialité ou de la forme galénique.

Trois cas sont possibles :

- Cas 4 : le demandeur envisage une modification de la formule portant exclusivement sur les excipients ;

** Si le titulaire de l'autorisation de mise sur le marché estime que son dossier ancien ne nécessite pas une actualisation, ce qui devrait correspondre à une situation exceptionnelle étant donnée la rapide obsolescence des dossiers pharmaceutiques, il fera parvenir un dossier complet avalisé par un expert agréé.

- Cas 5 : le demandeur envisage une modification de la formule portant sur le(s) principe(s) actif(s) (et éventuellement les excipients) et/ou sur la forme galénique :
- Cas 6 : le demandeur n'envisage pas de modification et souhaite connaître la position de la Direction de la Pharmacie et du Médicament.

Selon le cas dans lequel se situe la spécialité, les tableaux suivants résument :
- les pièces versées au moment de l'appel de la classe ;
- le déroulement de la procédure.

Dans tous les cas de demande de validation, un document de synthèse comportant des renseignements pharmaceutiques, toxicologiques, pharmacologiques et cliniques doit être déposé : la teneur du document de synthèse sur le plan pharmaceutique est évoquée plus loin.

La teneur du dossier pharmaceutique (fabrication - contrôle - étude de stabilité) est précisée plus loin.

PIECES A VERSER SUR LE PLAN PHARMACEUTIQUE AU MOMENT DE L'APPEL DE LA CLASSE
(en même temps que les éléments toxicologique, pharmacologique et clinique)

Cas n° 1 :
Dossier pharmaceutique récemment actualisé :
- dossier pharmaceutique allégé constitué de :
  - référence aux mises à jour récentes avalisées par la D.P.H.M. (photocopie de la lettre d'accord)
  - contrôle des principes actifs (cf. § C.1 - C.2)

Cas n° 2 :
Nécessité d'une actualisation du dossier :
- dossier pharmaceutique actualisé, avalisé par un expert agréé (1).

Cas n° 3 et cas n° 4 :
- Modification de formule portant exclusivement sur les excipients envisagée par le demandeur :
- demande de dispense selon l'article R. 5133 a du code de la santé publique avec proposition de dossier complémentaire:
  - dans tous les cas dossier pharmaceutique actualisé, avalisé par un expert agréé (1) ;
  - éventuellement étude de dissolution comparée, étude de biodisponibilité, étude de tolérance, etc.

Cas n° 5 :
- Modification de formule portant sur le(s) principe(s) actif(s) (et éventuellement les excipients) et/ou la forme galénique envisagée par le demandeur :
- demande de dispense selon l'article R. 5133 a du code de la santé publique avec proposition de dossier complémentaire:
  - dans tous les cas dossier pharmaceutique actualisé, avalisé par un expert agréé (1) ;
  - éventuellement étude de biodisponibilité, étude de tolérance, d'efficacité, etc.

Cas n° 6 :
- Pas de modification de formule envisagée par le demandeur qui attend les observations de l'administration:
  - le demandeur précise sa position dans la lettre de demande.

DOCUMENT DE SYNTHESE
prévu par l'avis aux fabricants publié au Journal Officiel du 20 décembre 1984

Le document de synthèse doit être rédigé par des experts répondant à la définition de la Directive 75/319/CEE du 20 Mai 1975 article premier, c'est-à-dire possédant les qualifications techniques ou professionnelles nécessaires dans le domaine considéré.

Il doit permettre au demandeur de dégager sous une forme synthétique et précise les éléments essentiels du dossier de validation.

Il doit être accompagné du résumé des caractéristiques du produit (cf. avis aux fabricants - J.O. du 20 décembre 1984).

Le numéro du dossier doit être porté sur la page de garde de chacun des exemplaires.

En première page, devront être indiquées la date d'octroi du visa ou de l'autorisation de mise sur le marché ainsi que la durée de commercialisation effective (mention des arrêts éventuels) de la spécialité sous ses diverses formulations.

En ce qui concerne les renseignements pharmaceutiques, ce document de synthèse doit préciser la composition qualitative et quantitative complète de la formule existante, son adéquation au but thérapeutique visé, les caractéristiques principales des principes actifs (notamment physico-chimiques), de la forme pharmaceutique, de sa fabrication (notamment du schéma du mode de préparation), de son contrôle et de sa conservation.

S'il est envisagé une modification de formule
- sur le plan des excipients,
- et/ou sur le plan des principes actifs,

il convient d'expliciter les raisons des modifications apportées : allègement envisagé pour améliorer la stabilité, ou faciliter le contrôle ; suppression de produits mal définis, ou présentant des difficultés d'approvisionnement ; opportunité d'ajouter ou de supprimer des conservateurs ...

COMPOSITION DU DOSSIER PHARMACEUTIQUE DE VALIDATION DES SPECIALITES PHARMACEUTIQUES

I. - Généralités

Le dossier pharmaceutique de validation sera élaboré en prenant pour guide l'arrêté du 10 août 1976 fixant le protocole applicable aux essais analytiques.

Afin de faciliter son élaboration, il ne comportera qu'un volume dans lequel on retrouvera l'esprit du dossier scientifique défini par l'avis n° 24 100 (publié au Bulletin Officiel du Ministère des Affaires Sociales le 12 janvier 1984).

Le niveau des exigences doit être adapté à chaque cas en faisant preuve de bon sens et de mesure ; deux aspects nécessitent cependant d'être soulignés :

a) l'actualisation des protocoles de contrôle des matières premières, des produits intermédiaires de fabrication et du produit fini, devra prendre en compte les méthodes modernes d'analyse.

Il convient toutefois de ne pas apporter systématiquement des modifications impliquant des travaux de mise au point ou de recherche, à partir du moment où les procédés donnent satisfaction et offrent les garanties requises ;

b) la vérification de la stabilité sera conduite selon des méthodes validées notamment par la mise en oeuvre d'études de dégradation forcée.

Le dossier pourra prendre en compte largement la mise en place des PRATIQUES DE BONNE FABRICATION, notamment leurs répercussions sur l'organisation générale de la fabrication et sur le système d'assurance de qualité (allègement de certains contrôles de routine par exemple).

II - Contenu du dossier pharmaceutique

Les différents chapitres du dossier pharmaceutique sont les suivants :

A. Description de la composition qualitative et quantitative.

(1) Le lieu de l'expertise, la provenance des données, la date et le nom du (des) expert(s) sont mentionnés.

Les demandes d'agrément d'expert doivent être adressées au bureau Ph 11 (curriculum vitae - moyens techniques disponibles).

B. Description du mode de préparation.
C. Contrôle des matières premières.
D. Contrôle sur les produits intermédiaires de la fabrication.
E. Contrôle du produit fini.
F. Essais de stabilité.

Selon que la spécialité concernée sera reformulée ou non, il est rappelé ici CERTAINES des données importantes qui devront être précisées au niveau des chapitres signalés.

1. Spécialité non reformulée :

A. Composition quantitative et qualitative.
En raison de l'ancienneté de la préparation il n'y a pas lieu de présenter une justification de la formulation.

B. Mode de préparation.
En cas de modification (s) du mode de préparation de la spécialité, il y a lieu de spécifier et le cas échéant de justifier les changements apportés.

C. Contrôle des matières premières
(les principes actifs et dans certains cas les excipients susceptibles d'influencer la qualité du médicament).
1. Dans tous les cas :
- Seront communiqués le nom du fournisseur ainsi que son engagement à faire connaître :
  - tout changement dans la synthèse ou la purification susceptible d'influer sur la qualité de la matière première;
  - le changement de fabricant lorsqu'il n'assure pas lui-même la fabrication des principes actifs.
- En cas d'impossibilité d'obtenir cet engagement du fournisseur, le titulaire de l'A.M.M. doit fournir lui-même, à tout le moins, l'engagement de n'utiliser que des matières premières préparées selon une méthode non susceptible de laisser des impuretés non mentionnées dans la monographie.
- Ces documents peuvent être annexés à la lettre de demande de validation.

2. Pour les matières premières,
- non inscrites à la Pharmacopée française ou européenne,
- inscrites à la Pharmacopée française ou européenne mais préparées selon une méthode susceptible de laisser des impuretés non mentionnées dans la monographie (cf. Protocole analytique - Arrêté du 10.VIII.76 - Chap. C1) :
  - Le schéma d'obtention ou d'extraction est indiqué.
  - Les méthodes actualisées d'analyse (mise au point et routine) sont détaillées avec justification de leur choix et précision des limites d'acceptation.
  - Les essais de pureté sont décrits en fonction de l'ensemble des impuretés prévisibles.

D.E. Contrôle des produits intermédiaires et/ou du produit fini.
- Les essais et les méthodes doivent correspondre à l'état d'avancement du progrès scientifique (exemple : essai de vitesse de dissolution sur les formes orales solides ...) et le dossier comporter les éléments qui expliquent leur choix.
- Les écarts maximaux tolérables doivent être fixés : ainsi, la teneur unitaire en principe actif est fixé à ± 5 pour cent au moment de la fabrication, sauf justification.

F. Essais de stabilité.
- La durée de validité proposée est fondée sur des essais de stabilité conduits dans les conditions normales de conservation, dans le récipient destiné à la vente ou équivalent (sauf justification) en utilisant des méthodes validées.
- En cas de modification du mode de préparation de la spécialité se reporter au paragraphe 2 suivant.

2. Spécialité reformulée.

Les points spécifiques précédemment énoncés en B, C, D, E sont valables également en cas de reformulation.
De plus, les chapitres A et F devront être complétés de façon suivante :

A. Composition quantitative et qualitative :
Donner la justification scientifique et/ou la raison de la modification de formule.

F. Essais de stabilité :
Proposer une nouvelle durée de conservation :
- la durée de conservation pourra être accordée à partir de :
  - études de stabilité en temps réel d'au moins 6 mois ;
  - données accumulées sur stabilité de l'ancienne formule et extrapolables à la nouvelle formule (exemple : connaissance de l'altérabilité du ou des principe (s) actif (s) ;
  - résultats d'études de dégradation forcée sur le principe actif et sur le produit terminé sous la nouvelle formulation, comparativement avec les résultats obtenus avec l'ancienne formulation.

Dans ces conditions, une durée de conservation au moins égale à 24 mois sera accordée.
- dans tous les cas, les études de conservation en temps réel devront être poursuivies et les résultats obtenus communiqués périodiquement.

PJ. 407

Annexe 2-10

- **AVIS aux fabricants** de spécialités pharmaceutiques relatif à l'application de l'article 39 (point 2) de la directive 75-319 C.E.E. Présentation des dossiers de validation (B.O.S.P. 86/19 du 3 juin 1986).

Cet avis concerne la présentation des dossiers de demande de validation.

Les dossiers devront être présentés selon le plan décrit dans les annexes I et II ci-jointes.

L'imprimé intitulé "Examen de recevabilité des dossiers de validation" figurant à la suite des annexes I et II devra être rempli par le demandeur et joint à tout dossier lors de son dépôt.

L'application de cette nouvelle présentation est effective pour le dépôt de la troisième tranche et des tranches suivantes.

ANNEXE I

Présentation d'une demande de validation
(premier dépôt)

Les pièces devront être présentées et numérotées dans l'ordre indiqué.

	Nombre d'exemplaires (chemises cartonnées bleues à élastique)	
	Dossier A	Dossier B
1. Bordereau de transmission de la redevance	1	-
- chèque et accusé de réception rempli ;		
- enveloppe timbrée		
2. Lettre de demande de validation	1	1+4 (*)
- date et signature ;		
- numéro du dossier ;		
- date d'octroi du visa ou de l'A.M.M. ;		
- lieu de fabrication, conditionnement, contrôle ;		
- composition intégrale ;		
- indication pour laquelle la validation est sollicitée avec n° de la tranche correspondante ;		
- autres indications qui ont fait ou qui feront également l'objet d'une demande de validation avec n° des tranches correspondantes ;		
- situation de la spécialité par rapport à la procédure de validation du dossier pharmaceutique. Indiquer le cas choisi (**).		
3. Engagement du fournisseur ou du titulaire de l'autorisation de mise sur le marché sur les matières premières (**)	1	1
4. Photocopie des pièces administratives (groupées dans une sous-chemise)	1	1
- visa ou A.M.M. ;		
- dernier renouvellement quinquennal ;		
- autorisations d'ouverture de ou des établissements pharmaceutiques (fabrication) ;		
- rectificatifs ;		
- monographie du Vidal étoilée.		
5. Résumé des caractéristiques du produit	1	1+4 (*)
6. Proposition du libellé de l'information destinée au public (à mettre dans le dossier clinique du dossier B)	1	1
7. Représentation du conditionnement	1	1
8. Pièces qui ont trait au dossier pharmaceutique : dossier ou lettre selon le cas choisi (**) dans une chemise ou une reliure jaune (***)	1	2
9. Document de synthèse (bleu) (***)	1	2

	Nombre d'exemplaires (chemises cartonnées bleues à élastique)	
	Dossier A	Dossier B
10. Documents complémentaires (éventuellement) (***)	1	1
- toxicologie et pharmacologie expérimentale (vert) ;		
- pharmacologie clinique, pharmacocinétique, et clinique (rouge), individualisés chacun dans une chemise de la couleur indiquée ou reliés séparément avec une couverture de la couleur indiquée.	☐	☐

11. Documents de synthèse : 15 exemplaires supplémentaires groupés à part.
Dans le document de synthèse doivent figurer en particulier :
- le résumé des caractéristiques du produit ;
- le niveau des ventes ;
- les pays dans lesquels l'autorisation de mise sur le marché a été donnée ;
- le bilan des effets indésirables signalés à la firme après mise sur le marché ; donnée de pharmacovigilance et de consommation globale du produit ; utilisation dans d'autres pays.

12. Résumé des caractéristiques du produit : 30 exemplaires supplémentaires groupés à part.
13. Cinq étiquettes autocollantes comportant le nom et l'adresse du laboratoire.

(*) Ventiler un exemplaire dans chacun des volumes constituant le dossier B : pharmaceutique (2), toxicologique (1), clinique (1).

(**) cf. Note de la Direction de la Pharmacie et du Médicament du 22 mai 1985

(***) Les chemises colorées devront être individualisées et comporter chacune le nom de la spécialité, le nom du laboratoire et le numéro du dossier.

ANNEXE II

Présentation d'une demande de validation
(dépôt ultérieur)

Concerne les dépôts de demande pour les produits ayant déjà fait l'objet d'un dépôt antérieur pour d'autres indications dans une tranche précédemment appelée.

	Nombre d'exemplaires (chemises cartonnées bleues à élastique)	
	Dossier A	Dossier B
1. Lettre de demande	1	1
- date et signataire ;		
- numéro de dossier ;		
- date d'octroi du visa ou de l'A.M.M. ;		
- composition intégrale ;		
- indication revendiquée et rappel des autres indications qui ont fait ou qui feront également l'objet d'une demande de validation avec n° des tranches correspondantes.		
2. Résumé des caractéristiques du produit	1	1
3. Proposition du libellé de l'information destinée au public ...	1	1
4. Document de synthèse (bleu) ..	1	1
5. Documents complémentaires (concernant la nouvelle indication) (*)	1	1
- toxicologie et pharmacologie expérimentale (vert) ;		
- pharmacologie clinique, clinique et pharmacocinétique (rouge),		
individualisés chacun dans une chemise de la couleur indiquée ou reliés séparément avec une couverture de la couleur indiquée.		

6. Documents de synthèse : 15 exemplaires supplémentaires groupés à part.
7. Résumé des caractéristiques du produit : 30 exemplaires supplémentaires groupés à part.
8. Cinq étiquettes autocollantes comportant le nom et l'adresse du laboratoire.

(*) Les chemises colorées devront être individualisées et comporter chacune le nom de la spécialité, le nom du laboratoire et le numéro du dossier.

EXAMEN DE RECEVABILITE
DES DOSSIERS DE VALIDATION

Nom de la spécialité et forme pharmaceutique : .....
D.C.I. ou D.C.F. :.....
Nom du titulaire de l'A.M.M. :.....
N° dossier :.....
Indication (s) thérapeutique (s) (selon le calendrier général) :.....
Autres indications qui ont fait ou qui feront également l'objet d'une demande de validation avec n° des tranches correspondantes :.....
Dossier pharmaceutique : cas n°..... (*)

	Dossier A (chemises cartonnées bleues à élastique)	Dossier B (chemises cartonnées bleues à élastique)	Doc à part
1. Bordereau de transmission de la redevance	☐	☐	
2. Lettre de demande	(1) ☐	(1+4) ☐	
3. Engagement du fournisseur ou du titulaire de l'A.M.M. sur les principes actifs	☐	☐	
4. Pièces administratives :			
- visa ou A.M.M. ;			
- dernier renouvellement quinquennal ;			
- rectificatifs ;			
- ouverture d'établissement ;			
- monographies Vidal.			
5. Résumé des caractéristiques du produit	(1) ☐	(1+4) ☐	
6. Libellé de l'information au public	☐	☐	
7. Dossier pharmaceutique ou lettre (jaune)	(1) ☐	(2) ☐	
8. Documents complémentaires :			
- toxicologie et pharmacologie expérimentale (vert)	☐	☐	
- pharmacologie clinique, clinique et pharmacocinétique (rouge)			
9. Document de synthèse (bleu)	(1) ☐	(2) ☐	
10. Document de synthèse (15 exemplaires)			☐
11. Résumé des caractéristiques (30 exemplaires) ...			☐
12. Etiquettes autocollantes (5 exemplaires)			☐

N.B. - Chaque chemise colorée devra être individualisée et comporter le nom de la spécialité, le nom du laboratoire et le n° du dossier.
* cf. Note de la Direction de la Pharmacie et du Médicament du 22 mai 1985

MINISTERE DES AFFAIRES SOCIALES
ET DE L'EMPLOI

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REPUBLIQUE FRANÇAISE

Annexe 2-11

DIRECTION DE LA PHARMACIE
ET DU MEDICAMENT

Sous-Direction des Affaires
Scientifiques et Techniques

D. E. M.

Réf. à rappeler : VS-EC/SB
Dossier : V NL 10008

1, Place de Fontenoy
75700 PARIS CEDEX 07
Tél : 45.67.55.44

Paris, le 22 AVR. 1987

Monsieur le titulaire de
l'autorisation de mise sur le marché
Laboratoires SERVIER
45400 GIDY

AUTORISATION DE MISE SUR LE MARCHE

Monsieur,

J'ai l'honneur de vous faire connaître que la validation de l'autorisation de mise sur le marché est accordée à la spécialité pharmaceutique :

M E D I A T O R 150 mg, comprimés enrobés

- Les conditions de fabrication et de contrôle de cette spécialité, prévues au dossier, devront être respectées ; toutefois, les méthodes de contrôle devront être modifiées en fonction des progrès de la science et de l'évolution des techniques.

- Les caractéristiques techniques dont vous ferez état, notamment dans le domaine de l'information destinée au corps médical (dictionnaire des spécialités, fiche signalétique, etc) et au public, devront être conformes à celles précisées respectivement dans les annexes I et II. Toutefois, l'indication de la composition de l'excipient pourra être omise ou indiquée de façon qualitative, dans la mesure où sa connaissance n'est pas nécessaire à une bonne administration du médicament.

- La validité de cette autorisation de mise sur le marché est limitée à cinq ans à compter de la date de la présente correspondance.

- L'autorisation de mise sur le marché octroyée le **16 Juillet 1974** pour la spécialité **MEDIATOR, comprimés dragéifiés** est abrogée par la présente décision.

Je vous prie d'agréer, Monsieur, l'assurance de ma considération distinguée.

P.J.-2 Annexes

POUR LE MINISTRE DES AFFAIRES SOCIALES
ET DE L'EMPLOI ET PAR DELEGATION

Pour ampliation

Le Pharmacien Inspecteur divisionnaire de la Santé
chargé de la Sous-Direction des Affaires Techniques,
et Scientifiques

D. LAGARDE-CHOMBARD

A. ARTIGES

M9010008

Annexe 2-11 2.

ANNEXE I — DATE

RESUME DES CARACTERISTIQUES DU PRODUIT

MEDIATOR 150 mg

Comprimés enrobés

- **COMPOSITION**

CHLORHYDRATE DE BENFLUOREX.....	150,0 mg
Amidon de maïs.....	60,0 mg
Polyvidone excipient.....	20,0 mg
Saccharose.....	245,0 mg
Stéarate de magnésium.....	5,0 mg
Talc.....	20,0 mg

pour un noyau de 500 mg

Saccharose.....	172,914 mg
Talc.....	17,651 mg
Polyvidone excipient.....	1,349 mg
Bicarbonate de sodium.....	0,480 mg
Carboxyméthylcellulose sodique.....	0,944 mg
Silice colloïdale.....	0,674 mg
Polysorbate 80.....	0,850 mg
Ethylcellulose.....	0,555 mg
Oléate de glycérol.....	0,278 mg
Dioxyde de titane.....	4,305 mg
Cire d'abeille blanche.....	q.s.

pour un comprimé enrobé de 700 mg

- **PROPRIETES PHARMACOLOGIQUES** : HYPOLIPEMIANT

Il agit sur plusieurs facteurs liés au risque athérogène.

Actions de MEDIATOR sur le métabolisme lipidique :

- MEDIATOR diminue l'absorption intestinale des triglycérides (rat).
- Cet effet confirmé chez l'homme en pharmacologie clinique repose sur la diminution d'activité de la lipase pancréatique.
- Il réduit la synthèse hépatique des triglycérides et du cholestérol in vitro et in vivo (rat).
- Il diminue la stéatose hépatique induite par des régimes riches en lipides, en glucides chez le rat obèse et au cours du diabète expérimental (rat).
- Il limite l'incorporation du cholestérol dans la paroi artérielle (lapin).

Ce mode d'action est susceptible d'expliquer la diminution du cholestérol et des triglycérides chez l'homme.

Actions de MEDIATOR sur le métabolisme glucidique :

. Il facilite la pénétration et l'utilisation cellulaires du glucose (rat).
. Il diminue l'hyperglycémie du rat diabétique (insulinoprive ou non) et l'aire d'H.P.O. chez le lapin.
. Dans le diabète asymptomatique chez les patients obèses il entraîne une baisse de la glycémie post prandiale et une amélioration de la courbe d'H.P.O. supérieure à celle qu'on obtient avec un régime identique associé à un placebo.

MEDIATOR n'ayant pas d'action sur l'insulino-sécrétion, ne peut pas provoquer d'hypoglycémie.

Effet complémentaire de MEDIATOR :

Chez des patients obèses hyperuricémiques traités par MEDIATOR et régime, une baisse de l'uricémie d'environ 14 % a été observée.
Aucune interférence indésirable de MEDIATOR avec les traitements associés au cours des études n'a été constatée. MEDIATOR :

. ne potentialise pas les anticoagulants.
. ne provoque pas d'hypoglycémie
. n'interfère pas avec la fonction thyroïdienne.

- **ELEMENTS DE PHARMACOCINETIQUE**

. Absorption gastro-intestinale rapide et totale avec un pic maximal survenant entre 1 à 2 heures après l'administration.
. Elimination rapide et totale par voie urinaire : en 8 heures, une excrétion moyenne d'environ 74 % de la dose administrée est constatée.

L'élimination se fait en 2 phases :

. une première phase rapide (60 % en 3 ou 4 heures).
. une deuxième phase lente, se terminant en 36 heures environ.

- **INDICATIONS THERAPEUTIQUES**

Adjuvant du régime adapté dans les hypertriglicéridémies.
La poursuite du régime est toujours indispensable.

Remarque :
L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

- **CONTRE-INDICATIONS**

Les pancréatites chroniques avérées.

- **MISE EN GARDE**

Les troubles métaboliques relevant d'un traitement par MEDIATOR sont essentiellement observés chez l'adulte. La prescription de MEDIATOR n'est donc pas justifiée chez l'enfant.

- PRECAUTIONS D'EMPLOI

Si, après une période d'administration de quelques mois (3 à 6 mois), une réduction satisfaisante des concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

Grossesse : les résultats des études réalisées chez l'animal n'ont pas mis en évidence d'effet tératogène, en l'absence de données chez l'Homme, ces résultats expérimentaux ne permettent pas de préjuger un effet malformatif dans l'espèce humaine, par conséquent par mesure de prudence ne pas prescrire pendant la grossesse.

Allaitement : en l'absence de données sur le passage dans le lait maternel l'allaitement est déconseillé pendant la durée du traitement.

- EFFETS SUR LA CAPACITE DE CONDUIRE DES VEHICULES OU D'UTILISER DES MACHINES

- INTERACTIONS MEDICAMENTEUSES ET AUTRES INTERACTIONS

- INCOMPATIBILITES MAJEURES

- EFFETS INDESIRABLES

Les effets secondaires suivants ont été observés : digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.

- POSOLOGIE ET MODE D'ADMINISTRATION

3 comprimés dragéifiés par jour.
Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

. 1 comprimé la première semaine au dîner.
. 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner.
. 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois à 1 comprimé par jour, en fonction des résultats biologiques.
En association avec le régime, MEDIATOR constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

- SURDOSAGE

Conduite à tenir en cas d'absorption massive : le traitement sera purement symptomatique : lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience, des fonctions respiratoire et cardiaque.

- CONDITION DE DELIVRANCE

TABLEAU A.

- PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE - NATURE DU RECIPIENT

317 557.9 : 30 comprimés enrobés sous plaquettes thermoformées (PVC - Aluminium)

- DUREE DE STABILITE

3 ans.

- PRECAUTIONS PARTICULIERES DE CONSERVATION

- TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

LABORATOIRES SERVIER
45400 GIDY

Annexe 2-11

A N N E X E II

INFORMATION DESTINEE AU PUBLIC

INDICATIONS THERAPEUTIQUES

Ce médicament est un hypolipémiant (il réduit le taux de lipides sanguins).

Il est préconisé en complément du régime alimentaire dans les hyperlipidémies (surcharge de lipides dans le sang).
Un taux élevé de lipides dans le sang est un facteur majeur d'athérome (dépôt de plaques graisseuses sur la paroi des artères).

CONTRE-INDICATIONS

Ce médicament NE DOIT PAS ETRE UTILISE dans les cas suivants :

En cas de pancréatite chronique (insuffisance du pancréas).

MISE EN GARDE

Dans le traitement des hyperlipidémies, le respect scrupuleux du régime alimentaire prescrit par le médecin est **INDISPENSABLE**. (Eviter de manger des aliments riches en graisses saturées, en sucre, en cholestérol).

EN CAS DE DOUTE NE PAS HESITER A DEMANDER L'AVIS DE VOTRE MEDECIN OU DE VOTRE PHARMACIEN.

PRECAUTIONS D'EMPLOI

AFIN D'EVITER D'EVENTUELLES INTERACTIONS ENTRE PLUSIEURS MEDICAMENTS IL FAUT SIGNALER SYSTEMATIQUEMENT TOUT AUTRE TRAITEMENT EN COURS A VOTRE MEDECIN OU A VOTRE PHARMACIEN.
NE JAMAIS LAISSER A LA PORTEE DES ENFANTS.
PREVENIR LE MEDECIN EN CAS DE GROSSESSE.

EFFETS SUR LA CAPACITE DE CONDUIRE DES VEHICULES OU D'UTILISER DES MACHINES

AUTRES EFFETS POSSIBLES DU MEDICAMENT

COMME TOUT PRODUIT ACTIF, CE MEDICAMENT PEUT, CHEZ CERTAINES PERSONNES, ENTRAINER DES EFFETS PLUS OU MOINS GENANTS :

Troubles digestifs (nausées, gastralgies)
Asthénie, sensation de fatigue, voire somnolence. (Ces effets s'observent particulièrement aux posologies supérieures à 3 comprimés par jour).

POSOLOGIE ET MODE D'ADMINISTRATION

3 comprimés drageifiés par jour.
Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

- 1 comprimé la première semaine au dîner.
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner.
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au diner.

Par la suite, la posologie peut être ramenée à 2, parfois à 1 comprimé par jour, en fonction des résultats biologiques.
En association avec le régime, MEDIATOR constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

Pour une bonne utilisation de ce médicament il est indispensable de vous soumettre à une surveillance médicale régulière. Celle-ci peut comporter : un dosage des lipides.

DANS TOUS LES CAS SE CONFORMER STRICTEMENT A L'ORDONNANCE DE VOTRE MEDECIN.

CONDITION DE DELIVRANCE

CE MEDICAMENT EST INSCRIT AU TABLEAU A.
VOTRE PHARMACIEN NE POURRA VOUS EN DELIVRER QUE SUR UNE NOUVELLE ORDONNANCE DE VOTRE MEDECIN.

CE MEDICAMENT VOUS A ETE PERSONNELLEMENT PRESCRIT DANS UNE SITUATION PRECISE :
. IL PEUT NE PAS ETRE ADAPTE A UN AUTRE CAS
. NE PAS LE REUTILISER SANS AVIS MEDICAL
. NE PAS LE CONSEILLER A UNE AUTRE PERSONNE.

DUREE DE STABILITE

NE PAS DEPASSER LA DATE LIMITE D'UTILISATION INDIQUEE EN CLAIR SUR L'EMBALLAGE.

MINISTERE DES AFFAIRES SOCIALES
ET DE L'EMPLOI

DIRECTION DE LA PHARMACIE
ET DU MEDICAMENT

Sous-Direction des Affaires
Scientifiques et Techniques

D. E. M.

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REPUBLIQUE FRANCAISE

Annexe 2-12

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PARIS, le - 1 SEP 1987

1, Place de Fontenoy 75700 PARIS
Tél : 40.56.60.00

Monsieur le Pharmacien Responsable
des Laboratoires SERVIER
45400 GIDY

VNL 100 08

Monsieur,

Le Médiator 150 mg a fait l'objet d'un passage en validation à la suite duquel l'indication "adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale" a été examinée mais n'a pas été retenue. Elle n'a donc pas été reprise dans l'annexe I de l'autorisation de mise sur le marché validée comme le sont les indications non encore examinées. Si vous souhaitez conserver cette indication, vous pourrez déposer un dossier complet lors de l'appel de la 6ème tranche (endocrinologie).

Je vous prie d'agréer, Monsieur, l'assurance de ma considération distinguée.

Le Directeur de la Pharmacie
et du Médicament

Professeur P. AMBROISE-THOMAS

A3NMEDIA

Annexe 2-13

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

N / Réf.

Monsieur le Professeur P. AMBROISE-THOMAS
Directeur de la Pharmacie et du Médicament
Ministère des Affaires Sociales et de l'Emploi
1 place de Fontenoy
75700 PARIS cedex 7

V. Ref. : VS-EC/SB
N. Ref. : 499/HML/al

Gidy, le 7 juillet 1987

Objet : **N/spécialité MEDIATOR**
Dossier V NL 10 008

Monsieur le Directeur,

Nous avons reçu de vos Services, le 22 avril 1987, la validation de l'Autorisation de Mise sur le Marché de notre spécialité pharmaceutique

MEDIATOR 150 mg, comprimés enrobés,

et le résumé des caractéristiques du produit qui l'accompagne. La lecture de ce dernier nous surprend.

En effet, les indications thérapeutiques figurant page 3 (Cf. annexe 1 ci-jointe) sont réduites à :

"Adjuvant du régime adapté dans les hypertriglycéridémies.
La poursuite du régime est toujours indispensable.

Remarque :
L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée".

Ceci correspond à une très importante réduction des indications thérapeutiques telles qu'elles figurent dans la monographie validée par la Commission de contrôle des Dictionnaires des Spécialités Pharmaceutiques (Cf. annexe 2 ci-jointe) puisque l'indication :

"Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale"

a disparu du texte de l'A.M.M. (Annexe I) validée le 22 avril 1987.

.../...

Adresser toute correspondance à : B.P.227 45402 Fleury-les-Aubrais Cedex
Bureaux et Siège Social : 905, route de Saran, Gidy 45400 Fleury-les-Aubrais
Tél. 38.73.45.94. Télex 760469 F
Société anonyme au capital de 2.220.000 F R.C. Orléans B 085 480 796

Annexe 2-13

499/HML/al

En revanche, les autres chapîtres, aussi bien de la validation de l'Autorisation de Mise sur le Marché de 1987, que de la monographie agréée précédemment par la Commission de Contrôle des Dictionnaires des Spécialités Pharmaceutiques sont strictement superposables. En particulier, nous attirons votre attention sur le fait que dans les propriétés du médicament, l'action de MEDIATOR sur le métabolisme lipidique et sur le métabolisme glucidique a été reprise intégralement dans le résumé de la validation.

Ne voyant pas ce qui aurait pû justifier entre temps une telle réduction, nous pensons qu'il s'agit là d'une erreur, et qu'ont été omises les indications concernant le diabète asymptomatique avec surcharge pondérale. Pour cette indication, des travaux sont en cours pour être soumis à la Commission lors de la Validation des hypoglycémiants oraux en juin 1989.

Par conséquent, nous vous serions reconnaissants de bien vouloir attirer l'attention de vos Services de manière à apporter les corrections souhaitables (Cf. annexe 3 ci-jointe).

Restant à votre entière disposition pour toute information complémentaire, nous vous prions d'agréer, Monsieur le Directeur, l'expression de notre considération distinguée et de nos sentiments très dévoués.

G. ADAM

Pharmacien responsable intérimaire inscrit à la Section B de l'Ordre National des Pharmaciens sous le n° 081.105 B

Annexe 2-14

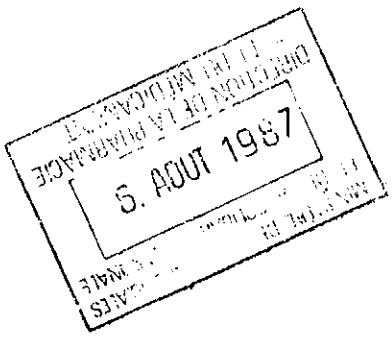
3.5

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

N / Réf. *ALR/MCMdS/71/87*

SG
11.8.87



Neuilly, le 29 juillet 1987

Monsieur le Professeur AMBROISE-THOMAS
Directeur de la Pharmacie et du Médicament
MINISTERE DES AFFAIRES SOCIALES ET DE L'EMPLOI
1, place Fontenoy
75700 PARIS CEDEX 7

Monsieur le Directeur,

L'examen de l'Autorisation de Mise sur le Marché de MEDIATOR 150 mg, dans le cadre de la validation des spécialités pharmaceutiques de la classe des hypolipémiants, a donné lieu à l'élaboration d'une nouvelle monographie en date du 22 avril 1987. Or, ce document ne comporte plus dans ses indications :

> "adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale".

Après entretien avec le Professeur ALEXANDRE, le 3 juillet 1987, il me confirme que conformément à l'article 39.2 de la Directive 75/319/CEE, la validation porte sur les indications thérapeutiques, et donc que des spécialités revendiquant plusieurs indications appartenant à différentes classes pharmaco-thérapeutiques devront faire l'objet d'une demande de validation pour chaque classe concernée au plan des indications.

L'indication "adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale" sera à valider lors de l'examen de la classe thérapeutique des antidiabétiques en 1989.

La monographie actuelle de MEDIATOR 150 mg doit donc logiquement conserver l'ancienne indication concernant le diabète.

Adresser toute correspondance à : B.P. 227 45402 Fleury-les-Aubrais Cedex
Bureaux et Siège Social : 905, Route de Saran, Gidy, 45400 Fleury-les-Aubrais
Tél. (38) 73.45.94. Télex 760469 F
Société anonyme au capital de 2.220.000 F. R.C. Orléans B 085 480 796

Div. 01

Par conséquent, nous vous serions reconnaissants de bien vouloir attirer l'attention de vos services de manière à apporter les corrections souhaitables, et de nous adresser un résumé des caractéristiques du produit, modifié de telle façon que nous puissions l'envoyer au dictionnaire Vidal dans les meilleurs délais.

Restant à votre entière disposition pour toute information complémentaire, nous vous prions d'agréer, Monsieur le Directeur, l'expression de notre considération distinguée et de nos sentiments très dévoués.

Docteur Alain LE RIDANT

c.c. Professeur J.M. ALEXANDRE

Annexe 2-15 3.8

MINISTERE DE LA SOLIDARITE, DE LA SANTE
ET DE LA PROTECTION SOCIALE

DIRECTION DE LA PHARMACIE
ET DU MEDICAMENT

Sous-Direction des Affaires
Scientifiques et Techniques

D.E.M.

REPUBLIQUE FRANCAISE

PARIS, le 02 AOUT 1989
1, Place Fontenoy 75700 PARIS
Tél : 40.56.60.00

Monsieur le pharmacien responsable
des laboratoires SERVIER
900, Route de SARAN CIDY
45400 - FLEURY-LES-AUBRAY

Réf. à rappeler : MD/LP
d. NL 10008

Monsieur,

Par lettre du 7 MARS 1989 vous avez sollicité le renouvellement de l'autorisation de mise sur le marché de la spécialité :

- MEDIATOR 150 mg, comprimés enrobés

J'ai l'honneur de vous faire connaître que, conformément aux dispositions de l'article R. 5137, 4ème alinéa, du code de la santé publique, cette autorisation de mise sur le marché doit être considérée comme renouvelée à compter du

- 16 JUILLET 1989 -

Toutefois, je vous rappelle que, selon les dispositions de l'article 39 (point 2) de la Directive 75-319 C.E.E. du 20 Mai 1975, les autorisations de mise sur le marché délivrées antérieurement au 1er Décembre 1976 doivent faire l'objet d'une validation dont le présent renouvellement ne saurait tenir lieu.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Ministre et par
délégation
Le Chef de Service,

J.-L. KEENE

00G1A

Annexe 2-16

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

N / Réf.

Ministère de la Solidarité, de la Santé et de la Protection Sociale

Direction de la Pharmacie et du Médicament

1 place de Fontenoy

75700 PARIS cedex 7

A l'attention du bureau chargé de procéder aux validations des A.M.M.

N.Réf. : HML/al/90/005

Gidy, le 19 janvier 1990

Objet : **VALIDATION 1990**
N/Spécialité MEDIATOR
Dossier V NL 10008
Tranche n° 8

Monsieur le Ministre,

Conformément à l'article 39 point 2 de la Directive 75/319/CEE du 20 mai 1975 et aux avis aux Fabricants parus au Journal Officiel le 20 décembre 1984, nous avions sollicité la validation de l'Autorisation de Mise sur le Marché pour notre spécialité

MEDIATOR, comprimés enrobés

lors de l'appel de la 1ère tranche : cardiovasculaire (hypolipémiant).

Nous avons l'honneur d'effectuer ce jour, le dépôt d'un nouveau dossier dans le cadre de l'appel de la 8ème tranche : ENDOCRINOLOGIE.

Numéro de dossier : NL 10008

Date d'octroi d'A.M.M. n° NL 10008 : 16 juillet 1974 sous les numéros :
- 317 553.3 : 10 comprimés enrobés
- 317 555.6 : 20 comprimés enrobés
- 317 556.2 : 24 comprimés enrobés
- 317 557.9 : 30 comprimés enrobés
- 317 558.5 : 60 comprimés enrobés
- 317 559.1 : 100 comprimés enrobés.

Adresser toute correspondance à : B.P.227 45402 Fleury-les-Aubrais Cedex
Bureaux et Siège Social : 905, route de Saran. Gidy 45400 Fleury-les-Aubrais
Tél. 38.73.45.94. Télex 760469 F
Société anonyme au capital de 2.220.000 F. R.C. Orléans B 085 480 796

HML/al/90/005
MEDIATOR - V NL 10008

Rectificatifs en date du 23 septembre 1974 et du 17 janvier 1976.

Renouvellements en date du 16 juillet 1979, 16 juillet 1984 et du 16 juillet 1989.

Composition intégrale du médicament :

Chlorhydrate de benfluorex	150,0 mg
Amidon de maïs	60,0 mg
Polyvidone excipient	20,0 mg
Saccharose	245,0 mg
Stéarate de magnésium	5,0 mg
Talc	20,0 mg

pour un noyau de 500 mg

Saccharose	172,914 mg
Talc	17,651 mg
Polyvidone excipient	1,349 mg
Bicarbonate de sodium	0,480 mg
Carboxyméthylcellulose sodique	0,944 mg
Silice colloïdale	0,674 mg
Polysorbate 80	0,850 mg
Ethylcellulose	0,555 mg
Oléate de glycérol	0,278 mg
Dioxyde de titane	4,305 mg
Cire d'abeille blanche	q.s.

pour un comprimé enrobé de 700 mg

Appel de la **huitième tranche.**
Indication pour laquelle la validation est sollicitée : ENDOCRINOLOGIE.

Appel de la **première tranche** (juin 1985) : cardiovasculaire (hypolipémiant).

Annexe 2-16

HML/al/90/005
MEDIATOR - V NL 10008

Situation de la spécialité par rapport à la procédure de validation du dossier pharmaceutique : dossier pharmaceutique actualisé, avalisé par un expert agréé.

A l'appui de cette demande, nous vous adressons :

I. Le dossier A, composé des documents suivants :

1. la proposition du résumé des caractéristiques du produit,
2. le libellé de l'information destinée au public,
3. le document de synthèse,
4. les documents complémentaires :
   * clinique.

II. Le dossier B, composé des mêmes documents que le dossier A.

III.
- 15 exemplaires du document de synthèse,
- 30 exemplaires du résumé des caractéristiques du produit,
- 5 étiquettes autocollantes avec le nom et l'adresse du laboratoire.

Nous vous informons que, par ailleurs, nous envoyons ce jour au Laboratoire National de la Santé (Paris et Montpellier) ainsi qu'à l'Inspection Régionale de la Santé (Orléans), les dossiers C, D et E comprenant les éléments suivants :

- la lettre de demande,
- la proposition du résumé des caractéristiques,
- la proposition du libellé de l'information destinée au public,
- le document de synthèse,

Nous vous prions d'agréer, Monsieur le Ministre, l'expression de nos sentiments distingués.

B. Papillaud

B. PAPILLAUD

Pharmacien responsable inscrit à la Section B de l'Ordre National des Pharmaciens sous le n° 61.067

Annexe 2-17

DATE : 23 mars 2000

NOMBRE DE PAGES : 6
(Number of pages)

EXPÉDITEUR (Caller) : Pierre MONTES

SOCIÉTÉ (Firm) : SCIENCE UNION (Groupe SERVIER)

MESSAGE :

Madame,

Comme convenu, je vous prie de bien vouloir trouver ci-joint, copie du PV du 12.07.91 validant l'indication de MEDIATOR® dans le diabète.

Je vous en souhaite bonne réception et vous prie d'agréer, Madame, mes sincères salutations.

Destinataire (Receiver) : C. REY-QUINIO

Société (Company) : AFSSAPS

VILLE / PAYS (Town / Country) : SAINT-DENIS

NUMÉRO DE TÉLÉFAX (Fax number) : 01.55.87.34.42

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Si vous ne recevez pas toutes les pages, merci de nous contacter au :
(If you don't receive all copies, please phone) :

Tél. : 01 55 72 65 33 ou (or) Fax : 01 55 72 33 02

Annexe 2-17

COMMISSION PLENIERE DU 12 JUILLET 1991

VALIDATION

8EME TRANCHE

QUALITE THERAPEUTIQUE

Annexe 2-17

MINISTERE DE LA SANTE

IRECTION DE LA PHARMACIE
ET DU MEDICAMENT

s-Direction des Affaires Scientifiques
et Techniques

1, place Fontenoy
75700 PARIS
Tél : 40.56.60.00

D.E.M.

COMMISSION D'AUTORISATION DES MEDICAMENTS
VALIDATION - QUALITE THERAPEUTIQUE

REUNION DU 1ER FEVRIER 1991

ENDOCRINOLOGIE - DIABETOLOGIE

PRESENTS

M. CAULIN
M. ALTMAN
M. STRAUCH
M. CLAUDE

ADMINISTRATION

Mme MOULON
Mme REIDIBOYM
Mme FOURET
Mme SIMON

S N I P

Mme PAULMIER-BIGOT

REMARQUE CONCERNANT LES SULFAMIDES HYPOGLYCEMIANTS ET LES BIGUANIDES :

Ces principes actifs ne constituent pas le traitement du diabète insulino-dépendant.
Cependant, ils peuvent être utilisés en association avec l'insuline.
Des études sont en cours sur l'intérêt clinique de cette association.
En conséquence, le diabète insulino-dépendant fera l'objet d'une contre-indication ainsi libellée :

CONTRE-INDICATIONS

Diabète de type I (insulino-dépendant)
Cependant cette spécialité peut être associée chez certains patients insulino traités.

I - A V I S F A V O R A B L E

A) Insulines

01534	ACTRAPID 5 MC (Insuline humaine hémisynthétique d'origine porcine)	Solution injectable	NOVO NORDISK PH
NL 9235	ENDOPANCRINE 10 (Insuline humaine hémi-synthétique) La dénomination sera : ORGASULINE 10 UI/ml	Solution injectable	ORGANON S.A.
NL 9232	ENDOPANCRINE 40 (Insuline porcine hautement purifiée)	Solution injectable	ORGANON S.A..
NL 9663	ENDOPANCRINE PROTAMINE CRISTALLISEE *N.P.H.* (Insuline porcine hautement purifiée, Protamine, Zinc)	Suspension injectable	ORGANON S.A.

NL 9237	ENDOPANCRINE ZINC PROTAMINE (Insuline porcine hautement purifiée. Protamine.	Suspension injectable	ORGANON S.A.
NL 10532	SEMILENTE MC (insuline porcine monocomposée, zinc)	Suspension injectable	NOVO NORDISK-PH

B) Sulfamides hypoglycémiants

NL 6487	DAONIL 5 mg (Glibenclamide)	Comprimés	HOECHST
NL 8265	DIAMICRON (Gliclazide)	Comprimés sécables	SERVIER
NL 6409	DOLIPOL (Tolbutamide)	Comprimés	HOECHST
NL 6486	EUGLUCAN 5 (Glibenclamide)	Comprimés	PIERRE FABRE MEDICAMENT
NL 9765	GLIBENESE 5 mg (Glipizide)	Comprimés sécables	PFIZER
NL 8041	GLUTRIL (Glibornuride)	Comprimés	PRODUITS ROCHE
NL 8507	HEMI-DAONIL (Glibenclamide)	Comprimés	HOECHST
NL 8506	MIGLUCAN 2,5 (Glibenclamide)	Comprimés	PIERRE FABRE MEDICAMENT
NL 9757	MINIDIAB 5 mg (Glipizide)	Comprimés sécables	FARMITALIA CARLO ERBA
NL 6309	GLUCIDORAL (Carbutamide)	Comprimés sécables	SERVIER

Annexe 2-17

C) Biguanides

NL 7627	GLUCINAN (Metformine)	Comprimés	ANPHAR-ROLLAND
09127	GLUCOPHAGE (Metformine)	Comprimés	ARON MEDICIA
NL 10269	STAGID (Embonate de Metformine)	Comprimés sécables	MERCK-CLEVENOT

D) Divers

V NL 10008	MEDIATOR (Chlorhydrate de benfluorex)	Comprimés enrobés	SERVIER

E) Hyperglycémiants

1) Indication validée :

- Hypoglycémies graves chez les diabétiques insulino traités.
- Intoxications par les β-bloquants : le glucagon n'est généralement utilisé qu'en 2ème intention, après l'atropine, l'isoprotérénol et éventuellement la dobutamine.

Indications diagnostiques : test au glucagon
- glycogénoses
- insulinome : sensibilisation de l'épreuve du jeûne
- comme méthode d'évaluation de l'insulino sécrétion résiduelle (dosage du peptide C)
- en tant qu'inhibiteur de la motilité, il est utilisé : dans les explorations du tube digestif : endoscopie et techniques d'imagerie (tomodensitométrie, RMN).

01535	GLUCAGON NOVO 1 mg (Glucagon)	Lyophilisat et solution pour usage parentéral	NOVO NORDISK Pm

(Meridan) 714 Hélène Maurice-Delorme Annexe 2-18 46-41 60.00

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

double

AGENCE DU MÉDICAMENT
Direction de l'Evaluation
143 - 147 boulevard Anatole France
93200 SAINT-DENIS

Gidy, le

A l'attention de Madame NORTH

N. Réf. : HML/vn/94/453
Tél. : 46.41.61.61
Mme MAURICE de LORRIS

Objet : **Rectificatif d'A.M.M.**
N/spécialité : MEDIATOR 150 mg
Dossier VNL 10008

Madame,

Faisant suite à un récent entretien entre Madame DUFFAU et le Docteur BATTAIS, nous vous adressons, à nouveau, trois exemplaires du dossier MEDIATOR 150 mg, comprimés enrobés, que nous avions déposé le 21 mai 1992, ainsi que copie du courrier correspondant (2 pages).

Il s'agit d'une proposition de modification du résumé des caractéristiques du produit au chapitre "PROPRIÉTÉS PHARMACOGIQUES" avec notamment :

1. *En pharmacologie animale (3 rapports)*

*Etude de l'effet du Benfluorex sur un modèle de rat rendu insulinorésistant par injection de streptozotocine 5 jours après la naissance (n 5STZ).
Pr. B. PORTHA - France (réf. : P 0992 01 043).

*Etude du Benfluorex : effets sur l'action de l'insuline in vivo.
Dr. L.G. STORLIEN - Australie (réf. : P 0992 01 044)
(version anglaise originale et traduction française).

*Etude de l'effet d'une perfusion intraportale de Benfluorex sur la tolérance au glucose chez le rat vigile.
Dr. J. DUHAULT - France (réf. : P 0992 01 045).

2. *En clinique (2 rapports)*
Etudes randomisées en double aveugle contre placebo :

*Evaluation du mécanisme hypoglycémiant du Benfluorex chez le diabétique de type II.
Pr. G.B. BOLLI et Pr. P. BRUNETTI - Italie (réf. : C 0780 31 067).

*Evaluation de l'utilisation périphérique du glucose et de l'insulino-résistance au cours d'un clamp euglycémique hyperinsulinémique chez des patients obèses atteints de diabète non insulino-dépendant traités par Benfluorex.
Pr. D.W. ERKELENS - Pays-Bas (réf. : C 0780 31 068)
(version anglaise originale et traduction française).

Annexe 2-18

HML/vn/94/453
MEDIATOR 150 mg
Dossier VNL 10008
Rectificatif d'A.M.M.

Nous joignons à ce nouveau courrier 50 exemplaires de :

- la copie de la proposition de la modification du résumé des caractéristiques du produit (1 page) ;

ainsi que :

- la copie de l'A.M.M. **initiale** de juillet 1974 avec les différents rectificatifs de septembre 1974, janvier 1976 et renouvellements d'août 1979, 1984 et 1989 ;

- la copie de l'A.M.M. **partiellement** validée du 22 avril 1987 avec seulement l'indication comme hypolipémiant, suite à notre dossier déposé en juin 1985 dans le cadre de l'appel de la tranche n° 1 des validations, l'indication "en association au régime dans le diabète asymptomatique avec surcharge pondérale et/ou hyperinsulinisme" ayant fait l'objet d'un dépôt de dossier dans le cadre de l'appel de la tranche n° 8, conformément à notre courrier du 19.01.1990 ;

- la copie de la monographie agréée par la Commission de Contrôle des Dictionnaires des Spécialités Pharmaceutiques du 29 octobre 1979.

Nous vous prions d'agréer, Madame, l'expression de notre considération distinguée.

B. PAPILLAUD
Pharmacien Responsable inscrit à la Section B de l'Ordre National des Pharmaciens sous le n° 61.067

Annexe 2-19

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

AGENCE DU MÉDICAMENT
Direction de l'Evaluation
143 - 147 boulevard Anatole France
93200 SAINT-DENIS

+ 4 Cartons
2 Dossiers Sol.

Gidy, le 1er août 1994

A l'attention de Madame NORTH

N. Réf. : HML/vn/94/453
Tél. : 46.41.61.61
Mme MAURICE de LORRIS

Objet : **Rectificatif d'A.M.M.**
N/spécialité : MEDIATOR 150 mg
Dossier VNL 10008

Madame,

Faisant suite à un récent entretien entre Madame DUFFAU et le Docteur BATTAIS, nous vous adressons, à nouveau, trois exemplaires du dossier MEDIATOR 150 mg, comprimés enrobés, que nous avions déposé le 21 mai 1992, ainsi que copie du courrier correspondant (2 pages).

Il s'agit d'une proposition de modification du résumé des caractéristiques du produit au chapitre "PROPRIÉTÉS PHARMACOLOGIQUES" avec notamment :

1. *En pharmacologie animale (3 rapports)*

*Etude de l'effet du Benfluorex sur un modèle de rat rendu insulinorésistant par injection de streptozotocine 5 jours après la naissance (n 5STZ).
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*Etude du Benfluorex : effets sur l'action de l'insuline in vivo.
Dr. L.G. STORLIEN - Australie (réf. : P 0992 01 044)
(version anglaise originale et traduction française).

*Etude de l'effet d'une perfusion intraportale de Benfluorex sur la tolérance au glucose chez le rat vigile.
Dr. J. DUHAULT - France (réf. : P 0992 01 045).

2. *En clinique (2 rapports)*
Etudes randomisées en double aveugle contre placebo :

*Evaluation du mécanisme hypoglycémiant du Benfluorex chez le diabétique de type II.
Pr. G.B. BOLLI et Pr. P. BRUNETTI - Italie (réf. : C 0780 31 067).

*Evaluation de l'utilisation périphérique du glucose et de l'insulino-résistance au cours d'un clamp euglycémique hyperinsulinémique chez des patients obèses atteints de diabète non insulino-dépendant traités par Benfluorex.
Pr. D.W. ERKELENS - Pays-Bas (réf. : C 0780 31 068)
(version anglaise originale et traduction française).

Annexe 2-19

HML/vn/94/453
MEDIATOR 150 mg
Dossier VNL 10008
Rectificatif d'A.M.M.

Nous joignons à ce nouveau courrier 50 exemplaires de :

- la copie de la proposition de la modification du résumé des caractéristiques du produit (1 page) ;

ainsi que :

- la copie de l'A.M.M. **initiale** de juillet 1974 avec les différents rectificatifs de septembre 1974, janvier 1976 et renouvellements d'août 1979, 1984 et 1989 ;

- la copie de l'A.M.M. **partiellement** validée du 22 avril 1987 avec seulement l'indication comme hypolipémiant, suite à notre dossier déposé en juin 1985 dans le cadre de l'appel de la tranche n° 1 des validations, l'indication "en association au régime dans le diabète asymptomatique avec surcharge pondérale et/ou hyperinsulinisme" ayant fait l'objet d'un dépôt de dossier dans le cadre de l'appel de la tranche n° 8, conformément à notre courrier du 19.01.1990 ;

- la copie de la monographie agréée par la Commission de Contrôle des Dictionnaires des Spécialités Pharmaceutiques du 29 octobre 1979.

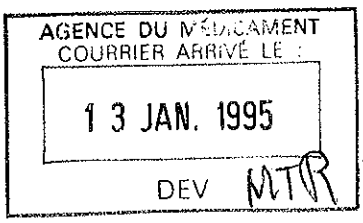
Nous vous prions d'agréer, Madame, l'expression de notre considération distinguée.

B. PAPILLAUD
Pharmacien Responsable inscrit à la Section B de l'Ordre National des Pharmaciens sous le n° 61.067

Annexe 2-20

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS



AGENCE DU MÉDICAMENT
Direction de l'Evaluation
143 - 147 boulevard Anatole France
93200 SAINT-DENIS

Gidy, le 11 janvier 1995

A l'attention de Madame NORTH

N. Réf. : HML/eg/95/009
Tél. : 46.41.61.61
Mme MAURICE de LORRIS

Objet : **Modification rubrique "Propriétés"**
N/spécialité : MEDIATOR 150 mg
Dossier VL 10008
Validation : Tranche n° 8

Dossier suivi par Madame REVEILLAUD

Monsieur le Directeur Général,

Notre spécialité qui a déjà fait l'objet d'un dossier de Validation comme **hypolipémiant** en avril 1987, à la suite de l'appel de la 1ère tranche en 1985, est toujours en cours d'examen pour la 8ème tranche en **diabétologie**.

Pour ce faire, en diabétologie, nous avions procédé au dépôt :

* d'un dossier initial en janvier 1990,
* puis d'un dossier complémentaire en mai 1992, dans le but de soutenir et rendre homogène le texte des "propriétés" avec celui de l'indication revendiquée.

A l'appui de cette demande, nous vous avions alors adressé :

- **3** rapports de pharmacologie animale
  - Pr B. PORTHA - FRANCE (réf. P.0992.01.043),
  - Dr L.H. STORLIEN - AUSTRALIE (réf. P.0992.01.044),
  - Dr J. DUHAULT - FRANCE (réf. P.0992.01.045).

- **2** études cliniques randomisées en double aveugle contre placebo
  - Pr G.B. BOLLI et P. BRUNETTI - ITALIE (réf. C.0780.31.067),
  - Pr D.W. ERKELENS - PAYS-BAS (réf. C.0780.31.068).

Nous vous transmettons, ce jour :

- **3 nouveaux rapports d'étude,** en deux exemplaires, de pharmacologie clinique qui démontrent l'action de MEDIATOR sur le contrôle métabolique glycémique (HbA1c) :
  - étude du Dr VELUSSI (3 volumes),
  - étude du Pr PONTIROLI (3 volumes),
  - étude du Pr ERKELENS (3 volumes),

- accompagnés en 50 exemplaires du **rapport d'expert** du Pr del PRATO qui reprend l'ensemble des études remises.

Veuillez agréer, Monsieur le Directeur Général, l'expression de nos salutations distinguées.

B. PAPILLAUD
Pharmacien Responsable inscrit à la Section B de l'Ordre National des Pharmaciens sous le n° 61.067

P.S. : la traduction française du rapport d'expert vous sera transmise, en 50 exemplaires, au plus tard le 26.01.95.

PROCEDURE NATIONALE

- MEDIATOR

dossier n° NL 10008

Laboratoires SERVIER

Demande déposée le 26 Juillet 1994

Principe actif :		chlorhydrate de benfluorex
Caractère d'originalité :		modification du RCP "propriétés pharmacologiques"
Classe ATC :		appareil digestif et métabolisme
Réf. Stat. :	VIDAL LIBRA	Antidiabétique

La modification des propriétés pharmacologiques demandée doit permettre d'obtenir une confirmation de l'indication suivante :

- "en association au régime dans le diabète non insulinodépendant avec surcharge pondérale et/ou pour hyperinsulinisme".

La firme revendique la modification suivante au chapitre "PROPRIETES PHARMACOLOGIQUES :

abroger :

Actions de Médiator sur le métabolisme glucidique :

- il facilite la pénétration et l'utilisation cellulaires du glucose (rat) ;
- il diminue l'hyperglycémie du rat diabétique (insulinoprive ou non) et l'aire d'HPO chez le lapin ;
- dans le diabète asymptomatique chez les patients obèses, il entraine une baisse de la glycémie post-prandiale et une amélioration de la courbe d'HPO supérieure à celle qu'on obtient avec un régime identique associé à un placebo.

Médiator n'ayant pas d'action sur l'insulinosécrétion, ne peut pas provoquer d'hypoglycémie.

Remplacer par :

Actions de Médiator sur le métabolisme glucidique :

* Chez l'animal :

- il diminue l'hyperglycémie et améliore la tolérance au glucose (rat diabétique et/ou insulinorésistant) ;
- il facilite la pénétration et l'utilisation cellulaires du glucose (rat), améliore l'action périphérique de l'insuline chez le rat diabétique insulinorésistant, et normalise la production hépatique de glucose (études de clamp) ;

Annexe 2-21

- il diminue l'insulinémie du rat diabétique hyperinsulinémique ;
- chez le rat, il ne modifie pas la glycémie ni l'insulinémie.

* Chez le diabétique non insulinodépendant en surpoids :

- il diminue la glycémie à jeûn et post-prandiale ;
- il diminue l'insulinorésistance : les études du clamp montrent que le benfluorex augmente l'utilisation périphérique du glucose et freine la production hépatique de glucose.

Médiator ne stimulant pas l'insulinosécrétion, ne peut pas provoquer d'hypoglycémie.

AVIS DE LA COMMISSION N° 199 DU 3 FEVRIER : AVIS DEFAVORABLE, à l'indication et aux propriétés pharmacologiques revendiquées.

Le bénéfice thérapeutique n'est pas établi dans l'indication concernée :
- les essais ne sont pas contrôlés,
- le bénéfice observé (sur la glycémie et l'hémoglobine glycosylée) est incomplet,
- le bénéfice ne concerne qu'une faible partie des patients traités.

Note Interne :

En clinique, les études non contrôlées, compilant des résultats sur un nombre important de patients mais traités pendant une durée trop courte de 90 jours, montrent une amélioration incomplète de la glycémie à jeûn qui reste à 9 mmoles et de l'hémoglobine glycosylée qui reste élevée (8,4%).

Annexe 2-22

AGENCE DU MEDICAMENT

Direction de l'Evaluation
CF/CB

REPUBLIQUE FRANCAISE

Saint Denis le
143/145, Bd Anatole France
93200 SAINT DENIS

Tél : 48.13.20.00
Fax : 48.13.24.75

CONFIDENTIEL

COMMISSIONS D'AUTORISATION DES MEDICAMENTS

COMMISSION N°199 DU 3 FEVRIER 1995

RELEVE D'AVIS

I. A ETE APPROUVE LE RELEVE D'AVIS DE LA COMMISSION N°198 DU 20/01/95

II ONT ETE APPROUVES LES RELEVES D'AVIS SUIVANTS:

- GROUPE DE TRAVAIL TOXICO-PHARMACO-CLINIQUE N°171 DU 13/01/95
- GROUPE DE TRAVAIL INTERNE N°44 DU 10/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE N°200 DU 12/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE N°201 DU 19/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE "Relevé d'Avis Partiel" n°203 DU 26/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE "VALIDATION" n°198 du 5/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE "VALIDATION" n°199 du 12/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE "VALIDATION" n°201 du 19/01/95
- GROUPE DE TRAVAIL PHARMACEUTIQUE "Relevé d'Avis Partiel modifié" DERIVES DU SANG " n°11 du 8/11/94
- GROUPE DE TRAVAIL TOXICO-PHARMACO-CLINIQUE "DERIVES DU SANG" n°18 du 15/12/94
- GROUPE DE TRAVAIL PLANTE N°130 du 19/01/95

Annexe 2-22

III A ETE PRESENTE ET APPROUVE LE RELEVE D'AVIS GROUPE DE TRAVAIL ANTI-CANCEREUX N° 50 DU 13/01/95 (M. MARTY), sous réserve des dispositions suivantes :

p.15 CASODEX 50mg, comprimés enrobés (Lab. ZENECA PHARMA)

Abroger "MESURE D'INSTRUCTION"
remplacer par " AVIS FAVORABLE"
Toutefois, il est demandé.....

IV A ETE PRESENTE ET APPROUVE LE RELEVE D'AVIS SUIVANT :

- GROUPE DE TRAVAIL SIDA n°37 du 20/01/95 (M. VITTECOQ)

V. EXAMEN DES DOSSIERS D'AMM :

Pages

6.7.8.
- AMAREL 1mg, comprimés (Lab. HOECHST)
- AMAREL 4mg, comprimés (Lab. HOECHST)
- AMAREL 4mg, comprimés (Lab. HOECHST)

9.10.11.12
- CELLCEPT 250mg, gélule (Lab. SYNTEX (ROCHE)

13.14.15
- CELLCEPT 500mg, gélule (Lab. SYNTEX (ROCHE)

16.17
- JOSIR 0,4mg, gélule à libération prolongée (Lab. BOEHRINGER INGELHEIM FRANCE) (dépôt conjoint avec YAMANOUCHI PHARMA)

18.19
- MEDIATOR (Lab. SERVIER)

20.21.22.
- MOBIC 7,5 mg, gélules (Lab. BOEHRINGER INGELHEIM)
- MOBIC 15 mg, gélules (Lab. BOEHRINGER INGELHEIM)
- MOBIC 7,5 mg, comprimés (Lab. BOEHRINGER INGELHEIM)
- MOBIC 15 mg, comprimés sécables (Lab. BOEHRINGER INGELHEIM)
- MOBIC 15 mg, suppositoires (Lab. BOEHRINGER INGELHEIM)
- MOBIC 15 mg/1,5 ml, solution injectable (Lab. BOEHRINGER INGELHEIM)

23.24
- OMIC 0,4mg, gélule à libération prolongée (Lab. YAMANOUCHI PHARMA (dépôt conjoint avec BOEHRINGER INGELHEIM)

25.26.27
- UMALOG 40UI/ml, solution pour usage parentéral en flacon (Lab. LILLY FRANCE S.A)
- UMALOG 100UI/ml, solution pour usage parentéral en flacon (Lab. LILLY FRANCE S.A)
- UMALOG 100UI/ml, solution pour usage parentéral en cartouche (Lab. LILLY FRANCE S.A)

Annexe 2-22

PRESENTS

PRESIDENT

M. CAULIN

VICE-PRESIDENTS

M. DUPUIS (+ rapporteur)
M. REYNIER

MEMBRES

M. ANKRI
M. ASLANIAN
M. BARRE
M. BELEGAUD
M. BOUVENOT
M. CALOP
M. CEZARD
M. DIQUET
M. DORDAIN
M. DUCHENE-MARULLAZ
Mme ELEFANT
M. FLOUVAT
Mme FORETTE
M. HENRY
M. JACQUOT (+ rapporteur)
Mme JACQZ AIGRAIN
M. LAROUSSE
M. LE HEUZEY
M. MARTY (+ rapporteur)
M. MARZIN
M. OLIVE
M. ORGIAZZI (+ rapporteur)
M. PALLARDY (+ rapporteur)
Mme POURCELOT
M. PRUGNAUD
M. PUECH
M. REVEILLAUD
M. SINGLAS (+ rapporteur)
M. SIOU (+ rapporteur)
M. VITAL-DURAND
M. VITTECOQ (+ rapporteur)

Annexe 2-22

ACADEMIE DE MEDECINE

M. LECHAT

ACADEMIE DE PHARMACIE

M. PEJOUAN
M. HAMON

PRESIDENTS DES COMMISSIONS

M. AVOUAC
M. BADER
M. FLEURY
M. LAGIER

INSERM

Mme DOYON

D.G.S

Mme BARON

SNIP

Mme JOUAN-FLAHAULT

CONSOMMATEURS

M. SEMLER-COLLERY

MUTUALITE FRANCAISE

M. BLANIE

Annexe 2-23

AGENCE DU MEDICAMENT

Direction de l'Evaluation

REPUBLIQUE FRANCAISE

16 MARS 1990

SAINT DENIS, le

143-145, boulevard Anatole France
93200 SAINT DENIS
Tél : 48.13.20.00

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
des Laboratoires SERVIER
GIDY
45400 FLEURY LES AUBRAIS

Dossier suivi par : **Madame M.T. REVEILLAUD**

Réf. à rappeler : VNL 10 008
COM 199
MTR/LC

Monsieur,

Vous m'avez adressé une demande de rectificatif d'Autorisation de Mise sur le Marché pour la spécialité : **MEDIATOR 150 mg**
dans le but de soutenir et rendre homogène le texte des "propriétés pharmacologiques" avec celui de l'indication revendiquée pour la 8ème tranche de validation en diabétologie.

Après avis de la commission prévu à l'article R. 5140 du code de la santé publique, je vous informe que **je ne suis pas en mesure de réserver une suite favorable** à cette modification du libellé des propriétés pharmacologiques et par conséquent, à l'indication qui s'y rapporte, pour les raisons suivantes :

1 - l'indication soumise à la validation n'est pas justifiée par les données fournies :

- les essais ne sont pas contrôlés ;
- le bénéfice observé sur la glycémie et l'hémoglobine glycosylée est incomplet ;
- le bénéfice ne concerne qu'une faible partie des patients traités.

2 - En conséquence, aucune mention de propriétés pharmacologiques en relation avec cette indication ne peut être acceptée.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

LE DIRECTEUR DE L'EVALUATION

Pr. Jean-Michel ALEXANDRE

Annexe 2-24

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT

DIRECTION DE L'EVALUATION Saint-Denis le 9 octobre 1995

Dossier suivi par : A. SAINT RAYMOND

COMPTE-RENDU DE LA REUNION DE CONCERTATION MEDIATOR du 22 Septembre 1995 A L'AGENCE DU MEDICAMENT

Etaient présents :

SERVIER / IRIS
Pr de Jong
Dr Desché
Dr Bessac

EXPERTS POUR SERVIER
Pr del Prato (Italie)
Pr Rekelens (Pays-Bas)
Dr Brun

EXPERTS POUR L'AGENCE
Pr Vexiau,
Dr Simon

Agence du Médicament
Pr Alexandre
Dr Abadie
Dr Saint Raymond.

L'objectif de cette réunion est d'entendre la firme sur l'indication non validée de Mediator (benfluorex) : "adjuvant du régime dans le diabète avec surcharge pondérale".

Rappel : Mediator a fait l'objet d'une validation (8ème tranche), et une seule indication a été maintenue :
-adjuvant du régime dans les hypertriglycéridémies.

La deuxième indication (adjuvant du régime dans le diabètte asymptomatique avec surcharge pondérale) ne semble plus justifiée ni adaptée à la prise en charge du diabète en 1995 ; elle ne repose que sur des études anciennes, non contrôlées pour la plupart et incluant un très petit effectif (67 au total dans les études en aveugle). La firme, ayant demandé le 26/7/94 une modification des propriétés pharmacologiques afin de confirmer cette indication, s'est vue notifier un avis défavorable (COM 199 du 3/2/95).

La firme désire présenter, en complément d'un rappel des essais cliniques disponibles, le programme d'études cliniques en cours dans cette indication, afin de justifier le maintien de l'indication.

Le Pr del Prato fait une présentation des mécanismes de l'insulinosécrétion et de l'insulinorésistance.
L'insulinorésistance est caractérisée par une augmentation de la production hépatique de glucose et une diminution de son utilisation périphérique. Le benfluorex agirait essentiellement en diminuant la production hépatique du glucose et à un moindre degré en favorisant l'utilisation périphérique. Il est sans effet sur l'insulinosécrétion.

Le Pr Rekelens présente les techniques qui permettent de mesurer l'insulinorésistance (clamp, etc) et d'étudier la place du benfluorex.

Le Dr Brun précise qu'il existe une place, dans la pratique, pour la prescription de benfluorex chez le diabétique obèse intolérant aux biguanides car les sulfonylurées majorent la prise de poids. De même, il y aurait, selon lui, une indication chez le diabétique âgé à fonction rénale altérée ou dans les "petits diabètes" ou le syndrome X (hypertriglycéridémie, obésité et hyperinsulinisme). Enfin, il pense que chez le diabétique (type 2) insulino-traité, le benfluorex aurait la même efficacité que les 2 autres types de traitement.

Le Pr Vexiau rappelle que ce sont les résultats des essais chez l'Homme qui doivent être les éléments de jugement en démontrant des effets sur le poids, la glycémie et les facteurs de risque (et non les études de pharmacologie).
Compte-tenu des effets d'autres variables, en particulier des variations de poids dans cette pathologie, les études ouvertes et non contrôlées menées avec le benfluorex n'ont pas de valeur.
Les résultats des études contre placebo fournies ont seulement fait l'objet d'analyse intra-groupe et non de comparaison versus placebo. De plus, il n'y a pas d'études versus molécule de référence.
En revanche, la baisse observée de l'hémoglobine glycosylée (de l'ordre de 2%) pourrait être un bénéfice intéressant si elle est confirmée dans des essais rigoureux.

Il semble donc que le benfluorex puisse avoir une place dans les intolérances aux autres molécules si une démonstration d'efficacité est apportée.

La firme présente le programme d'études qui démarre et qui devrait pouvoir répondre de manière plus rigoureuse aux questions en suspens actuellement (études en double aveugle contre placebo et produit de référence).

NB : bien qu'apparenté aux amphétamines, le benfluorex n'a jamais été associé à la survenue d'hypertension artérielle pulmonaire primitive.

En conclusion, le benfluorex pourrait avoir une place dans la stratégie thérapeutique du diabète (ie, intolérance à la metformine) mais celle-ci reste entièrement à démontrer. Dans l'intervalle, l'indication chez le diabétique n'est pas maintenue.

PROCEDURE NATIONALE

- **MEDIATOR 150 mg**, comprimé

dossier N° V NL 10008

Laboratoires SERVIER

Demande déposée le 21 MAI 1995

Principe actif : chlorhydrate de benfluorex

Caractère d'originalité : VALIDATION 8ÈME TRANCHE
ENDOCRINOLOGIE

Classe A.T.C. : ANTIDIABETIQUES HYPOGLYCEMIANTS ORAUX
(A: appareil digestif et métabolisme)

Réf.Stat.: VIDAL
LIBRA

L'indication : "Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale" devait faire l'objet d'une validation 8ème tranche. La firme a demandé une modification de cette indication et des propriétés pharmacologiques. Cette demande de modification a fait l'objet d'un avis défavorable de la Commission (199, 3/2/95).
La firme a demandé une réunion de concertation dont les conclusions sont que cette première indication n'est plus adaptée car non soutenue par les études appropriées. La firme met en place un programme d'études destiné à soutenir cette indication.
Actuellement, la firme dispose toujours de l'AMM dans cette indication.

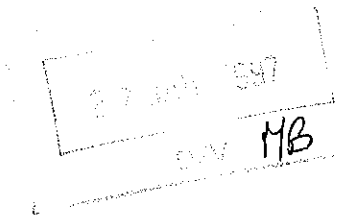
AVIS DU GTI N° 53 DU 5 DECEMBRE 1995 : PROJET DE REJET de la validation de l'indication de Mediator : "adjuvant du régime dans le diabète avec surcharge pondérale", pour insuffisance de données d'efficacité.

Le dossier clinique transmis ne permet pas d'établir l'efficacité du benfluorex dans l'indication revendiquée. Les résultats des études contrôlées contre placebo qui, seules, pourraient être retenues, n'ont pas fait l'objet de comparaison statistique entre le groupe traité et le groupe placebo mais uniquement intra-groupe. Il n'y a pas d'études menées versus produit de référence. L'insuffisance de données d'efficacité ne permet donc pas de définir un bénéfice clinique pertinent chez les patients diabétiques en surcharge pondérale.

Annexe 2-26

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS



AGENCE DU MÉDICAMENT
Direction de l'Evaluation
143 - 145 boulevard Anatole France
93200 SAINT-DENIS

Neuilly-sur-Seine, le 24 janvier 1997

A l'attention de Madame NORTH

N. Réf. : HML/ss/97.007
Tél. : 46.41.61.61
Mme MAURICE de LORRIS

Objet : **Demande de renouvellement d'A.M.M.**
N/spécialité : MEDIATOR® 150 mg
comprimé enrobé
Dossier VNL 10 008

Monsieur le Directeur,

Conformément à l'article R.5137 du Code de la Santé Publique, nous avons l'honneur de solliciter, pour notre spécialité pharmaceutique :

MEDIATOR® 150 mg, comprimé enrobé

une demande de renouvellement d'Autorisation de Mise sur le Marché.

Présentation et numéro d'identification administrative :

317 553.3 : 10 comprimés sous plaquette thermoformée (PVC - Aluminium)
317 555.6 : 20 comprimés sous plaquette thermoformée (PVC - Aluminium)
317 556.2 : 24 comprimés sous plaquette thermoformée (PVC - Aluminium)
317 557.9 : 30 comprimés sous plaquette thermoformée (PVC - Aluminium)
317 558.5 : 60 comprimés sous plaquette thermoformée (PVC - Aluminium)
317 559.1 : 100 comprimés sous plaquette thermoformée (PVC - Aluminium)

Titulaire de l'Autorisation de la Mise sur le Marché et Exploitant :

Les Laboratoires SERVIER
22, rue Garnier
92200 NEUILLY-SUR-SEINE

.../...

SERVIER

Annexe 2-26

HML/ss/97.007
Demande de renouvellement d'A.M.M.
MEDIATOR® 150 mg

Composition intégrale dn médicament :

Chlorhydrate de benfluorex	150,0 mg
Amidon de maïs	60,0 mg
Polyvidone excipient	20,0 mg
Saccharose	245,0 mg
Stéarate de magnésium	5,0 mg
Talc	20,0 mg

pour un noyau de 500 mg

Saccharose	172,914 mg
Talc	17,651 mg
Polyvidone excipient	1,349 mg
Bicarbonate de sodium	0,480 mg
Carboxyméthylcellulose sodique	0,944 mg
Silice colloïdale	0,674 mg
Polysorbate 80	0,850 mg
Ethylcellulose	0,555 mg
Oléate de glycérol	0,278 mg
Dioxyde de titane	4,305 mg
Cire d'abeille blanche	q.s.

pour un comprimé enrobé de 700 mg

Nous vous prions de bien vouloir trouver ci-joint, en deux exemplaires, les documents suivants :

- une photocopie de l'A.M.M. validée en tant qu'hypolipémiant le 22 avril 1987 [l'indication "adjuvant du régime dans le diabète insulino-dépendant avec surcharge pondérale"- validation tranche n°8 endocrinologie - étant en attente], accompagnée des rectificatifs du 29 mai 1987, 14 février 1996 et du renouvellement du 11 mai 1992.
- une copie du texte de l'annexe I (R.C.P.) conforme au dernier avis aux fabricants et des textes de l'Annexe II (notice) et de l'Annexe III (étiquetage) mis en conformité avec les dispositions des articles R 5143 et R 5143-5 du code de la Santé Publique, selon le Décret 94-19 du 5 janvier 1994 ;
- une attestation de non-modification des éléments produits à l'appui de la demande d'A.M.M.

Par ailleurs, nous vous informons que nous adressons, ce jour, copie de ce courrier à la Direction des Laboratoires et des Contrôles (Saint-Denis et Montpellier) et à l'Inspection Régionale de la Santé (Orléans).

Nous vous remettons, enfin, un bordereau de transmission de la redevance accompagné d'un chèque bancaire d'un montant de 4.000 Frs (quatre mille francs) établi à l'ordre de Monsieur l'Agent Comptable de l'Agence du Médicament.

En espérant que vous voudrez bien réserver une suite favorable à notre demande, nous vous prions de croire, Monsieur le Directeur, à l'expression de notre considération distinguée.

Claude SANTINI
Pharmacien Responsable

Annexe 2-27

Rectificatif d'autorisation cyclo

[redacted]

[redacted]

AGENCE DU MEDICAMENT

Direction de l'Évaluation

RÉPUBLIQUE FRANÇAISE

SAINT DENIS, le 16 AVR. 1997

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
Laboratoires SERVIER
Route de Saran
45400 GIDY

Réf. à rappeler : VNL 10008
GTI 53
ASR/BH/SV/VB

AUTORISATION DE MISE SUR LE MARCHE
RECTIFICATIF

LE DIRECTEUR GENERAL DE L'AGENCE DU MEDICAMENT

VU le livre V du code de la santé publique, notamment les articles L.601 et R.5128 à R. 5140 et R. 5143-5-1 à R. 5143-5-5 ;

VU l'autorisation de mise sur le marché validée octroyée le **22 Avril 1987**

aux laboratoires **SERVIER**

pour la spécialité pharmaceutique : **MEDIATOR 150 mg, comprimé enrobé**

VU l'avis de la commission prévu à l'article R. 5140 du code de la santé publique ;

D E C I D E

ARTICLE 1er.-

ABROGER

Annexe I et Annexe II, du 22 avril 1987

VNL10008.R

REMPLACER PAR :

Annexe I, Annexe II, Annexe III ci-jointes.

ARTICLE 2.- La présente décision est notifiée à l'intéressé.

16 AVR

FAIT A SAINT DENIS, le

LE DIRECTEUR GENERAL
DE L'AGENCE DU MEDICAMENT

Pour le Directeur Général
et par délégation

Le Pharmacien Inspecteur
Arielle NORTH
Coordination des Affaires Réglementaires

P.J. : 3 annexes

VNL100038.R

Annexe 2-27

ANNEXE I

RESUME DES CARACTERISTIQUES DU PRODUIT

16

1. DENOMINATION

MEDIATOR 150 mg, comprimé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorhydrate de benfluorex	150,0 mg
Amidon de maïs	60,0 mg
Povidone	20,0 mg
Saccharose	245,0 mg
Stéarate de magnésium	5,0 mg
Talc	20,0 mg

pour un comprimé nu de 500 mg

Saccharose	172,914 mg
Talc	17,651 mg
Povidone	1,349 mg
Bicarbonate de sodium	0,480 mg
Carmellose sodique	0,944 mg
Silice colloïdale	0,674 mg
Polysorbate 80	0,850 mg
Ethylcellulose	0,550 mg
Oléate de glycérol	0,278 mg
Dioxyde de titane	4,305 mg
Cire d'abeille blanche	q.s.

pour un comprimé enrobé de 700 mg

3. FORME PHARMACEUTIQUE

Comprimé enrobé

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

Adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable

Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée

4.2 Posologie et mode d'administration

Réservé à l'adulte.
La posologie habituelle est de 3 comprimés par jour.

Cette posologie peut être prescrite d'emblée ou atteinte progressivement :
- 1 comprimé la première semaine au dîner,
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner,
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois à 1 comprimé par jour, en fonction des résultats biologiques.
Le traitement par le benfluorex est un traitement symptomatique qui doit être régulièrement surveillé.

4.3 Contre-indications

Pancréatites chroniques.

4.4 Mises en garde et précautions particulières d'emploi

Si, après une période d'administration de quelques mois (3 à 6 mois), une réduction satisfaisante des concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

4.5 Interactions avec d'autres médicaments et autres formes d'interactions

4.6 Grossesse et allaitement

Grossesse : les résultats des études réalisées chez l'animal n'ont pas mis en évidence d'effet tératogène du benfluorex. En clinique, le nombre de grossesses exposées est insuffisant pour pouvoir exclure tout risque malformatif ou foetotoxique. En conséquence, il est préférable de ne pas utiliser le benfluorex pendant la grossesse, et ce d'autant que les hyperlipoprotéinémies de la femme enceinte ne représentent pas une indication de ce produit.

Allaitement : en l'absence de données sur le passage dans le lait maternel, l'allaitement est déconseillé pendant la durée du traitement.

4.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

Le prescripteur doit attirer l'attention des conducteurs ou utilisateurs de machines sur le risque de somnolence ou de vertiges.

4.8 Effets indésirables

Les effets secondaires suivants ont été observés : digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou état vertigineux.

4.9 Surdosage

Conduite à tenir en cas d'absorption massive :

Le traitement sera purement symptomatique, lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience, des fonctions respiratoire et cardiaque.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

HYPOLIPIDEMIANT
(B : Sang, organes hématopoïétiques)

Chez le rat, le benfluorex diminue l'absorption intestinale des triglycérides. Cet effet, confirmé chez l'homme en pharmacologie clinique, repose sur la diminution d'activité de la lipase pancréatique.

5.2 Propriétés pharmacocinétiques

5.3 Données de sécurité précliniques

6. DONNEES PHARMACEUTIQUES

6.1 Incompatibilités

6.2 Durée de conservation

3 ans

6.3 Précautions particulières de conservation

6.4 Nature et contenance du récipient

Plaquettes thermoformées (PVC - Aluminium).

6.5 Mode d'emploi, instructions concernant la manipulation

7. PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE

317 557.9 : 30 comprimés enrobés sous plaquettes thermoformées (PVC - Aluminium).

8. CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste I

9. TITULAIRE DE L'AUTORISATION TEMPORAIRE D'UTILISATION

Laboratoires SERVIER
45400 GIDY

10. DATE D'APPROBATION/REVISION

VNL1000S.R

Annexe 2-27

ANNEXE II

NOTICE

1. IDENTIFICATION DU MEDICAMENT

a) DENOMINATION

MEDIATOR 150 mg, comprimé enrobé

b) COMPOSITION QUALITATIVE

Chlorhydrate de benfluorex

Amidon de maïs, povidone, saccharose, stéarate de magnésium, talc, bicarbonate de sodium, carmellose sodique, silice colloïdale, polysorbate 80, éthylcellulose, oléate de glycérol, dioxyde de titane, cire d'abeille blanche.

COMPOSITION QUANTITATIVE

Chlorhydrate de benfluorex ..... 150 mg

pour un comprimé

c) FORME PHARMACEUTIQUE

Comprimé. Boîte de 30

d) CLASSE PHARMACO-THERAPEUTIQUE

HYPOLIPIDEMIANT
(B : Sang, organes hématopoïétiques)

e) NOM ET ADRESSE DE L'EXPLOITANT

Laboratoires SERVIER
45400 GIDY

2. DANS QUEL(S) CAS UTILISER CE MEDICAMENT (INDICATIONS THERAPEUTIQUES)

Ce médicament est un hypolipémiant (il réduit le taux de lipides sanguins).

Il est préconisé en complément du régime alimentaire dans certaines hyperlipidémies (surcharge de triglycérides dans le sang). Le régime alimentaire doit être poursuivi.
Réservé à l'adulte.

Annexe 2-27

3. ATTENTION !

a) DANS QUEL(S) CAS NE PAS UTILISER CE MEDICAMENT (CONTRE-INDICATIONS)

Ce médicament NE DOIT PAS ETRE UTILISE en cas de : pancréatite chronique (insuffisance du pancréas).

EN CAS DE DOUTE, IL EST INDISPENSABLE DE DEMANDER L'AVIS DE VOTRE MEDECIN OU DE VOTRE PHARMACIEN

b) MISES EN GARDE SPECIALES

Dans le traitement des hypertriglycéridémies, le respect scrupuleux du régime alimentaire prescrit par votre médecin est **INDISPENSABLE**. (évitez de manger des aliments riches en graisses saturées, en sucre, en cholestérol).

c) PRECAUTIONS D'EMPLOI

Si, après quelques mois, une diminution satisfaisante de votre taux de lipides dans le sang n'est pas obtenue, votre médecin pourra vous prescrire un autre traitement.

EN CAS DE DOUTE NE PAS HESITER A DEMANDER L'AVIS DE VOTRE MEDECIN OU DE VOTRE PHARMACIEN.

d) INTERACTIONS MEDICAMENTEUSES ET AUTRES INTERACTIONS

AFIN D'EVITER D'EVENTUELLES INTERACTIONS ENTRE PLUSIEURS MEDICAMENTS IL FAUT SIGNALER SYSTEMATIQUEMENT TOUT AUTRE TRAITEMENT EN COURS A VOTRE MEDECIN OU A VOTRE PHARMACIEN.

e) GROSSESSE - ALLAITEMENT

D'UNE MANIERE GENERALE AU COURS DE LA GROSSESSE OU DE L'ALLAITEMENT, IL CONVIENT DE TOUJOURS DEMANDER L'AVIS DE VOTRE MEDECIN OU DE VOTRE PHARMACIEN AVANT DE PRENDRE UN MEDICAMENT

Prévenez votre médecin si vous êtes enceinte, il vous prescrira un traitement plus approprié à votre état. L'allaitement est déconseillé au cours du traitement par le benfluorex.

f) CONDUCTEURS ET UTILISATEURS DE MACHINES

Ce médicament peut entraîner vertige ou somnolence. Dans ce cas, il est dangereux de conduire un véhicule ou d'utiliser des machines.

g) SPORTIFS

Annexe 2-27

b) **LISTE DES EXCIPIENTS DONT LA CONNAISSANCE EST NECESSAIRE POUR UNE UTILISATION SANS RISQUE CHEZ CERTAINS PATIENTS**

4. COMMENT UTILISER CE MEDICAMENT

a) **POSOLOGIE**

Elle sera déterminée par votre médecin, à titre indicatif, la posologie habituelle est de 1 à 3 comprimés par jour, en 3 prises.

b) **MODE ET VOIE D'ADMINISTRATION**

Voie orale.

c) **FREQUENCE ET MOMENT AUQUEL LE MEDICAMENT DOIT ETRE ADMINISTRE**

Il est conseillé de prendre ce médicament au moment des principaux repas.

d) **DUREE DU TRAITEMENT**

En association avec le régime, le benfluorex constitue un traitement de longue durée.

e) **CONDUITE A TENIR EN CAS DE SURDOSAGE**

Il faut interrompre le traitement par le benfluorex et avertir un médecin qui pourra mettre en œuvre des mesures appropriées.

f) **CONDUITE A TENIR AU CAS OU L'ADMINISTRATION D'UNE OU PLUSIEURS DOSES A ETE OMISE**

Prenez la dose suivante à l'heure habituelle, ne doublez pas la dose.

g) **RISQUE DE SYNDROME DE SEVRAGE**

5. EFFETS NON SOUHAITES ET GENANTS (EFFETS INDESIRABLES)

COMME TOUT PRODUIT ACTIF, CE MEDICAMENT PEUT CHEZ CERTAINES PERSONNES, ENTRAINER DES EFFETS PLUS OU MOINS GENANTS

Ont été rapportés, des troubles digestifs : nausées, vomissements, douleurs abdominales, diarrhée. Ont également été rapportés des sensations de fatigue, vertige ou somnolence.

Annexe 2-27

6. CONSERVATION

a) NE PAS DEPASSER LA DATE LIMITE D'UTILISATION FIGURANT SUR LE CONDITIONNEMENT EXTERIEUR

b) PRECAUTIONS PARTICULIERES DE CONSERVATION

c) MISE EN GARDE EN CAS DE SIGNES VISIBLES DE DETERIORATION

7. DATE DE REVISION DE LA NOTICE

Annexe 2-27

10

ANNEXE III

ETIQUETAGE

DENOMINATION

MÉDIATOR 150 mg, comprimé enrobé

COMPOSITION QUALITATIVE

Chlorhydrate de benfluorex

COMPOSITION QUANTITATIVE

Chlorhydrate de benfluorex ..... 150 mg

pour un comprimé

FORME PHARMACEUTIQUE

Comprimé

LISTE DES EXCIPIENTS QUI ONT UN EFFET NOTOIRE

INDICATIONS THERAPEUTIQUES

MODE ET VOIE D'ADMINISTRATION

Voie orale

NE PAS LAISSER A LA PORTEE DES ENFANTS

MISES EN GARDE SPECIALES

Lire attentivement la notice

PRECAUTIONS PARTICULIERES DE CONSERVATION

PRECAUTIONS PARTICULIERES D'ELIMINATION DES PRODUITS NON UTILISES OU DES DECHETS DERIVES DE CES PRODUITS

NOM ET ADRESSE DE L'EXPLOITANT

Laboratoires SERVIER
45400 GIDY

VNL10008.R

Annexe 2-27

11.

MEDICAMENT AUTORISE No

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste I

NUMERO DE LOT DE FABRICATION

DATE LIMITE D'UTILISATION
(en clair)

VNL10008.R

RÉPUBLIQUE FRANÇAISE

Annexe 2-28

AGENCE DU MEDICAMENT

Direction de l'Evaluation

SAINT DENIS, le 29 AVR. 1997

143, boulevard Anatole France
93285 SAINT DENIS Cedex
Tél : 48.13.20.00

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
Les Laboratoires SERVIER
22, rue Garnier
92200 Neuilly-sur-seine

Dossier suivi par : Arila POCHET
Référence à rappeler :AP
NL 14557 / VNL 10008

Monsieur,

Par courrier reçu en date du 27 janvier 1997, vous avez déposé un projet de notice et d'étiquetage de vos spécialités :

HYPERIUM 1 mg, comprimés
MEDIATOR 150 mg, comprimé enrobé

A cet égard, je vous informe que ces projets de notice et d'étiquetage appellent de ma part les observations ci jointes.

Aussi, je vous demande de bien vouloir mettre en oeuvre les modifications demandées afin de vous mettre en conformité avec les dispositions des articles R.5143 et R.5143-5 du code de la santé publique.

Je vous rappelle que conformément aux dispositions du troisième alinea de l'article R.5139 du code de la santé publique, l'autorisation de mise sur le marché est suspendue ou retirée par le Directeur Général de l'Agence du médicament, lorsque l'étiquetage ou la notice ne sont pas conformes aux dispositions réglementaires en vigueur.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation
Le Pharmacien Inspecteur
Arielle NORTH
Coordinateur des Affaires [illegible]

Annexe 2-28

ANNEXE II

N O T I C E

1. IDENTIFICATION DU MÉDICAMENT

a) **DÉNOMINATION**
MEDIATOR® 150 mg

b) **COMPOSITION QUALITATIVE**
Chlorhydrate de Benfluorex
Excipients :
Amidon de maïs - bicarbonate de sodium - carboxyméthycellulose sodique - cire d'abeille blanche - dioxyde de titane - éthylcellulose - oléate de glycérol - polysorbate 80 - polyvidone excipient - saccharose - silice colloïdale - stéarate de magnésium - talc.

COMPOSITION QUANTITATIVE
Chlorhydrate de Benfluorex ..... 150 mg pour un comprimé.

c) Forme pharmaceutique : Boîte de 30 comprimés enrobés.

d) **CLASSE PHARMACO-THERAPEUTIQUE**
HYPOLIPEMIANT
~~ANTIDIABETIQUE HYPOGLYCEMIANT ORAL~~
(~~A : Appareil digestif et métabolisme~~ -C : Système cardiovasculaire).

e) **NOM ET ADRESSE DE L'EXPLOITANT**
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY-SUR-SEINE

Fabricant
LES LABORATOIRES SERVIER Industrie
905, route deSaran
45520 GIDY

2. DANS QUEL CAS UTILISER CE MÉDICAMENT (INDICATIONS THÉRAPEUTIQUES)

Il est préconisé en complément du régime alimentaire adapté :

- dans les hyperlipidémies (pour diminuer le taux de lipides dans le sang). Un taux élevé de lipides dans le sang est un facteur majeur d'athérome (dépôt de plaques graisseuses sur la paroi des artères).

- dans le traitement du diabète avec surcharge pondérale (pour diminuer le taux de glucose dans le sang).

Annexe 2-28

3. ATTENTION !

a) DANS QUELS CAS NE PAS UTILISER CE MÉDICAMENT (CONTRE-INDICATIONS)

Ce médicament NE DOIT PAS ETRE UTILISÉ en cas de pancréatite chronique (insuffisance du pancréas).

EN CAS DE DOUTE, IL EST INDISPENSABLE DE DEMANDER L'AVIS DE VOTRE MÉDECIN OU DE VOTRE PHARMACIEN.

b) MISES EN GARDE SPÉCIALES

Le respect scrupuleux du régime alimentaire prescrit par le médecin est indispensable, (éviter de manger des aliments riches en graisses saturées, en sucre, en cholestérol).

c) PRÉCAUTIONS D'EMPLOI

EN CAS DE DOUTE, NE PAS HÉSITER À DEMANDER L'AVIS DE VOTRE MÉDECIN OU DE VOTRE PHARMACIEN.

d) INTERACTIONS MÉDICAMENTEUSES ET AUTRES INTERACTIONS

AFIN D'ÉVITER D'ÉVENTUELLES INTERACTIONS ENTRE PLUSIEURS MÉDICAMENTS, IL FAUT SIGNALER SYSTÉMATIQUEMENT TOUT AUTRE TRAITEMENT EN COURS À VOTRE MÉDECIN OU À VOTRE PHARMACIEN,

e) GROSSESSE - ALLAITEMENT

L'utilisation de ce médicament est déconseillé pendant la grossesse ou chez la femme allaitante .

D'UNE FACON GÉNÉRALE, IL CONVIENT AU COURS DE LA GROSSESSE OU DE L'ALLAITEMENT DE TOUJOURS DEMANDER L'AVIS DE VOTRE MÉDECIN OU DE VOTRE PHARMACIEN AVANT D'UTILISER CE MÉDICAMENT.

f) CONDUCTEURS ET UTILISATEURS DE MACHINES

L'attention est attirée sur la somnolence attachée à l'emploi de ce médicament

g) SPORTIFS

Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage .

h) LISTE DES EXCIPIENTS DONT LA CONNAISSANCE EST NÉCESSAIRE POUR UNE UTILISATION SANS RISQUE CHEZ CERTAINS PATIENTS

Oleate de glycérol

Annexe 2-28

4. COMMENT UTILISER CE MÉDICAMENT

a) POSOLOGIE

Réservé à l'adulte

3 comprimés enrobés par jour.

Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

- 1 comprimé la première semaine au dîner.
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner.
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois à 1 comprimé par jour, en fonction des résultats biologiques.

En association avec le régime, MEDIATOR® constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

Pour une bonne utilisation de ce médicament, il est indispensable de vous soumettre à une surveillance médicale régulière . Celle-ci peut comporter un dosage des lipides ~~ou du glucose~~.

DANS TOUS LES CAS SE CONFORMER À LA PRESCRIPTION DE VOTRE MÉDECIN.

b) MODE ET VOIE D'ADMINISTRATION

Voie orale.

c) FRÉQUENCE ET MOMENT AUQUEL LE MÉDICAMENT DOIT ÊTRE ADMINISTRÉ

Au moment des repas.

d) DURÉE DU TRAITEMENT

Se conformer à la prescription de votre médecin.

~~e) CONDUITE A TENIR EN CAS DE SURDOSAGE~~

f) CONDUITE A TENIR AU CAS OU L'ADMINISTRATION D'UNE OU PLUSIEURS DOSES A ÉTÉ OMISE

Contactez votre médecin, ne prenez pas double dose le lendemain de votre oubli.

~~g) RISQUE DE SYNDROME DE SEVRAGE~~

5. EFFETS NON SOUHAITÉS ET GÊNANTS (EFFETS INDÉSIRABLES)

COMME TOUT PRODUIT ACTIF CE MÉDICAMENT PEUT ENTRAÎNER CHEZ CERTAINES PERSONNES DES EFFETS PLUS OU MOINS GÊNANTS :

- Troubles digestifs (nausées, vomissements, diarrhée),
- Sensation de fatigue, voire somnolence.

Ces effets s'observent particulièrement aux posologies supérieures à 3 comprimés par jour.

SIGNALEZ À VOTRE MÉDECIN OU À VOTRE PHARMACIEN, TOUT EFFET NON SOUHAITÉ ET GÊNANT QUI NE SERAIT PAS MENTIONNÉ DANS CETTE NOTICE.

6. CONSERVATION

a) NE PAS DÉPASSER LA DATE LIMITE D'UTILISATION FIGURANT SUR LE CONDITIONNEMENT EXTÉRIEUR

~~b) PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION~~

~~c) MISE EN GARDE EN CAS DE SIGNES VISIBLES DE DÉTÉRIORATION~~

7. DATE DE RÉVISION DE LA NOTICE

Avril 1997.

ANNEXE III

E T I Q U E T A G E

DÉNOMINATION
MEDIATOR® 150 mg.

COMPOSITION QUALITATIVE
Chlorhydrate de Benfluorex.

COMPOSITION QUANTITATIVE
Chlorhydrate de Benfluorex .....150 mg pour un comprimé enrobé

FORME PHARMACEUTIQUE
Boîte de 30 comprimés enrobés.

LISTE DES EXCIPIENTS QUI ONT UN EFFET NOTOIRE oleate de glycerol

INDICATIONS THÉRAPEUTIQUES

MODE ET VOIE D'ADMINISTRATION
Voie orale

NE PAS LAISSER A LA PORTÉE DES ENFANTS

MISES EN GARDE SPÉCIALES : lire attentivement la notice

PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

PRÉCAUTIONS PARTICULIERES D'ÉLIMINATION DES PRODUITS NON UTILISÉS OU DES DÉCHETS DÉRIVES DE CES PRODUITS

NOM ET ADRESSE DE L'EXPLOITANT
LES LABORATOIRES SERVIER
22 rue Garnier
92200 NEUILLY-SUR-SEINE

Fabricant :
LES LABORATOIRES SERVIER Industrie
905, route de Saran
45520 GIDY

Mentions minimales sur le blister :
- MEDIATOR 150 mg
- Les Laboratoires SERVIER
- N° de lot de fabrication
- Date limite d'utilisation

MÉDICAMENT AUTORISE N° 317 557-9

CLASSIFICATION EN MATIERE DE DÉLIVRANCE
Liste I.

NUMÉRO DE LOT DE FABRICATION

DATE LIMITE D'UTILISATION
(en clair).

Annexe 2-29

AGENCE DU MEDICAMENT

DIRECTION DE L'EVALUATION

REPUBLIQUE FRANCAISE

05 JUIN 1997

SAINT-DENIS, le

143, 145 Blv Anatole France
93200 SAINT-DENIS
Tél : 48 13 20 00

Monsieur le Pharmacien responsable
des Laboratoires SERVIER
22,rue Garnier
92200 - NEUILLY SUR SEINE

Réf : MB
VNL 10008

Monsieur,

Par lettre du 24 JANVIER 1997, vous avez sollicité le renouvellement de l'autorisation de mise sur le marché de la spécialité :

MEDIATOR 150 mg, comprimés enrobés

J'ai l'honneur de vous faire connaître que cette autorisation de mise sur le marché doit être conformément aux dispositions de l'article R.5137, 4ème alinéa du Code de la Santé publique, considérée comme renouvelée à compter du 22 AVRIL 1997.

Toutefois, je vous rappelle que les spécialités dont les autorisations de mise sur le marché ont été délivrées antérieurement au 1er décembre 1976 sont soumises à une validation dont le présent renouvellement ne saurait tenir lieu.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation

Le Pharmacien Inspecteur
Arielle NORTH

AGENCE DU MEDICAMENT

Direction de l'Evaluation

751

REPUBLIQUE FRANCAISE

Annexe 2-30

SAINT DENIS, le 04 AOUT 1997

143, boulevard Anatole France
93285 SAINT DENIS Cedex
Tél : 48.13.20.00

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
Laboratoires SERVIER
22, rue Garnier
92200 Neuilly-sur-Seine

Dossier suivi par : Mélanie HERPIN
Référence à rappeler : MH
VNL 10008

Monsieur,

Suite à votre entretien avec Madame Arielle NORTH, vous avez souhaité modifier les corrections notifiées par l'Agence du Médicament du 28 avril 1997, concernant un projet de notice et d'étiquetage de votre spécialité :

MEDIATOR 150mg, comprimé enrobé

A cet égard, je vous informe que vous pouvez maintenir les mentions concernant l'indication thérapeutique du diabète. Par conséquent, vous trouverez ci-joint votre projet de notice et d'étiquetage revu et corrigé.

Aussi, je vous demande de bien vouloir mettre en oeuvre les modifications demandées afin de vous mettre en conformité avec les dispositions des articles R.5143 et R.5143-5 du code de la santé publique.

Je vous rappelle que conformément aux dispositions du troisième alinea de l'article R.5139 du code de la santé publique, l'autorisation de mise sur le marché est suspendue ou retirée par le Directeur Général de l'Agence du médicament, lorsque l'étiquetage ou la notice ne sont pas conformes aux dispositions réglementaires en vigueur.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation

Pharmacien Inspecteur
Arielle NORTH
Affaires Réglementaires

ANNEXE II

N O T I C E

1. IDENTIFICATION DU MÉDICAMENT

a) **DÉNOMINATION**
MEDIATOR® 150 mg

b) **COMPOSITION QUALITATIVE**
Chlorhydrate de Benfluorex
Excipients :
Amidon de maïs - bicarbonate de sodium - carboxyméthycellulose sodique - cire d'abeille blanche - dioxyde de titane - éthylcellulose - oléate de glycérol - polysorbate 80 - polyvidone excipient - saccharose - silice colloïdale - stéarate de magnésium - talc.

COMPOSITION QUANTITATIVE
Chlorhydrate de Benfluorex ..... 150 mg pour un comprimé.

c) Forme Pharmaceutique : Boîte de 30 comprimés enrobés

d) **CLASSE PHARMACO-THERAPEUTIQUE**
HYPOLIPEMIANT
ANTIDIABETIQUE HYPOGLYCEMIANT ORAL
(A : Appareil digestif et métabolisme -C : Système cardiovasculaire).

e) **NOM ET ADRESSE DE L'EXPLOITANT**
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY-SUR-SEINE

Fabricant
LES LABORATOIRES SERVIER Industrie
905, route deSaran
45520 GIDY

2. DANS QUEL CAS UTILISER CE MÉDICAMENT (INDICATIONS THÉRAPEUTIQUES)

Il est préconisé en complément du régime alimentaire adapté :

- dans les hyperlipidémies (pour diminuer le taux de lipides dans le sang). Un taux élevé de lipides dans le sang est un facteur majeur d'athérome (dépôt de plaques graisseuses sur la paroi des artères).

- dans le traitement du diabète avec surcharge pondérale (pour diminuer le taux de glucose dans le sang) .

3. ATTENTION !

a) DANS QUELS CAS NE PAS UTILISER CE MÉDICAMENT (CONTRE-INDICATIONS)

Ce médicament NE DOIT PAS ETRE UTILISÉ en cas de pancréatite chronique (insuffisance du pancréas).

EN CAS DE DOUTE, IL EST INDISPENSABLE DE DEMANDER L'AVIS DE VOTRE MÉDECIN OU DE VOTRE PHARMACIEN.

b) MISES EN GARDE SPÉCIALES

Le respect scrupuleux du régime alimentaire prescrit par le médecin est indispensable, (éviter de manger des aliments riches en graisses saturées, en sucre, en cholestérol).

c) PRÉCAUTIONS D'EMPLOI

EN CAS DE DOUTE, NE PAS HÉSITER À DEMANDER L'AVIS DE VOTRE MÉDECIN OU DE VOTRE PHARMACIEN.

d) INTERACTIONS MÉDICAMENTEUSES ET AUTRES INTERACTIONS

AFIN D'ÉVITER D'ÉVENTUELLES INTERACTIONS ENTRE PLUSIEURS MÉDICAMENTS, IL FAUT SIGNALER SYSTÉMATIQUEMENT TOUT AUTRE TRAITEMENT EN COURS À VOTRE MÉDECIN OU À VOTRE PHARMACIEN,

e) GROSSESSE - ALLAITEMENT

L'utilisation de ce médicament est déconseillé pendant la grossesse ou chez la femme allaitante .

D'UNE FACON GÉNÉRALE, IL CONVIENT AU COURS DE LA GROSSESSE OU DE L'ALLAITEMENT DE TOUJOURS DEMANDER L'AVIS DE VOTRE MÉDECIN OU DE VOTRE PHARMACIEN AVANT D'UTILISER CE MÉDICAMENT.

f) CONDUCTEURS ET UTILISATEURS DE MACHINES

L'attention est attirée sur la somnolence attaché à l'emploi de ce médicament.

g) SPORTIFS

Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage .

h) LISTE DES EXCIPIENTS DONT LA CONNAISSANCE EST NÉCESSAIRE POUR UNE UTILISATION SANS RISQUE CHEZ CERTAINS PATIENTS

oléate de glycol

4. COMMENT UTILISER CE MÉDICAMENT

a) POSOLOGIE

Réservé à l'adulte :

3 comprimés enrobés par jour.

Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

- 1 comprimé la première semaine au dîner.
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner.
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois à 1 comprimé par jour, en fonction des résultats biologiques.

En association avec le régime, MEDIATOR® constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

Pour une bonne utilisation de ce médicament, il est indispensable de vous soumettre à une surveillance médicale régulière . Celle-ci peut comporter un dosage des lipides ou du glucose .

DANS TOUS LES CAS SE CONFORMER À LA PRESCRIPTION DE VOTRE MÉDECIN.

b) MODE ET VOIE D'ADMINISTRATION

Voie orale.

c) FRÉQUENCE ET MOMENT AUQUEL LE MÉDICAMENT DOIT ÊTRE ADMINISTRÉ

Au moment des repas.

d) DURÉE DU TRAITEMENT

Se conformer à la prescription de votre médecin.

e) CONDUITE A TENIR EN CAS DE SURDOSAGE

f) CONDUITE A TENIR AU CAS OU L'ADMINISTRATION D'UNE OU PLUSIEURS DOSES A ÉTÉ OMISE

Contactez votre médecin, ne prenez pas double dose le lendemain de votre oubli.

g) RISQUE DE SYNDROME DE SEVRAGE

5. EFFETS NON SOUHAITÉS ET GÊNANTS
(EFFETS INDÉSIRABLES)

COMME TOUT PRODUIT ACTIF CE MÉDICAMENT PEUT ENTRAÎNER CHEZ CERTAINES PERSONNES DES EFFETS PLUS OU MOINS GÊNANTS :

- Troubles digestifs (nausées, vomissements, diarrhée),
- Sensation de fatigue, voire somnolence.

Ces effets s'observent particulièrement aux posologies supérieures à 3 comprimés par jour.

SIGNALEZ À VOTRE MÉDECIN OU À VOTRE PHARMACIEN, TOUT EFFET NON SOUHAITÉ ET GÊNANT QUI NE SERAIT PAS MENTIONNÉ DANS CETTE NOTICE.

6. CONSERVATION

a) NE PAS DÉPASSER LA DATE LIMITE D'UTILISATION FIGURANT SUR LE CONDITIONNEMENT EXTÉRIEUR

b) PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

c) MISE EN GARDE EN CAS DE SIGNES VISIBLES DE DÉTÉRIORATION

7. DATE DE RÉVISION DE LA NOTICE Juillet 1997

Annexe 2-30

ANNEXE III

E T I Q U E T A G E

DÉNOMINATION
MEDIATOR® 150 mg.

COMPOSITION QUALITATIVE
Chlorhydrate de Benfluorex.

COMPOSITION QUANTITATIVE
Chlorhydrate de Benfluorex .....150 mg pour un comprimé enrobé

FORME PHARMACEUTIQUE
Boîte de 30 comprimés enrobés.

LISTE DES EXCIPIENTS QUI ONT UN EFFET NOTOIRE oleate de glycérol

INDICATIONS THÉRAPEUTIQUES

MODE ET VOIE D'ADMINISTRATION
Voie orale

NE PAS LAISSER A LA PORTÉE DES ENFANTS

MISES EN GARDE SPÉCIALES : lire attentivement la notice

PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

PRÉCAUTIONS PARTICULIERES D'ÉLIMINATION DES PRODUITS NON UTILISÉS OU DES DÉCHETS DÉRIVES DE CES PRODUITS

NOM ET ADRESSE DE L'EXPLOITANT
LES LABORATOIRES SERVIER
22 rue Garnier
92200 NEUILLY-SUR-SEINE

Fabricant :
LES LABORATOIRES SERVIER Industrie
905, route de Saran
45520 GIDY

MÉDICAMENT AUTORISE N° 317 557-9

Mentions Minimales sur le Blister.
- MEDIATOR 150 mg
- SERVIER
- Numéro de lot de fabrication
- Date limite d'utilisation.

CLASSIFICATION EN MATIERE DE DÉLIVRANCE
Liste I.

NUMÉRO DE LOT DE FABRICATION

DATE LIMITE D'UTILISATION
(en clair).

Historique de la spécialité MEDIATOR VNL10008

de l'AMM à Année 2000

AMM 16/07/1974
indication : - troubles métaboliques glucido-lipidiques athérogènes
- troubles du métabolisme des lipides
- troubles du métabolisme des glucides

juin 1985 : demande de validation

22 mai 1987 : validation partielle dans l'indication :
"adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée."

janvier 1990 : demande de validation à l'appel de la 8ème tranche "endocrinologie" pour l'indication :
"en association au régime dans le diabète non insulinodépendant avec surcharge pondérale et/ou hyperinsulinisme."

22 septembre 1995 : réunion de concertation (ASR) dont l'objectif était d'entendre la firme sur l'indication non validée de Médiator "adjuvant de régime dans le diabète avec surcharge pondérale"

GTI 53 du 5/12/95 : projet de rejet de la validation de cette indication

27 janvier 1997 : dépôt d'un projet de notice-étiquetage pour mise en conformité -décret 94.

➤**16 avril 1997** : notification du rectificatif achevant la validation dans la seule indication
" Adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas pronvée"

Le courrier d'accompagnement précisait :
la démonstration d'efficacité dans l'indication "adjuvant de régime dans le diabète avec surcharge pondérale" est insuffisante
En effet, le dossier clinique transmis ne permet pas d'établir l'efficacité du benfluorex dans l'indication revendiquée. Les résultats des études contrôlées contre placebo qui, seules, pourraient être retenues, n'ont pas fait l'objet de comparaison statistique entre le groupe traité et le groupe placebo mais uniquement intra-groupe. Il n'y a pas d'études menées contre produit de référence. L'insuffisance de données d'efficacité ne permet donc pas de définir un bénéfice clinique pertinent chez les patients diabétiques en surcharge pondérale.

28 avril 1997 : notification du projet de notice corrigé, supprimant l'indication diabète

Mai-juin 1997 : la firme rapporte à l'agence l'original de la notification du 28 avril. Après accord avec AN et JMA (cf note manuscrite d'AN) : ⚠ C Rey Quinior ne retrouve pas ce document.

4 août 1997 : courrier de l'Agence autorisant la firme à maintenir l'indication diabète

29 mai 1998 : demande de modification du RCP : extension d'indication au "diabète de type II(non insulino-dépendant, en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique" (courrier absent en feuille de garde)

Avis de la COM 289 du 8/07/99 : sursis à statuer, notifié le 10/09/99

Vidal 2000 : l'information mentionne toujours les 2 indications.

Annexe 2-32

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

AGENCE DU MÉDICAMENT
Direction de l'Evaluation
143 - 145 Boulevard Anatole France
93200 SAINT-DENIS

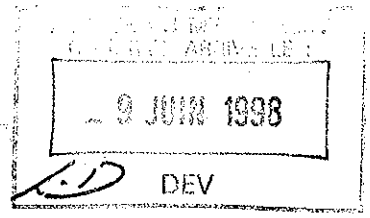
Neuilly-sur-Seine, le 29 mai 1998

A l'attention de Madame NORTH

N/Réf. : HML/sp/98.599
☎ 01 46 41 61 61
Fax 01 46 41 23 02
Mme MAURICE de LORRIS

Objet : **MEDIATOR® 150 mg,**
Dossier V NL 10 008
Validation : Tranche 8

T : 21
E : 828
et
T : 20
E : 826



Monsieur le Directeur Général,

En réponse au courrier du Professeur ALEXANDRE en date du 16 mars 1995, et en concertation étroite avec l'Agence du Médicament (lettre du Docteur ABADIE du 26 janvier 1996), nous avons réalisé une étude coordonnée par les Professeurs LEUTENEGGER, DEL PRATO et ERKELENS :

"Efficacité du benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul.
Etude de phase III randomisée à double insu durant 6 mois versus placebo et versus chlorhydrate de metformine (850 mg à 2550 mg/j)",

en vue de soutenir l'indication thérapeutique suivante :

"Diabète de type II (non insulino-dépendant) en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique".

Nous vous avions adressé, le 30 décembre 1997, la **première analyse** de cette étude.

Nous vous transmettons, ce jour, en 3 exemplaires, **l'analyse finale** confirmant les résultats de l'analyse principale relative à l'efficacité de Benfluorex versus placebo et démontrant la non infériorité de Benfluorex par rapport à la Metformine.

Ce document comporte 29 volumes, dont 15 volumes (du 14/29 au 28/29) relatifs aux cahiers d'observation que nous nous engageons, conformément à l'Avis aux demandeurs, à tenir à la disposition de l'Administration.

Nous joignons par ailleurs, en 50 exemplaires, une nouvelle rédaction du R.C.P., avec modification des rubriques 4.1 "Indications thérapeutiques" et 5.1 "Propriétés pharmacodynamiques", ces dernières étant également soutenues par 3 études de pharmacologie clinique des Dr VELUSSI, PONTIROLI et du Pr ERKELENS dont les rapports ont été déposés à l'Agence du Médicament, en janvier 1995.

Nous vous prions de croire, Monsieur le Directeur Général, à l'expression de notre considération distinguée.

Claude SANTINI
Pharmacien Responsable

PJ : *3 exemplaires de l'étude (14 volumes sans les cahiers d'observation),*
50 exemplaires de la nouvelle rédaction du R.C.P.

SERVIER

Annexe 2-32

Réponse au courrier du Professeur ALEXANDRE en date du 16 mars 1995
N/spécialité : MEDIATOR® 150 mg
Dossier V NL 10 008
Validation : Tranche 8

9 cartons comprenant :

- 1 courrier (HML/sp/98.599), accompagné de :
  - ☞ 50 exemplaires de la nouvelle rédaction du R.C.P.,
  - ☞ 3 exemplaires de l'étude (14 volumes sans les cahiers d'observation);

Carton n° 1	Volumes 1 à 6 + 50 ex. du RCP
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Carton n° 3	Volumes 11 à 13 - Volume 29
Carton n° 4	Volumes 1 à 6
Carton n° 5	Volumes 7 à 10
Carton n° 6	Volumes 11 à 13 - Volume 29
Carton n° 7	Volumes 1 à 6
Carton n° 8	Volumes 7 à 10
Carton n° 9	Volumes 11 à 13 - Volume 29

Annexe 2-32

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Carton n° 4	Volumes 1 à 6
Carton n° 5	Volumes 7 à 10
Carton n° 6	Volumes 11 à 13 - Volume 29
Carton n° 7	Volumes 1 à 6
Carton n° 8	Volumes 7 à 10
Carton n° 9	Volumes 11 à 13 - Volume 29

Annexe 2-33

DEMANDE DU LABORATOIRE SERVIER D'INDICATION DU MEDIATOR 150 mg POUR LE TRAITEMENT DU DIABÈTE DE TYPE II

(Réunion de la Commission d'AMM du vendredi 2 octobre 1998)

Il s'agit, en fait, au-delà de cette demande extension d'indication, de statuer sur la reconnaissance du Médiator comme agent antidiabétique et hypolipémiant. La modification proposée du RCP du Médiator porte en effet la mention suivante : "Antidiabétique oral différent des sulfamides hypoglycémiants et des biguanides, le Médiator diminue la glycémie à jeûn et post-prandiale chez les diabétiques de type II (non insulino-dépendants)...". Or, jusqu'à présent, dans ses indications retenues, le Médiator est considéré comme adjuvant du régime dans le traitement des hypertriglycéridémies et du diabète asymptomatique avec surcharge pondérale.

L'actuelle demande du Laboratoire SERVIER se fonde sur les résultats d'une étude de phase III, randomisée à double insu, d'une durée de 7 mois, versus placebo et versus Metformine, intitulée "Efficacité du Benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type II mal contrôlés par le régime seul". Il s'est agi d'une étude multicentrique co-coordonnée par les Professeurs Leutenegger de Reims, Del Prato de Padoue et Erkelins d'Utrecht. 316 centres ont été impliqués, 294 en France, 20 en Italie et 2 au Pays Bas. L'étude a duré du 1er juillet 1996 au 4 mars 1998. Après une période de pré-inclusion de 2 mois, la période de traitement était de 6 mois après une période de 5 semaines d'adaptation de la posologie. Le critère principal de jugement était l'HbA1c, de dosage centralisé, mesurée à S0, S17 et S29. Les critères secondaires ont comporté glycémie à jeûn (S0, S17 et S29), insulinémie sérique (S0 et S29), bilan lipidique (S0 et S29) ainsi que les arrêts de traitement pour inefficacité, l'évolution du poids et la mesure mensuelle de la glycémie dosée localement. Un protocole d'évaluation de tolérance a été conduit parallèlement.

Des 1210 patients sélectionnés (diabète de type II, âge : 35 - 70 ans, traitement par régime seul, glycémie à jeûn comprise entre 7,8 et 13,9 mmol/l et/ou HbA1c comprise entre 7,5 et 10,0 %), 722 ont été inclus dont 573 ont terminé l'étude. L'analyse fine de la structure de l'étude, de son déroulement et de ses critères de validité a été réalisée par ailleurs par des collègues spécialistes de ces méthodologies. Ce rapport ne vise qu'à évaluer les principaux résultats de l'étude selon les critères de la diabétologie clinique. Les points suivants méritent commentaires :

- dans le goupe Benfluorex, 6,8 % des traitements ont été arrêtés par manque d'effet (glycémie à jeûn > 2,5 g/l), contre 10,4 % dans le groupe placebo mais 1 % dans le groupe Metformine. Cette observation mérite discussion. Ce taux d'échec différencie fortement l'effet thérapeutique du Benfluorex de celui de la Metformine et amène à relativiser la comparaison des groupes Benfluorex versus Metformine ;

- un autre élément concerne la population des diabétiques inclus dans l'étude : bien que l'éventail des valeurs d'HbA1c d'inclusion soit assez large, la valeur moyenne des taux parait singulièrement peu élevée (7,48-7,79 %) ; cet échantillon est-il bien représentatif des diabétiques non insulino-dépendants ? La déviation standard des valeurs d'HbA1c est donnée,

Annexe 2-33

mais la distribution est-elle gaussienne? En d'autres termes, comment évolue l'efficacité du Médiator en fonction du degré du déséquilibre du diabète ?

- la comparaison Benfluorex-placébo fait apparaître une diminution de 0,79-0,86 % (valeurs absolues) de l'HbA1c quelle que soit la population retenue pour le calcul (population "intention de traiter", population "per-protocole"). Mais la comparaison de l'évolution des moyennes des HbA1c des groupes "cas complets" placébo et Benfluorex est difficile compte-tenu des différences des valeurs de départ et du fait que l'on ne sait pas si les comparaisons intra-groupes S17-S29 montrent une différence significative ;

- la comparaison des valeurs d'insulinémie basale des groupes placébo et Benfluorex n'a pas grande signification ; en revanche, il aurait pu être intéressant d'étudier l'évolution par groupe des rapports "glycémie-insulinémie" individuels ;

- pour la comparaison Benfluorex versus Metformine, les modalités de l'analyse statistique ne semblent pas avoir été conduites, ou au moins présentées, comme pour la comparaison précédente ce qui obscurcit la lisibilité des résultats ; en particulier, manque, apparemment, l'équivalent du tableau 17 figurant les valeurs S0, S17 et S29. Compte-tenu de ces difficultés d'interprétation, la lecture des valeurs des HbA1c moyennes suggère une efficacité du Benfluorex moindre que celle de la Metformine. Le commentaire est similaire pour ce qui concerne les glycémies à jeûn et les insulinémies ;

- un autre commentaire concerne l'éventuelle efficacité "antidiabétique" du Benfluorex en fonction du surpoids. Le poids moyen des patients inclus (82,7 ± 14,4 kg ; IMC : 29,8 ± 4,1 kg/m^2), sans doute conforme aux critères de sélection, apparaît singulièrement élevé. Il serait peut-être utile de tenter de stratifier la présentation des résultats en fonction de l'IMC initial.

Au total, cette étude révèle une certaine action, significative et favorable, du Benfluorex sur le contrôle de la glycémie de diabétiques non insulino-dépendants. Cet effet semble moindre que celui de la Metformine. Cependant, l'étude présentée n'apporte pas d'éléments suffisamment convainquants pour extrapoler cet effet à des segments plus larges de la population des patients diabétiques de type II, d'autant plus que, quantitativement, et bien que significatif, l'effet est limité. En conséquence, il n'est pas approprié d'appliquer le qualificatif "d'antidiabétique" au Benfluorex dans l'état des études actuelles. De même, le qualificatif "hypolipémiant" n'est pas justifié à la lecture des résultats de l'étude présentée dans laquelle, toutefois, l'évolution du bilan lipidique n'était qu'un critère secondaire.

Un dernier commentaire concerne les métabolites du Benfluorex. Il est indispensable que la contribution du Benfluorex à la production éventuelle de dérivés de type fenfluramine soit discutée, en particulier dans le contexte des études récentes sur l'impact de ces molécules sur le risque d'anomalies valvulaires cardiaques.

Le 1er octobre 1998
Professeur J. ORGIAZZI

Relevé d'avis

Annexe 2-34

REUNION COMMISSION N°273 DU 2 OCTOBRE 1998

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoires SERVIER

Demande déposée le 29 Mai 1998

Principe actif :	Benfluorex chlorhydrate
Caractère d'originalité :	Extension d'A.M.M. (Modification de l'ANNEXE I).
Classe ATC :	Système cardio-vasculaire/ Hypolipidémiants (C10A : hypocholestérolémiants et hypotriglycéridémiants)

Le benfluorex chlorhydrate a depuis 1987 (date d'A.M.M : 22.04.1987) les indications suivantes :

"- adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours obligatoire.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée."

Pour information, une **enquête de Pharmacovigilance** concernant le benfluorex a été réalisée et présentée au Comité Technique de Pharmacovigilance le 10 Septembre 1997.
Cette mise au point s'était avérée nécessaire en raison de la nature de l'un des métabolites du benfluorex (norfenfluramine) et en raison de la constatation d'une dérive de prescription comme anorexigène.
Les conclusions ont été les suivantes :

- les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60ng/l).Mais à partir de la fenfluramine, la norfenfluramine produite n'est plus biotransformée et se retrouve dans les urines à 7.4%; à partir du Benfluorex, la norfenfluramine est transformée en un produit désaminé et oxydé et la dose excrétée ne serait que de 2%.
- la réévaluation n'a pas permis d'écarter un passage de la barrière hémato-méningée de la norfenfluramine produite par le benfluorex. Les études pharmacodynamiques n'ont cependant pas mis en évidence d'effet anorexigène du benfluorex.
- le Comité Technique a proposé que la firme fournisse rapidement (avant le 2 Octobre) une analyse précise des prescriptions de MEDIATOR (nouvelles prescriptions, renouvellements de prescriptions) à partir des panels de vente à leur disposition (DOREMA, IMS).

En ce qui concerne le dossier actuel,

1. **TYPE DE DEMANDE :**
   La firme souhaite une extention d'A.M.M dans l'indication suivante :

   "Diabète de type II (non insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique".

Cette demande est étayée par une étude clinique de Phase III de *"l'efficacité du benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul".*

2. PARTICULARITÉS DE CETTE DEMANDE :

L'étude a été réalisée en réponse à la question de l'Agence du Médicament (lettre du 26 Janvier 1996) afin de valider l'efficacité du benfluorex (dépôt d'élément complémentaire, validation tranche N°8 : diabétologie) dans son indication.

Les résultats ont été soumis en deux étapes :

- analyse de l'efficacité du benfluorex versus placebo : 1ère analyse (décembre 97),
- analyse de l'efficacité du benfluorex versus metformine : 2ème analyse (mai 98).

3. ETUDE BENFLUOREX VERSUS PLACEBO ET METFORMINE

Méthodologie :

- Etude de phase III, randomisée en double insu versus placebo et versus chlorhydrate de metformine (850 mg à 2550 mg/j),
- Nombre de patients prévus : 500 (placebo : 100, benfluorex: 200, metformine : 200),
- Nombre de patients analysés :
  - **1ère phase** : analyse intermédiaire à 6 mois de l'efficacité du benfluorex versus placebo 195 patients (placebo : 67 et benfluorex : 128),
  - **2ème phase** : analyse finale de l'efficacité du benfluorex versus metformine Groupe benfluorex: 252 sujets; groupe metformine : 232 sujets,
- Critère principal d'efficacité: **HbA1c** centralisée mesurée à S0, S17 et S29,
- Critères d'efficacité secondaires : glycémie à jeun (S0, S17 et S29), arrêts de traitement pour inefficacité, insulinémie sérique centralisée, bilan lipidique centralisé (cholestérol, HDL-cholestérol, triglycérides), poids (S0,S3,S5,S13,S17 et S29), glycémie locale à jeun (mesurée tous les 3 mois)
- Tolérance : fréquence et nature des événements indésirables, pression artérielle et fréquence cardiaque à toutes les visites, dosage de la créatininémie (S0 et S17).

Résultats :

1. Phase 1 : EFFICACITE benfluorex versus placebo

HbA1c (en %)		**Placebo**		**Benfluorex**	
Analyse en ITT	(n)	Moy+/-ds	(N)	Moy+/-ds	
S0	127	7.43 +/- 1.48	258	7.65 +/- 1.58	
Dernière valeur	128	7.91 +/- 1.86	259	7.05 +/- 1.46	
Dernière valeur -S0	127	0.50 +/- 1.32	258	- 0.60 +/- 1.42	
Différence des moyennes (se)		**- 0.86 (0.17)**	IC à 95 %	(-1.20, - 0.52)	
Effet traitement (p)		P < 0.001			
Effet temps (p)		< 0.001		< 0.001	

Glycémie à jeun (mmol/L)		**Placebo**		**Benfluorex**	
Analyse en ITT	(n)	Moy+/-ds	(N)	Moy+/-ds	
S0	123	9.74 +/- 2.28	253	10.04 +/- 2.01	
Dernière valeur	124	10.13 +/- 3.11	256	8.80 +/- 2.29	
Dernière valeur -S0	123	0.36 +/- 2.73	253	- 1.24 +/- 2.30	
Différence des moyennes (se)		**- 1.33 (0.28)**	IC à 95 % de la différence	(- 1.89, - 0.77)	
Effet traitement (p)		< 0.001			
Effet temps (p)		0.147		< 0.001	

2. Phase II. EFFICACITE benfluorex versus metformine

HbA1c (en %) Analyse en ITT		**Benfluorex** (n) Moy+/-ds		**Metformine** (N) Moy+/-ds	
S0	258	7.65 +/- 1.58		250	7.79 +/- 1.61
Dernière valeur		259	7.05 +/- 1.46	252	6.77 +/- 1.34
Dernière valeur -S0		258	- 0.60 +/- 1.42	250	- 1.01 +/- 1.38
Différence des moyennes (se)			**0.28 (0.212)**	90 % IC de la différence (0.07 - **0.48)**	
Test de non-infériorité (p)			P = 0.037		

Glycémie à jeun (mmol/L) Analyse en ITT		**Benfluorex** (n) Moy+/-ds		**Metformine** (N) Moy+/-ds	
S0	253	10.04 +/- 2.01		246	10.15 +/- 2.47
Dernière valeur		256	8.80 +/- 2.29	248	8.16 +/- 1.90
Dernière valeur -S0		253	- 1.24 +/- 2.30	246	- 1.97 +/- 2.32
Différence des moyennes (se)			**0.64 (0.19)**		
90 % de l'IC de la différence			(0.33 , 0.95)		

Les résultats de la phase I de cette étude (benfluorex versus placebo) montrent qu'après 6 mois de traitement :
- l'évolution de l'HbA1c est *significativement différente entre les deux groupes de traitement (p<0.001)* avec un effet groupe significatif à S17 et S29 en faveur du benfluorex,
- la différence entre les deux groupes sur la valeur finale de la glycémie à jeun est de -1.32 mmol/l, p=0.007.

3.Tolérance

Au cours de l'étude (phase I + phase II), 28% des patients du groupe placebo et 38 % de ceux du groupe benfluorex ont rapporté au moins un événement indésirable concernant le système gastro-intestinal, des troubles de l'état général et le système respiratoire.
Dans le groupe benfluorex, les événements émergents les plus fréquemment rapportés ont été: asthénie (7), diarrhée (6), vertiges (5) et céphalées (4 patients).

Note interne d'évaluation : L'évaluation de l'étude a soulevé les commentaires suivants:

1. Commentaires concernant la METHODOLOGIE de l'essai (phase I + phase II).

➪ *Rappel de la méthodologie :*

722 patients diabétiques âgés de 35 à 70 ans, traités par régime seul avec une glycémie comprise entre 7.8 et 13.8 mmol/l et/ou une HbA1c entre 7.5 et 10 % ont participé à cette étude.
Les *critères d'efficacité* ont été :
- l'HbA1c à 0, S17 et S29 (critère principal),
- la glycémie à jeun, l'insulinémie, les lipides, le poids (critères secondaires).

La *tolérance* a été évaluée sur l'incidence et la nature des événements indésirables, les chiffres de pression artérielle et de fréquence cardiaque, le taux de créatininémie (S0 et S17).

➪ *Commentaires :*

- le **nombre de sujets inclus** dépasse celui prévu initialement dans le protocole (722 au

lieu
de 500 patients) ce qui entraîne :
* une augmentation de la puissance de l'essai,
* une incidence bénéfique sur les résultats concernant les critères secondaires d'efficacité, (l'analyse des résultats en terme d'efficacité avec seulement 500 patients inclus n'est pas transmise).

- **l'analyse intermédiaire** de l'efficacité du benfluorex versus placebo n'était pas prévue dans
le protocole de l'essai. Par ailleurs, aucun ajustement du seuil de significativité (valeur de p)
n'a été effectué pour l'analyse finale.

- il manque de nombreuses valeurs, en particulier de l'HbA1c. 45.4 % (soit 328 cas) de **déviations majeures** ont été notifiées, ce qui pose un problème de qualité générale de l'essai.

- **Intervalle de confiance (IC)** à 95 % pour l'HbA1c et les critères secondaires dans la partie
I de l'essai (benfluorex versus placebo) alors que l'IC est à 90 % dans la seconde partie (benfluorex versus metformine).

- analyse de l'efficacité benfluorex versus metformine : les résultats montrent une diminution de 0.28 % de l'HbA1c (IC à 90 % : 0.07-0.48). La borne supérieure de cet intervalle est en-dessous de celle de 0.50 %, valeur fixée dans le protocole comme seuil de significativité d'un
antidiabétique oral pour une étude d'équivalence.

- pour les **"cas-complets"**, une analyse de l'évolution des moyennes de l'HbA1c des groupes
placebo et benfluorex à S0, S17 et S29 serait souhaitable.

2. Commentaires concernant les RESULTATS de l'essai **(phase I + phase II).**

⇨ *Rappel des principaux résultats :*

1. Efficacité du **benfluorex versus placebo** (6 mois de traitement par benfluorex)
   - réduction de l'HBA1c de **0.86 % (IC à 95 % : - 1,89 ; - 0.52)**,
   - réduction de la valeur moyenne de la glycémie de **- 1.33 mmol/l (IC à 95 % : -1.98 ;- 0.77)**,
   - pas d'effet sur l'insulinémie, les triglycérides ou le HDL-cholestérol,
   - diminution très modérée mais *significative* du poids sous benfluorex (- 1.96 kg +/- 3.13).

2. Efficacité de **benfluorex versus metformine**.
   - HbA1c :différence de **0.28 %** (IC à 90 % : 0.07; 0.48), soit benfluorex : 7.05 % et metformine : 6.77 %
   - glycémie à jeun : différence de **0.6 mmol/l** (IC à 90 % : 0.66 ; 0.94), soit benfluorex : 8.80
     mmol/L et benfluorex : 8.16 mmol/L

3. En terme de **tolérance** :
   - le nombre total de patients ayant présenté des effets indésirables est réparti de la façon suivante :
   * placebo : 20.8 %

* benfluorex : 24.8 %
* metformine : 26.4 %

- quel que soit le type d'événements indésirables, il n'y a pas de différence significative entre benfluorex
et metformine.

Les effets indésirables les plus fréquents sont de type **gastro-intestinal** (benfluorex : 5.1 % ; metformine : 13.7 %), nausées, douleurs abdominales. Les autres effets sont de type asthénie, vertige, myalgies et lombalgies.

- les effets *indésirables émergents sévères* attribués à benfluorex sont :
  * 1 cas de trouble de l'équilibre,
  * 1 cas de vertige,
  * 2 cas de diarrhées,
  * 1 cas de ballonnement intestinal.

➪ *Commentaires :*

1. La présentation des résultats est ambiguë et les groupes concernés ne sont pas toujours définis.
   Les résultats donnés sont variables selon les tableaux (ex. : données en ITT du groupe Benfluorex versus placebo et versus metformine sur HbA1c).

2. **Concernant l'HbA1c. Bien que l'éventail des valeurs d'HbA1c soit large,** la valeur moyenne des taux **d'HbA1c est peu élevée (7.48-7.79 %),** et n'est pas représentative d'une population de sujets diabétiques. Les patients inclus sont en moyenne peu sévèrement atteints.
   La distribution est-elle Gaussienne? Comment évolue l'efficacité du benfluorex en fonction du déséquilibre du diabète?

3. Les **arrêts de traitements par manque d'efficacité (glycémie > 2.5 g/l)** ont été de 10.4% dans le groupe placebo, 6.8 % dans le groupe benfluorex et de 1 % dans le groupe metformine.

4. La comparaison de l'efficacité du benfluorex versus metformine ne tient pas compte des doses des deux traitements, en particulier **les posologies réelles de metformine utilisées ne sont pas précisées** (posologie minimale, maximale et moyenne).

5. Enfin, il est noté que dans cette étude **aucun effet sur les lipides, en particulier sur les triglycérides n'est mis en évidence** alors que l'A.M.M actuelle précise qu'il s'agit d'un traitement "adjuvant adapté dans les hypertriglycéridémies".

CONCLUSIONS :

Cette étude met en évidence une *action significative et favorable du benfluorex versus placebo sur le contrôle de la glycémie* de sujets diabétiques de type II.

Toutefois, l'évaluation globale de l'efficacité du benfluorex dans l'indication du diabète de type 2 devra tenir compte des réponses aux questions et commentaires soulevées par l'analyse de cette étude, tant sur le plan méthodologique que sur l'interprétation des résultats de l'essai (notamment versus metformine).

Enfin, il serait important de prendre connaissance des données récentes de l'enquête de pharmacovigilance.

AVIS DE LA COMMISSION N° 273 DU 2 OCTOBRE 1998 : SURSIS A STATUER en l'attente d'une réévaluation du dossier au plan méthodologique, notamment afin de situer l'efficacité du benfluorex vis à vis de la metformine.

N.B. :

1) l'efficacité du benfluorex vesus placebo sur la réduction de l'HBA1c paraît établie. Elle est de faible amplitude : 0,9 % et porte sur des patients initialement peu sévèrement atteints (HbA1c de 7,5 à 7,8 %).
2) L'absence d'efficacité du benfluorex sur l'hypertriglycéridémie du diabète est à noter alors que l'hypertriglycéridémie est une des indications actuelles du produit.

Annexe 2-35

Compte-rendu de la réunion interne concernant MEDIATOR (AFSSAPS, 18 mars 1999)

Etaient présents :
Mr. le Dr. Fricker
Mr. le Pr. Berthezene
Mr. le Pr. Halimi
Mr. le Dr. Saltiel

pour l'AFSSAPS :
Dr E. Abadie
Pr. C. Caulin
Dr L.Duranteau
Dr C. Rey-quinio
Dr G. Rostoker

Etaient absents et excusés :
Mr. le Pr. Altman
Mr. le Pr. Orgiazzi
Mr. le Pr. Timsit
Mr. le Pr. Vicaut

Objectif de la réunion :
1) situer l'efficacité du benfluorex vis à vis d'autres thérapeutiques hypoglycémiantes.
2) déterminer la place éventuelle du benfluorex dans la stratégie thérapeutique du diabète de type 2.

Rappel :
avis de la COM du 2 octobre 1998 : SURSIS À STATUER en l'attente d'une réévaluation du dossier au plan méthodologique, notamment afin de situer l'efficacité du benfluorex vis-à-vis de la metformine.
N.B. :
1) l'efficacité du benfluorex versus placebo sur la réduction de l'HBA_{1c} parait établie. Elle est de faible amplitude : 0,9 % et porte sur des patients initialement peu sévèrement atteints (HbA_{1c} de 7,5 % à 7,8 %).
2) L'absence d'efficacité du benfluorex sur l'hypertriglycéridémie du diabète est à noter alors que l'hypertriglycéridémie est une des indications actuelles du produit actuelles du produit.

I. Au plan méthodologique :
1) nous disposons d'un rapport du Pr. E.Vicaut dont les principales conclusions sont les suivantes :

"Concernant l'analyse de non infériorité du benfluorex vs metformine:
1) dans cet essai 2 hypothèses sont testées simultanément :
-supériorité vis à vis du placebo
-non-infériorité vis à vis de la metformine

- Le rapporteur est tout à fait d'accord avec la plupart des remarques méthodologiques telles qu'elles apparaissent dans le rapport de la Commission du 2/10/99. ...dont les plus importantes sont:

-une justification peu claire de la différence entre la taille de l'échantillon prévue et la taille effective. Le problème ne se situe pas à notre avis dans l'augmentation de puissance qu'elle induit, car après tout on ne peut reprocher à un essai d'être trop puissant, mais parce qu'elle introduit un doute sur le maintien de l'aveugle tout au long de l'essai.
(Il faut noter qu'il existe des justifications détaillées des procédures de maintien de l'aveugle après l'analyse intermédiaire du bras vs placebo mais que celles-ci ne répondent pas directement au problème évoqué ci-dessous)

-le nombre de déviations majeures apparaît très important.

- Commentaires concernant le test de non infériorité

Il est noté que l'intervalle de confiance utilisé pour les comparaisons vs placebo étant des intervalles de confiance à 95 %, alors que celui utilisé dans la comparaison vs metformine était un intervalle de confiance à 90 %.
En fait, il y a effectivement un manque de clarté dans la description des procédures utilisées dans cette étude.Il semble que dans le dossier les auteurs ont utilisé un intervalle de confiance BILATERAL à 90 % plutôt que l'intervalle UNILATERAL à 95 %. Si c'est le cas il s'agit d'une erreur formelle mais qui ne modifierait pas leurs conclusions.

En pratique, il me semble nécessaire de leur demander une clarification sur ce point en leur demandant simplement soit de préciser si l'intervalle qu'ils ont considéré est un intervalle BILATERAL, soit (et ce serait plus souhaitable d'un point de vue formel) de fournir le calcul des intervalles de confiance UNILATERAUX à 95 %. (pour ITT et per protocole). Il est intéressant de noter en faveur de l'étude et en rapport avec le problème du grand nombre de déviations que les conclusions basées sur la population per protocole sont similaires (et même plutôt franches) qu'avec la population ITT.
Ce point est important car dans certain cas l'analyse en ITT d'une étude d'équivalence biaise en faveur de la conclusion d'équivalence.

En ce qui concerne les études secondaires : la procédure est très curieuse car aucune borne d'équivalence n'est fixée a priori, même pas en terme de variation relative acceptable. Les auteurs se contentent de comparer les bornes des intervalles de confiance à des variations cliniques pertinentes qui seraient donc déterminées a posteriori. Ceci pourrait être admis dans une phase exploratrice mais n'est pas acceptable dans une procédure à visée démonstratrice.

Annexe 2-35

II. Principaux commentaires des experts cliniciens présents :

-sur la méthodologie :

- les sorties d'étude par manque d'efficacité dans le groupe benfluorex ne sont pas négligeables : 6.8 % vs 1 %; des clarifications sont souhaitables;

- il apparaît dans le groupe metformine que l'ajustement thérapeutique n'ait pas été toujours réalisé dans les conditions prévues de l'essai;

- dans l'essai ont été inclus des patients ayant des HbA_1c dans les limites de la normale et donc non diabétiques ;

-concernant le rapport efficacité/sécurité :

- la non- infériorité vs metformine nécessite d'être réanalysée en tenant compte des manques méthodologiques déjà cités ;

- les résultats mériteraient d'être exprimés :
  . en fonction des quartilles d'HbA_{1c} de départ
  . en fonction du BMI et de la perte de poids en fin de traitement

Il faut remarquer que dans cet essai, les résultats ne montrent aucun effet de diminution du taux des triglycérides dans le groupe benfluorex

III. Commentaires généraux et conclusion :

- l'efficacité du benfluorex dans la réduction de l'HbA_{1c} est faible ;

- la qualité de l'essai parait discutable ;

- l'indication éventuelle se discute si la non-infériorité vs metformine est démontrée :
  - pour un sous-groupe défini de patients diabétiques ; les limites de l'HbA_{1c} seraient à définir :
  - en première intention ;
  - l'efficacité serait à évaluer à 6 mois et le traitement arrêté s'il n'apporte pas de bénéfice (i.e normalisation de l'HbA_{1c})
- manquent des études en association avec d'autres thérapeutiques hypoglycémiantes;
- le benfluorex n'a pas apporté de preuve de diminution de l'incidence des complications à long-terme du diabète.

En conclusion, des clarifications sont nécessaires :

- sur la qualité de l'essai (causes de sortie pour inefficacité, ajustement thérapeutique dans le groupe metformine, qualité des centres investigateurs.): une inspection de l'essai sera discutée (P-H Bertoye)
- sur les résultats d'efficacité dans des sous-groupes :
  . en fonction du quartille d'HbA_{1C}
  . en fonction du poids

- des données manquent :
  . en association avec d'autres thérapeutiques hypoglycémiantes
  . dans le diabète sévère : par ex, lorsque l'HbA_{1c} est supérieur à 8 %)
  . dans les situations où la metformine serait contre-indiquée.

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoires SERVIER

Demande déposée le 29 Mai 1998

Principe actif :	Benfluorex chlorhydrate
Caractère d'originalité :	Extension d'A.M.M. (Modification de l'ANNEXE I).
Classe ATC :	Système cardio-vasculaire/ Hypolipidémiants (C10A : hypocholestérolémiants et hypotriglycéridémiants)

Le benfluorex chlorhydrate a depuis 1987 (date d'A.M.M : 22.04.1987) les indications suivantes :

"- adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours obligatoire.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée."

Pour information, une **enquête de Pharmacovigilance** concernant le benfluorex a été réalisée et présentée au Comité Technique de Pharmacovigilance le 10 Septembre 1997.
Cette mise au point s'était avérée nécessaire en raison de la nature de l'un des métabolites du benfluorex (norfenfluramine) et en raison de la constatation d'une dérive de prescription comme anorexigène.
Les conclusions ont été les suivantes :

- les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60ng/l).Mais à partir de la fenfluramine, la norfenfluramine produite n'est plus biotransformée et se retrouve dans les urines à 7.4%; à partir du Benfluorex, la norfenfluramine est transformée en un produit désaminé et oxydé et la dose excrétée ne serait que de 2%.
- la réévaluation n'a pas permis d'écarter un passage de la barrière hémato-méningée de la norfenfluramine produite par le benfluorex. Les études pharmacodynamiques n'ont cependant pas mis en évidence d'effet anorexigène du benfluorex.
- le Comité Technique a proposé que la firme fournisse rapidement (avant le 2 Octobre) une analyse précise des prescriptions de MEDIATOR (nouvelles prescriptions, renouvellements de prescriptions) à partir des panels de vente à leur disposition (DOREMA, IMS).

En ce qui concerne le dossier actuel,

1. **TYPE DE DEMANDE :**
La firme souhaite une extention d'A.M.M dans l'indication suivante :

"Diabète de type II (non insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique".

Cette demande est étayée par une étude clinique de Phase III de *"l'efficacité du benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul".*

2. **PARTICULARITÉS DE CETTE DEMANDE :**
L'étude a été réalisée en réponse à la question de l'Agence du Médicament (lettre du 26 Janvier 1996) afin de valider l'efficacité du benfluorex (dépôt d'élément complémentaire, validation tranche N°8 : diabétologie) dans son indication.
Les résultats ont été soumis en deux étapes :
- analyse de l'efficacité du benfluorex versus placebo : 1ère analyse (décembre 97),
- analyse de l'efficacité du benfluorex versus metformine : 2ème analyse (mai 98).

Méthodologie :
- Etude de phase III, randomisée en double insu versus placebo et versus chlorhydrate de metformine (850 mg à 2550 mg/j),
- Nombre de patients prévus : 500 (placebo : 100, benfluorex: 200, metformine : 200),
- Nombre de patients analysés :
  - **1ère phase** : analyse intermédiaire à 6 mois de l'efficacité du benfluorex versus placebo 195 patients (placebo : 67 et benfluorex : 128),
  - **2ème phase** : analyse finale de l'efficacité du benfluorex versus metformine Groupe benfluorex: 252 sujets; groupe metformine : 232 sujets,
- Critère principal d'efficacité: HbA1c centralisée mesurée à S0, S17 et S29,
- Critères d'efficacité secondaires : glycémie à jeun (S0, S17 et S29), arrêts de traitement pour inefficacité, insulinémie sérique centralisée, bilan lipidique centralisé (cholestérol, HDL-cholestérol, triglycérides), poids (S0,S3,S5,S13,S17 et S29), glycémie locale à jeun (mesurée tous les 3 mois)
- Tolérance : fréquence et nature des événements indésirables, pression artérielle et fréquence cardiaque à toutes les visites, dosage de la créatininémie (S0 et S17).

Résultats :

1. Phase 1 : EFFICACITE benfluorex versus placebo

HbA1c (en %)		Placebo		Benfluorex	
Analyse en ITT	(n)	Moy+/-ds	(N)	Moy+/-ds	
S0	127	7.43 +/- 1.48	258	7.65 +/- 1.58	
Dernière valeur		128	7.91 +/- 1.86	259	7.05 +/- 1.46
Dernière valeur -S0		127	0.50 +/- 1.32	258	- 0.60 +/- 1.42
Différence des moyennes (se)		- 0.86 (0.17)	IC à 95 % (-1.20, - 0.52)		
Effet traitement (p)		P < 0.001			
Effet temps (p)		< 0.001		< 0.001	

Annexe 2-36

Glycémie à jeun (mmol/L) Analyse en ITT		Placebo (n) Moy+/-ds		Benfluorex (N) Moy+/-ds	
S0	123	9.74 +/- 2.28		253	10.04 +/- 2.01
Dernière valeur		124	10.13 +/- 3.11	256	8.80 +/- 2.29
Dernière valeur -S0		123	0.3 +/- 2.73	253	- 1.24 +/- 2.30
Différence des moyennes (se)			- 1.33 (0.28)	IC à 95 % de la différence (- 1.89, - 0.77)	
Effet traitement (p)				< 0.001	
Effet temps (p)		0.147		< 0.001	

2. *Phase II. EFFICACITE benfluorex versus metformine*

HbA1c (en %) Analyse en ITT		Benfluorex (n) Moy+/-ds		Metformine (N) Moy+/-ds	
S0	258	7.65 +/- 1.58		250	7.79 +/- 1.61
Dernière valeur		259	7.05 +/- 1.46	252	6.77 +/- 1.34
Dernière valeur -S0		258	- 0.60 +/- 1.42	250	- 1.01 +/- 1.38
Différence des moyennes (se)			0.28 (0.212)	90 % IC de la différence (0.07 - 0.48)	
Test de non-infériorité (p)				P = 0.037	

Glycémie à jeun (mmol/L) Analyse en ITT		Benfluorex (n) Moy+/-ds		Metformine (N) Moy+/-ds	
S0	253	10.04 +/- 2.01		246	10.15 +/- 2.47
Dernière valeur		256	8.80 +/- 2.29	248	8.16 +/- 1.90
Dernière valeur -S0		253	- 1.24 +/- 2.30	246	- 1.97 +/- 2.32
Différence des moyennes (se)			0.64 (0.19)		
90 % de l'IC de la différence			(0.33 , 0.95)		

Les résultats de la phase I de cette étude (benfluorex versus placebo) montrent qu'après 6 mois de traitement :

- l'évolution de l'HbA1c est *significativement différente entre les deux groupes de traitement (p<0.001)* avec un effet groupe significatif à S17 et S29 en faveur du benfluorex,
- la différence entre les deux groupes sur la valeur finale de la glycémie à jeun est de -1.32 mmol/l, p=0.007.

3. *Tolérance*

Au cours de l'étude (phase I + phase II), 28% des patients du groupe placebo et 38 % de ceux du groupe benfluorex ont rapporté au moins un événement indésirable concernant le système gastro-intestinal, des troubles de l'état général et le système respiratoire.
Dans le groupe benfluorex, les événements émergents les plus fréquemment rapportés ont été: asthénie (7), diarrhée (6), vertiges (5) et céphalées (4 patients).

Annexe 2-36

Note interne d'évaluation : L'évaluation de l'étude a soulevé les commentaires suivants:

***1. Commentaires concernant la METHODOLOGIE de l'essai* (phase I + phase II).**

➪ *Rappel de la méthodologie :*

722 patients diabétiques âgés de 35 à 70 ans, traités par régime seul avec une glycémie comprise entre 7.8 et 13.8 mmol/l et/ou une HbA1c entre 7.5 et 10 % ont participé à cette étude.

Les *critères d'efficacité* ont été :

- l'HbA1c à 0, S17 et S29 (critère principal),
- la glycémie à jeun, l'insulinémie, les lipides, le poids (critères secondaires).

La *tolérance* a été évaluée sur l'incidence et la nature des événements indésirables, les chiffres de pression artérielle et de fréquence cardiaque, le taux de créatininémie (S0 et S17).

➪ *Commentaires :*

- le **nombre de sujets inclus** dépasse celui prévu initialement dans le protocole (722 au lieu de 500 patients) ce qui entraîne :
  * une augmentation de la puissance de l'essai,
  * une incidence bénéfique sur les résultats concernant les critères secondaires d'efficacit (l'analyse des résultats en terme d'efficacité avec seulement 500 patients inclus n'est pas transmise).

- **l'analyse intermédiaire** de l'efficacité du benfluorex versus placebo n'était pas prévue dans le protocole de l'essai. Par ailleurs, aucun ajustement du seuil de significativité (valeur de p) n'a été effectué pour l'analyse finale.

- il manque de nombreuses valeurs, en particulier de l'HbA1c. 45.4 % (soit 328 cas) de **déviations majeures** ont été notifiées, ce qui pose un problème de qualité générale de l'essai.

- **Intervalle de confiance (IC)** à 95 % pour l'HbA1c et les critères secondaires dans la partie I de l'essai (benfluorex versus placebo) alors que l'IC est à 90 % dans la seconde partie (benfluorex versus metformine).

- analyse de l'efficacité benfluorex versus metformine : les résultats montrent une diminution de 0.28 % de l'HbA1c (IC à 90 % : 0.07-0.48). La borne supérieure de cet intervalle est en-dessous de celle de 0.50 %, valeur fixée dans le protocole comme seuil de significativité d'u antidiabétique oral pour une étude d'équivalence.

- pour les **"cas-complets"**, une analyse de l'évolution des moyennes de l'HbA1c des groupes placebo et benfluorex à S0, S17 et S29 serait souhaitable.

***2. Commentaires concernant les RESULTATS de l'essai* (phase I + phase II).**

➪ *Rappel des principaux résultats :*

1. Efficacité du **benfluorex versus placebo** (6 mois de traitement par benfluorex)
   - réduction de l'HBA1c de **0.86 % (IC à 95 % : - 1,89 ; - 0.52)**,
   - réduction de la valeur moyenne de la glycémie de - 1.33 mmol/l (IC à 95 % : -1.98 ;-0.77),
   - pas d'effet sur l'insulinémie, les triglycérides ou le HDL-cholestérol,
   - diminution très modérée mais *significative* du poids sous benfluorex (- 1.96 kg +/- 3.13).

2. Efficacité de **benfluorex versus metformine**.
   - HbA1c :différence de **0.28 %** (IC à 90 % : 0.07; 0.48), soit benfluorex : 7.05 % et metformine : 6.77 %

Annexe 2-36

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***1. Commentaires concernant la METHODOLOGIE de l'essai* (phase I + phase II).**

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Les *critères d'efficacité* ont été :
- l'HbA1c à 0, S17 et S29 (critère principal),
- la glycémie à jeun, l'insulinémie, les lipides, le poids (critères secondaires).

La *tolérance* a été évaluée sur l'incidence et la nature des événements indésirables, les chiffres de pression artérielle et de fréquence cardiaque, le taux de créatininémie (S0 et S17).

➪ *Commentaires :*

- le **nombre de sujets inclus** dépasse celui prévu initialement dans le protocole (722 au lieu de 500 patients) ce qui entraîne :
  * une augmentation de la puissance de l'essai,
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- **l'analyse intermédiaire** de l'efficacité du benfluorex versus placebo n'était pas prévue dans le protocole de l'essai. Par ailleurs, aucun ajustement du seuil de significativité (valeur de p) n'a été effectué pour l'analyse finale.

- il manque de nombreuses valeurs, en particulier de l'HbA1c. 45.4 % (soit 328 cas) de **déviations majeures** ont été notifiées, ce qui pose un problème de qualité générale de l'essai.

- **Intervalle de confiance (IC)** à 95 % pour l'HbA1c et les critères secondaires dans la partie I de l'essai (benfluorex versus placebo) alors que l'IC est à 90 % dans la seconde partie (benfluorex versus metformine).

- analyse de l'efficacité benfluorex versus metformine : les résultats montrent une diminution de 0.28 % de l'HbA1c (IC à 90 % : 0.07-0.48). La borne supérieure de cet intervalle est en-dessous de celle de 0.50 %, valeur fixée dans le protocole comme seuil de significativité d'un antidiabétique oral pour une étude d'équivalence.

- pour les **"cas-complets"**, une analyse de l'évolution des moyennes de l'HbA1c des groupes placebo et benfluorex à S0, S17 et S29 serait souhaitable.

***2. Commentaires concernant les RESULTATS de l'essai* (phase I + phase II).**

➪ *Rappel des principaux résultats :*

1. Efficacité du **benfluorex versus placebo** (6 mois de traitement par benfluorex)
   - réduction de l'HBA1c de **0.86 % (IC à 95 % : - 1,89 ; - 0.52)**,
   - réduction de la valeur moyenne de la glycémie de - 1.33 mmol/l (IC à 95 % : -1.98 ;-0.77),
   - pas d'effet sur l'insulinémie, les triglycérides ou le HDL-cholestérol,
   - diminution très modérée mais *significative* du poids sous benfluorex (- 1.96 kg +/- 3.13).

2. Efficacité de **benfluorex versus metformine**.
   - HbA1c :différence de **0.28 %** (IC à 90 % : 0.07; 0.48), soit benfluorex : 7.05 % et metformine : 6.77 %

- glycémie à jeun : différence de **0.6 mmol/l** (IC à 90 % : 0.66 ; 0.94), soit benfluorex : 8.80 mmol/L et benfluorex : 8.16 mmol/L

3. En terme de **tolérance** :
   - le nombre total de patients ayant présenté des effets indésirables est réparti de la façon suivante :
   * placebo : 20.8 %
   * benfluorex : 24.8 %
   * metformine : 26.4 %
   - quel que soit le type d'événements indésirables, il n'y a pas de différence significative entre benfluorex et metformine.
   Les effets indésirables les plus fréquents sont de type **gastro-intestinal** (benfluorex : 5.1 % ; metformine : 13.7 %), nausées, douleurs abdominales. Les autres effets sont de type asthénie, vertige, myalgies et lombalgies.
   - les effets *indésirables émergents sévères* attribués à benfluorex sont :
     * 1 cas de trouble de l'équilibre,
     * 1 cas de vertige,
     * 2 cas de diarrhées,
     * 1 cas de ballonnement intestinal.

⇨ *Commentaires :*

1. La présentation des résultats est ambiguë et les groupes concernés ne sont pas toujours définis.
   Les résultats donnés sont variables selon les tableaux (ex. : données en ITT du groupe Benfluorex versus placebo et versus metformine sur HbA1c).

2. **Concernant l'HbA1c. Bien que l'éventail des valeurs d'HbA1c soit large,** la valeur moyenne des taux **d'HbA1c est peu élevée (7.48-7.79 %),** et n'est pas représentative d'une population de sujets diabétiques. Les patients inclus sont en moyenne peu sévèrement atteints.
   La distribution est-elle Gaussienne? Comment évolue l'efficacité du benfluorex en fonction du déséquilibre du diabète?

3. Les **arrêts de traitements par manque d'efficacité (glycémie > 2.5 g/l)** ont été de 10.4% dans le groupe placebo, 6.8 % dans le groupe benfluorex et de 1 % dans le groupe metformine.

4. La comparaison de l'efficacité du benfluorex versus metformine ne tient pas compte des doses des deux traitements, en particulier **les posologies réelles de metformine utilisées ne sont pas précisées** (posologie minimale, maximale et moyenne).

5. Enfin, il est noté que dans cette étude **aucun effet sur les lipides, en particulier sur les triglycérides n'est mis en évidence** alors que l'A.M.M actuelle précise qu'il s'agit d'un traitement "adjuvant adapté dans les hypertriglycéridémies".

CONCLUSIONS :

Cette étude met en évidence une *action significative et favorable du benfluorex versus placebo sur le contrôle de la glycémie* de sujets diabétiques de type II.

Annexe 2-36

Toutefois, l'évaluation globale de l'efficacité du benfluorex dans l'indication du diabète de type 2 devra tenir compte des réponses aux questions et commentaires soulevées par l'analyse de cette étude, tant sur le plan méthodologique que sur l'interprétation des résultats de l'essai (notamment versus metformine).

Enfin, il serait important de prendre connaissance des données récentes de l'enquête de pharmacovigilance.

AVIS DE LA COMMISSION N° 273 DU 2 OCTOBRE 1998 : **SURSIS A STATUER** en l'attente d'une réévaluation du dossier au plan méthodologique, notamment afin de situer l'efficacité du benfluorex vis à vis de la metformine.

N.B. :

1) l'efficacité du benfluorex versus placebo sur la réduction de l'HbA1c paraît établie. Elle est de faible amplitude : 0,9 % et porte sur des patients initialement peu sévèrement atteints (HbA1c de 7,5 à 7,8 %).
2) L'absence d'efficacité du benfluorex sur l'hypertriglycéridémie du diabète est à noter alors que l'hypertriglycéridémie est une des indications actuelles du produit.

Note interne d'évaluation :

Les questions nécessitant des réponses et un avis complémentaire sont :

1/ sur le plan méthodologique et de la qualité de l'essai :
- le choix de l'intervalle de confiance à 95% pour la comparaison versus placebo ; à 90% pour la comparaison versus metformine ;
- le maintien de l'aveugle pendant la durée de l'essai ;
- la qualité des inclusions (certains patients inclus avaient une HbA_{1C} dans les limites de la normale) ; les causes de sortie pour inefficacité : l'ajustement thérapeutique dans le groupe metformine.

2/ concernant l'efficacité
- l'efficacité du benfluorex dans la réduction de l'HbA_{1c} est faible ;
- l'indication éventuelle se discute si la non-infériorité vs metformine est démontrée :
  - pour un sous-groupe défini de patients diabétiques ; les limites de l'HbA_{1c} seraient à définir :
  - en première intention ;
  - l'efficacité serait à évaluer à 6 mois et le traitement est arrêté s'il n'apporte pas de bénéfice (i.e normalisation de l'HbA_{1c})

Enfin, le benfluorex n'a pas apporté de preuve de diminution de l'incidence des complications à long-terme du diabète.

Les données sont insuffisantes pour évaluer l'efficacité du benfluorex :
dans les sous-groupes de patients qui ont un diabète plus sévère,
- en association avec d'autres thérapeutiques hypoglycémiantes
- en fonction du poids
- éventuellement chez les patients ayant une contre indication aux biguanides

enfin, l'absence d'effet sur les triglycérides est souligné

Annexe 2-36

3/ D'autre part, la tolérance du benfluorex est remise en question en raison de la notification récente d'une hypertension artérielle pulmonaire d'allure primitive chez une patiente de 51 ans traitée par benfluorex depuis 4 à 5 ans.

Le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen de pharmacovigilance (Italie et France, rapporteurs).

Au total, une mise à jour des données de tolérance, des données de pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines ont été demandées à la firme.

AVIS DE LA COMMISSION N°289 DU 8 JUILLET 1999 : **SURSIS A STATUER** en l'attente

- des conclusions de l'inspection sur la qualité de l'essai ;
- de l'évaluation des données disponibles de pharmacovigilance.
- de l'avis de l'expert méthodologiste.

En tout état de cause le dossier actuel ne permettrait pas de donner l'indication "traitement du diabète de type II" en raison :
- de la faible efficacité hypoglycémiante observée,
- de l'absence de données suffisantes chez les diabétiques ayant une hémoglobine HbA1c élevée (supérieure à celle des patients de l'étude versée, soit en moyenne 7.48 - 7.79 %),
- de l'absence de données en association aux antidiabétiques,
- de l'absence de données à long terme ,
- de la difficulté de positionner le benfluorex dans la stratégie de prise en charge du diabète.

Des études chez les patients chez qui la metformine est contre-indiquée seraient utiles.

FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTE

Annexe 2-37

Direction de l'inspection
et des établissements

*Département d'inspection des essais cliniques
et non cliniques*

Personne chargée du dossier : O. Le Blaye
Téléphone : 01.55.87.40.19
Télécopie : 01.55.87.40.12
Réf. : mediator/demeb/notjma.ben

Saint-Denis, le 25 AOUT 1999

Note
à l'attention de Monsieur J.M. ALEXANDRE,
Directeur de l'évaluation des médicaments et des produits biologiques

Objet : Mediator - inspection de l'essai CL3-780-144 - note d'étape.

Par note en date du 12 juin 1999, la direction de l'évaluation des médicaments et des produits biologiques a demandé l'inspection de l'essai intitulé "Efficacité du benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul. Etude de phase III randomisée à double insu durant 6 mois versus placebo et versus chlorhydrate de metformine (850 à 2550 mg/j) (Essai CL3-780-144)", présenté par les laboratoires Servier à l'appui d'une demande d'extension d'indication pour leur spécialité Médiator 150 mg.

L'examen du dossier de cette demande par le département d'inspection des essais cliniques et non cliniques a mis en évidence plusieurs limites et insuffisances concernant le protocole de l'essai et l'analyse des résultats. Par ailleurs, les premières inspections réalisées ont mis en évidence une erreur dans la formule de calcul de l'HbA1c utilisée par le laboratoire centralisé en charge de cette analyse.

*** Limites du protocole et commentaires relatifs aux résultats :**

- Limites du protocole :

Le critère principal d'évaluation de l'efficacité était l'hémoglobine glyquée HbA1c. Les critères d'inclusion dans l'essai étaient une glycémie à jeun ≥ 1,40 g/l (7,8 mmol/l) et ≤ 2,50 g/l (13,9 mmol/l) à la visite d'inclusion (V0) et/ou une HbA1c ≥ 7,5 % et ≤ 10 % à la visite V-1. La présence d'une HbA1c élevée n'était donc pas un critère obligatoire pour l'inclusion. De ce fait, la valeur de base de l'HbA1c de 79 des 722 patients inclus dans l'essai était inférieure ou égale à 5,8 %, valeur de référence du laboratoire ; 281 autres patients avaient une HbA1c inférieure à 7,5 %.

. Limites de l'analyse des résultats :

Ces limites ont été examinées principalement pour l'analyse d'efficacité entre les groupes benfluorex et metformine concernant le critère d'évaluation principal.
L'analyse statistique réalisée pour l'HbA1c a consisté principalement en une comparaison des moyennes des HbA1c à la dernière visite entre les différents groupes.
Le rapport de l'essai et son annexe 16.4. (listing des analyses statistique) ne présentent pas clairement de comparaison statistique des groupes à l'inclusion pour ce paramètre ; les moyennes des HbA1c à l'inclusion dans la population ITT ayant au moins une valeur sous traitement présentent pourtant une différence de 0,14 % entre les groupes metformine (7,79 %) et benfluorex (7,65 %), en faveur du médicament à l'essai, alors que la limite d'équivalence thérapeutique était fixée à 0,50 %.
Pour ce paramètre, la principale analyse statistique mise en évidence dans le rapport de l'essai (tableau 25), dont les résultats ont été repris dans le relevé d'avis de la commission n°273 du 2 octobre 1998, compare les moyennes des HbA1c entre les groupes benfluorex et metformine à la dernière visite. Cette analyse ne tient pas compte des valeurs à l'inclusion. Les résultats de cette analyse concluent à la non-infériorité du benfluorex par rapport à la metformine.
Une deuxième analyse a comporté une analyse de covariance prenant en compte la valeur basale à l'inclusion. Les résultats de cette analyse ne permettent plus de conclure à la non-infériorité du benfluorex (p = 0,059). Enfin, aucune analyse n'a comparé la diminution de l'HbA1c sous traitement entre les deux groupes ; la différence des diminutions (0,41 % en faveur de la metformine, pour une limite d'équivalence fixée à 0,50 %) ne permettrait vraisemblablement pas de conclure en faveur du benfluorex.

. Erreur de calcul de l'HbA1c :

L'HbA1c a été dosée par un laboratoire centralisé, l'Institut Pasteur de Lille, par chromatographie liquide haute performance par échange d'ions. L'inspection de ce laboratoire a montré que la formule de calcul utilisée pour le dosage de l'HbA1c était erronée *(Cf. annexe 1)*. Au vu des résultats des deux séries de dosages examinées au cours de l'inspection, il semble que les résultats d'HbA1c calculés par le laboratoire soient légèrement surestimés pour les valeurs d'HbA1c inférieures à 8 % environ et sous-estimés pour les valeurs supérieures à 8 % environ. Pour ces deux séries, l'écart entre la valeur calculée au cours de l'essai et la valeur réelle est cependant faible et ne dépasse pas 0,1 % d'HbA1c pour chaque patient. Pour chaque patient, l'écart entre l'HbA1c à l'inclusion et à la dernière visite pourrait donc être sous-estimé au maximum de 0,2 %.
Cette erreur peut avoir des conséquences sur plusieurs points :

- inclusion à tort de patients : des patients ont pu être inclus à tort dans l'essai si leur glycémie était inférieure à 1,4 g/l (7,8 mmol/l) et si leur HbA1c a été calculée de manière erronée à 7,5 % au lieu de 7,4 %. Le nombre de patients concernés est cependant vraisemblablement faible ;

L'HbA1c a été dosée par chromatographie liquide haute performance par échange d'ions, avec une calibration en un point. Le calibrant utilisé, fourni par la société Biorad, avait un titre en HbA1c de 8,70 %.

La formule de calcul figurant dans la procédure opératoire standardisée établie par l'Institut Pasteur de Lille préalablement à l'essai est exacte et tient compte du pourcentage de l'aire du pic d'HbA1c par rapport à la somme des aires (HbA1c + HbA0) pour l'échantillon de calibration et pour l'échantillon à analyser ainsi que du titre en HbA1c de l'échantillon de calibration :

% HbA1c patient = (% HbA1c calibrant) x (% aires patient) / (% aires calibrant).

La méthode de calcul réellement utilisée par l'Institut Pasteur de Lille *(voir exemple en pièce jointe)* comporte le calcul de la pente de deux droites de calibration, l'une pour l'HbA1c et l'autre pour l'HbA0, à partir de l'aire du pic de ces fractions d'hémoglobine pour l'échantillon de calibration et de la concentration relative d'HbA1c et d'HbA0 dans cet échantillon, connue uniquement en pourcentage :

pente = aire du pic / "concentration", avec "concentration" = 8,70 % pour HbA1c et 91,30 % pour HbA0.

Ces pentes sont ensuite utilisées pour calculer une "concentration" d'HbA1c et une "concentration" d'HbA0 dans l'échantillon à doser :

"concentration" HbA1c = aire HbA1c patient / pente HbA1c
"concentration" HbA0 = aire HbA0 patient / pente HbA0

On calcule ensuite, à l'aide de ces résultats, un pourcentage d'HbA1c dans l'échantillon :

% HbA1c = "concentration" HbA1c / ("concentration" HbA1c + "concentration" HbA0).

Les "concentrations" d'HbA1c et d'HbA0 dans l'échantillon étant exprimées en %, on calcule donc un pourcentage de pourcentages, et non pas un pourcentage de concentrations.

La formule de calcul utilisée par l'Institut Pasteur de Lille serait acceptable si les concentrations d'HbA1c et d'HbA0 dans l'échantillon de calibration étaient connues de manière indépendante et absolue (exprimées en g/l par exemple). Elle n'est cependant pas exacte dans le cas de l'échantillon de calibration utilisé, pour lequel les concentrations ne sont pas connues de manière absolue mais uniquement en relation l'une avec l'autre.

- comparaison benfluorex - placebo : la sous-estimation de la diminution de l'HbA1c sous benfluorex est en défaveur de ce médicament ;

- comparaison benfluorex - metformine : la diminution de l'HbA1c est plus importante sous metformine que sous benfluorex. La sous-estimation de cette diminution serait donc en faveur du benfluorex. L'erreur maximale réalisée pour chaque patient (0,2 % pour les deux séries de dosages examinées) est à rapprocher de la limite d'équivalence entre les traitements fixée par le protocole de l'essai (0,5 %).

*** Poursuite de l'inspection dans ce contexte :**

Les investigations seront poursuivies pour ce dossier par l'inspection d'investigateurs en France, afin de contrôler les conditions de réalisation de la recherche et l'acceptabilité des données soumises à l'Agence, en fonction de la disponibilité d'inspecteurs médecins habilités et assermentés. En revanche, au vu des éléments présentés dans les paragraphes précédents, l'inspection d'investigateurs aux Pays-Bas et éventuellement en Italie est différée.

Dans ce contexte, je vous remercie de me faire part de vos intentions concernant ce dossier afin que je puisse considérer les actions d'inspection les plus adaptées.

Le Directeur de l'Inspection
et des Etablissements

Philippe LEDENVIC

Project Name HBA1C_17_03_9
User Name System
Software Version 3.05

Service de Biologie Spéciale
Dr [illegible]
1, rue du Prof. A. [illegible]
B.P. 245 - 590 [illegible]
Tél. 20877984 et 20[illegible]

785

Current Date 8/6/99

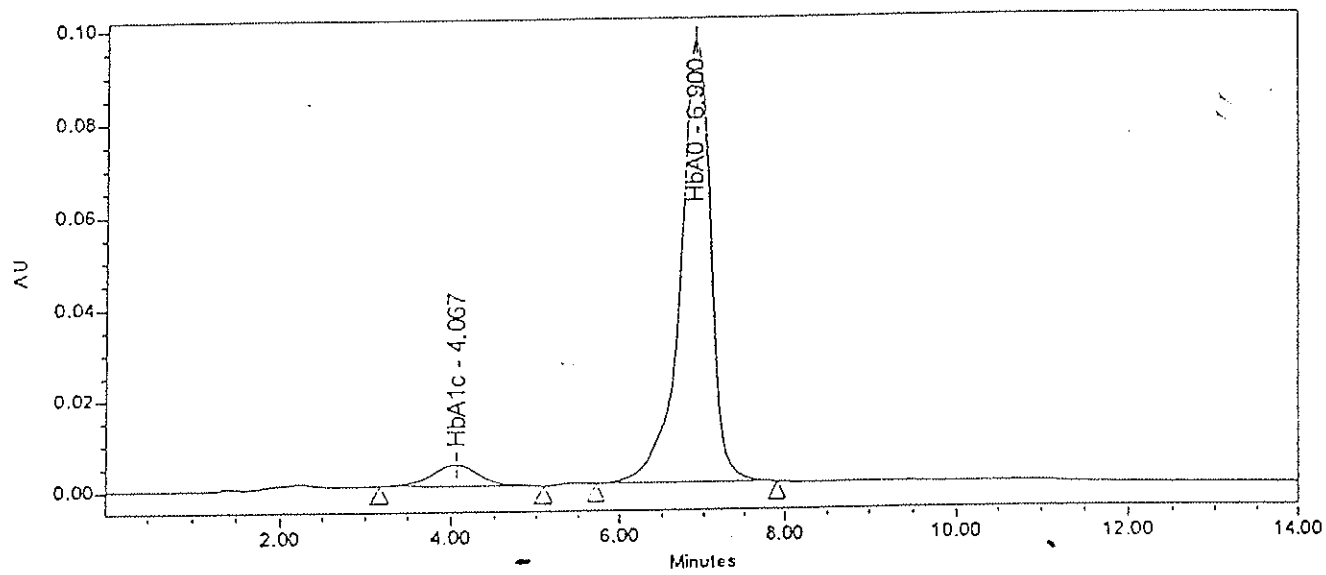
Annexe 2-37

Sample Information

SampleName	std 61335
Vial	1
Injection	1
Injection Volume	20.00 ul
Channel	486
Run Time	14.0 Minutes

Sample Type	Standard
Date Acquired	2/11/97 03:24:05 PM
Acq Method Set	HbA1c_set
Processing Method	process_HbA1c
Date Processed	2/11/97 04:02:49 PM

Auto-Scaled Chromatogram



Peak Results

	Name	RT	B	Response	Area	Amount	% Amount	Units
1	HbA1c	4.067	2.024586e+004	1.761e+005	176139	8.700e+000	8.70	%
2	HbA0	6.900	2.681938e+004	2.445e+006	2448609	9.130e+001	91.30	%

Calcul à partir d'une calibration en 1 point à partir d'un standard d'HbA1c à 5,7 %:

① Calcul de la pente de la droite de calibration:

$$B = \frac{\text{Response (Area)}}{\text{Amount} \rightarrow (8,7) \quad \searrow (91,3)} = \begin{cases} \rightarrow 2,024586\ 10^4 \text{ en HbA1c} \\ \searrow 2,681938\ 10^4 \text{ en HbA0} \end{cases}$$

② Utilisation de ces 2 valeurs respectives de B pour calculer "Amount" des échantillons de la même série (cf exemple ch+1 33531)

6.08.99

Software Version 3.05

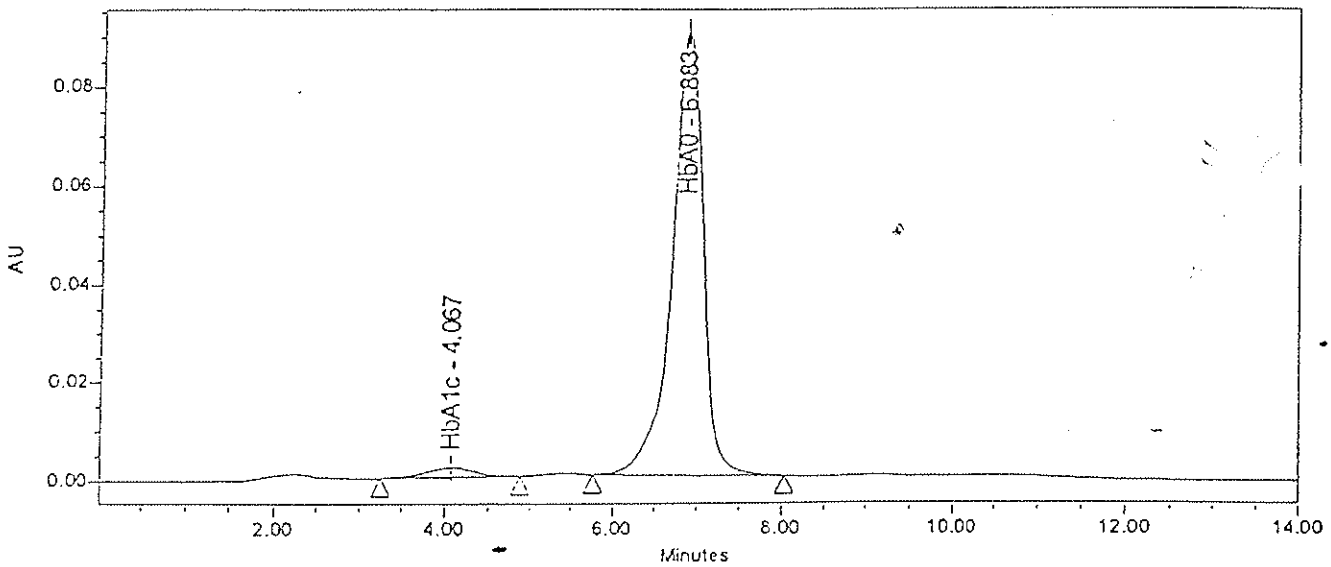
1, rue du Prof. A. Calmette
B.P. 245 - 59019 LILLE CEDEX
Tél. 20577954 et 20877968

Annexe 2-37

Sample Information

SampleName	ctrl 33531	Sample Type	Unknown
Vial	2	Date Acquired	2/11/97 03:39:28 PM
Injection	1	Acq Method Set	HbA1c_set
Injection Volume	20.00 ul	Processing Method	process_HbA1c
Channel	486	Date Processed	2/11/97 04:03:23 PM
Run Time	14.0 Minutes		

Auto-Scaled Chromatogram



Peak Results

	Name	RT	B	Response	Area	Amount	% Amount	Units
1	HbA1c	4.067	2.024586e+004	7.542e+004	75419	3.725e+000	4.26	%
2	HbA0	6.883	2.681938e+004	2.245e+006	2246130	8.375e+001	95.74	%

③ Amount HbA1c = Response (Aire) / 3 = 7,542 / 2,024586 = 3,725

= 83,750

④ Idem pour HbA0

⑤ Calcul en % : HbA1c = 3,725 / (83,750 + 3,725) = 4,26 %

6.08.99

Annexe 2-38

REUNION COMMISSION N° 296 DU 09 DECEMBRE 1999

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoires SERVIER

Demande déposée le 29 Mai 1998

Principe actif : Benfluorex chlorhydrate

Caractère d'originalité : Extension d'A.M.M. (Modification de l'ANNEXE I).

Classe ATC : Système cardio-vasculaire/ Hypolipidémiants (C10A : hypocholestérolémiants et hypotriglycéridémiants)

Le benfluorex chlorhydrate a depuis 1987 (date d'A.M.M : 22.04.1987) les indications suivantes :

"- adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours obligatoire.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée."

Pour information, une **enquête de Pharmacovigilance** concernant le benfluorex a été réalisée et présentée au Comité Technique de Pharmacovigilance le 10 Septembre 1997 (2) 98
Cette mise au point s'était avérée nécessaire en raison de la nature de l'un des métabolites du benfluorex (norfenfluramine) et en raison de la constatation d'une dérive de prescription comme anorexigène.
Les conclusions ont été les suivantes :

- les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60ng/l).Mais à partir de la fenfluramine, la norfenfluramine produite n'est plus biotransformée et se retrouve dans les urines à 7.4%; à partir du Benfluorex, la norfenfluramine est transformée en un produit désaminé et oxydé et la dose excrétée ne serait que de 2%.
- la réévaluation n'a pas permis d'écarter un passage de la barrière hémato-méningée de la norfenfluramine produite par le benfluorex. Les études pharmacodynamiques n'ont cependant pas mis en évidence d'effet anorexigène du benfluorex.
- le Comité Technique a proposé que la firme fournisse rapidement (avant le 2 Octobre) une analyse précise des prescriptions de MEDIATOR (nouvelles prescriptions, renouvellements de prescriptions) à partir des panels de vente à leur disposition (DOREMA, IMS).

En ce qui concerne le dossier actuel,

Annexe 2-38

1. TYPE DE DEMANDE :

La firme souhaite une extention d'A.M.M dans l'indication suivante :

"Diabète de type II (non insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique".

Cette demande est étayée par une étude clinique de Phase III de *"l'efficacité du benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul".*

2. PARTICULARITÉS DE CETTE DEMANDE :

L'étude a été réalisée en réponse à la question de l'Agence du Médicament (lettre du 26 Janvier 1996) afin de valider l'efficacité du benfluorex (dépôt d'élément complémentaire, validation tranche N°8 : diabétologie) dans son indication.
Les résultats ont été soumis en deux étapes :
- analyse de l'efficacité du benfluorex versus placebo : 1ère analyse (décembre 97),
- analyse de l'efficacité du benfluorex versus metformine : 2ème analyse (mai 98).

3. ETUDE BENFLUOREX VERSUS PLACEBO ET METFORMINE

Méthodologie :

- Etude de phase III, randomisée en double insu versus placebo et versus chlorhydrate de metformine (850 mg à 2550 mg/j),
- Nombre de patients prévus : 500 (placebo : 100, benfluorex: 200, metformine : 200),
- Nombre de patients analysés :
  - **1ère phase** : analyse intermédiaire à 6 mois de l'efficacité du benfluorex versus placebo 195 patients (placebo : 67 et benfluorex : 128),
  - **2ème phase** : analyse finale de l'efficacité du benfluorex versus metformine Groupe benfluorex: 252 sujets; groupe metformine : 232 sujets,
- Critère principal d'efficacité: **HbA1c** centralisée mesurée à S0, S17 et S29,
- Critères d'efficacité secondaires : glycémie à jeun (S0, S17 et S29), arrêts de traitement pour inefficacité, insulinémie sérique centralisée, bilan lipidique centralisé (cholestérol, HDL-cholestérol, triglycérides), poids (S0,S3,S5,S13,S17 et S29), glycémie locale à jeun (mesurée tous les 3 mois)
- Tolérance : fréquence et nature des événements indésirables, pression artérielle et fréquence cardiaque à toutes les visites, dosage de la créatininémie (S0 et S17).

Résultats :

1. Phase 1 : EFFICACITE benfluorex versus placebo

HbA1c (en %) Analyse en ITT	Placebo (n)	Moy+/-ds	Benfluorex (N)	Moy+/-ds
S0	127	7.43 +/- 1.48	258	7.65 +/- 1.58
Dernière valeur	128	7.91 +/- 1.86	259	7.05 +/- 1.46
Dernière valeur -S0	127	0.50 +/- 1.32	258	- 0.60 +/- 1.42
Différence des moyennes (se)		**- 0.86 (0.17)**	IC à 95 % (-1.20, - 0.52)	
Effet traitement (p)		P < 0.001		
Effet temps (p)		< 0.001		< 0.001

Glycémie à jeun (mmol/L) Analyse en ITT	Placebo (n)	Moy+/-ds	Benfluorex (N)	Moy+/-ds
S0	123	9.74 +/- 2.28	253	10.04 +/- 2.01
Dernière valeur	124	10.13 +/- 3.11	256	8.80 +/- 2.29
Dernière valeur -S0	123	0.36 +/- 2.73	253	- 1.24 +/- 2.30
Différence des moyennes (se)		**- 1.33 (0.28)**	IC à 95 % de la différence (- 1.89, - 0.77)	
Effet traitement (p)		< 0.001		
Effet temps (p)		0.147		< 0.001

2. Phase II. EFFICACITE benfluorex versus metformine

HbA1c (en %) Analyse en ITT	Benfluorex (n)	Moy+/-ds	Metformine (N)	Moy+/-ds
S0	258	7.65 +/- 1.58	250	7.79 +/- 1.61
Dernière valeur	259	7.05 +/- 1.46	252	6.77 +/- 1.34
Dernière valeur -S0	258	- 0.60 +/- 1.42	250	- 1.01 +/- 1.38
Différence des moyennes (se)		**0.28 (0.212)**	90 % IC de la différence (0.07 - **0.48**)	
Test de non-infériorité (p)		P = 0.037		

Glycémie à jeun (mmol/L) Analyse en ITT	Benfluorex (n)	Moy+/-ds	Metformine (N)	Moy+/-ds
S0	253	10.04 +/- 2.01	246	10.15 +/- 2.47
Dernière valeur	256	8.80 +/- 2.29	248	8.16 +/- 1.90
Dernière valeur -S0	253	- 1.24 +/- 2.30	246	- 1.97 +/- 2.32
Différence des moyennes (se)		**0.64 (0.19)**		
90 % de l'IC de la différence		(0.33 , 0.95)		

Les résultats de la phase I de cette étude (benfluorex versus placebo) montrent qu'après 6 mois de traitement :

- l'évolution de l'HbA1c est *significativement différente entre les deux groupes de traitement (p<0.001)* avec un effet groupe significatif à S17 et S29 en faveur du benfluorex,
- la différence entre les deux groupes sur la valeur finale de la glycémie à jeun est de -1.32 mmol/l, p=0.007.

3.Tolérance

Au cours de l'étude (phase I + phase II), 28% des patients du groupe placebo et 38 % de ceux du groupe benfluorex ont rapporté au moins un événement indésirable concernant le système gastro-intestinal, des troubles de l'état général et le système respiratoire.
Dans le groupe benfluorex, les événements émergents les plus fréquemment rapportés ont été: asthénie (7), diarrhée (6), vertiges (5) et céphalées (4 patients).

Annexe 2-38

Note interne d'évaluation : L'évaluation de l'étude a soulevé les commentaires suivants:

***1. Commentaires concernant la METHODOLOGIE de l'essai* (phase I + phase II).**

⇨ *Rappel de la méthodologie :*

722 patients diabétiques âgés de 35 à 70 ans, traités par régime seul avec une glycémie comprise entre 7.8 et 13.8 mmol/l et/ou une HbA1c entre 7.5 et 10 % ont participé à cette étude.

Les *critères d'efficacité* ont été :

- l'HbA1c à 0, S17 et S29 (critère principal),
- la glycémie à jeun, l'insulinémie, les lipides, le poids (critères secondaires).

La *tolérance* a été évaluée sur l'incidence et la nature des événements indésirables, les chiffres de pression artérielle et de fréquence cardiaque, le taux de créatininémie (S0 et S17).

⇨ *Commentaires :*

- le **nombre de sujets inclus** dépasse celui prévu initialement dans le protocole (722 au lieu de 500 patients) ce qui entraîne :
  * une augmentation de la puissance de l'essai,
  * une incidence bénéfique sur les résultats concernant les critères secondaires d'efficacité, (l'analyse des résultats en terme d'efficacité avec seulement 500 patients inclus n'est pas transmise).

- **l'analyse intermédiaire** de l'efficacité du benfluorex versus placebo n'était pas prévue dans le protocole de l'essai. Par ailleurs, aucun ajustement du seuil de significativité (valeur de p) n'a été effectué pour l'analyse finale.

- il manque de nombreuses valeurs, en particulier de l'HbA1c. 45.4 % (soit 328 cas) de **déviations majeures** ont été notifiées, ce qui pose un problème de qualité générale de l'essai.

- **Intervalle de confiance (IC)** à 95 % pour l'HbA1c et les critères secondaires dans la partie I de l'essai (benfluorex versus placebo) alors que l'IC est à 90 % dans la seconde partie (benfluorex versus metformine).

- analyse de l'efficacité benfluorex versus metformine : les résultats montrent une diminution de 0.28 % de l'HbA1c (IC à 90 % : 0.07-0.48). La borne supérieure de cet intervalle est en-dessous de celle de 0.50 %, valeur fixée dans le protocole comme seuil de significativité d'un antidiabétique oral pour une étude d'équivalence.

- pour les **"cas-complets"**, une analyse de l'évolution des moyennes de l'HbA1c des groupes placebo et benfluorex à S0, S17 et S29 serait souhaitable.

***2. Commentaires concernant les RESULTATS de l'essai* (phase I + phase II).**

⇨ *Rappel des principaux résultats :*

1. Efficacité du **benfluorex versus placebo** (6 mois de traitement par benfluorex)
   - réduction de l'HBA1c de **0.86 % (IC à 95 % : - 1,89 ; - 0.52)**,
   - réduction de la valeur moyenne de la glycémie de **- 1.33 mmol/l (IC à 95 % : -1.98 ;-0.77)**,
   - pas d'effet sur l'insulinémie, les triglycérides ou le HDL-cholestérol,
   - diminution très modérée mais *significative* du poids sous benfluorex (- 1.96 kg +/- 3.13).

2. Efficacité de **benfluorex versus metformine**.
   - HbA1c :différence de **0.28 %** (IC à 90 % : 0.07; 0.48), soit benfluorex : 7.05 % et metformine : 6.77 %
   - glycémie à jeun : différence de **0.6 mmol/l** (IC à 90 % : 0.66 ; 0.94), soit benfluorex : 8.80 mmol/L et benfluorex : 8.16 mmol/L

3. En terme de **tolérance** :
   - le nombre total de patients ayant présenté des effets indésirables est réparti de la façon suivante :

   * placebo : 20.8 %
   * benfluorex : 24.8 %
   * metformine : 26.4 %

   - quel que soit le type d'événements indésirables, il n'y a pas de différence significative entre benfluorex et metformine.

   Les effets indésirables les plus fréquents sont de type **gastro-intestinal** (benfluorex : 5.1 % ; metformine : 13.7 %), nausées, douleurs abdominales. Les autres effets sont de type asthénie, vertige, myalgies et lombalgies.
   - les effets *indésirables émergents sévères* attribués à benfluorex sont :
     * 1 cas de trouble de l'équilibre,
     * 1 cas de vertige,
     * 2 cas de diarrhées,
     * 1 cas de ballonnement intestinal.

➪ *Commentaires :*

1. La présentation des résultats est ambiguë et les groupes concernés ne sont pas toujours définis.
   Les résultats donnés sont variables selon les tableaux (ex. : données en ITT du groupe Benfluorex versus placebo et versus metformine sur HbA1c).

2. **Concernant l'HbA1c. Bien que l'éventail des valeurs d'HbA1c soit large,** la valeur moyenne des taux **d'HbA1c est peu élevée (7.48-7.79 %),** et n'est pas représentative d'une population de sujets diabétiques. Les patients inclus sont en moyenne peu sévèrement atteints.
   La distribution est-elle Gaussienne? Comment évolue l'efficacité du benfluorex en fonction du déséquilibre du diabète?

3. Les **arrêts de traitements par manque d'efficacité (glycémie > 2.5 g/l)** ont été de 10.4% dans le groupe placebo, 6.8 % dans le groupe benfluorex et de 1 % dans le groupe metformine.

4. La comparaison de l'efficacité du benfluorex versus metformine ne tient pas compte des doses des deux traitements, en particulier **les posologies réelles de metformine utilisées ne sont pas précisées** (posologie minimale, maximale et moyenne).

5. Enfin, il est noté que dans cette étude **aucun effet sur les lipides, en particulier sur les triglycérides n'est mis en évidence** alors que l'A.M.M actuelle précise qu'il s'agit d'un traitement "adjuvant adapté dans les hypertriglycéridémies".

CONCLUSIONS :

Cette étude met en évidence une *action significative et favorable du benfluorex versus placebo sur le contrôle de la glycémie* de sujets diabétiques de type II.

Toutefois, l'évaluation globale de l'efficacité du benfluorex dans l'indication du diabète de type 2 devra tenir compte des réponses aux questions et commentaires soulevées par l'analyse de cette étude, tant sur le plan méthodologique que sur l'interprétation des résultats de l'essai (notamment versus metformine).

Enfin, il serait important de prendre connaissance des données récentes de l'enquête de pharmacovigilance.

AVIS DE LA COMMISSION N° 273 DU 2 OCTOBRE 1998 : SURSIS A STATUER en l'attente d'une réévaluation du dossier au plan méthodologique, notamment afin de situer l'efficacité du benfluorex vis à vis de la metformine.

N.B. :

1) l'efficacité du benfluorex versus placebo sur la réduction de l'HbA1c paraît établie. Elle est de faible amplitude : 0,9 % et porte sur des patients initialement peu sévèrement atteints (HbA1c de 7,5 à 7,8 %).
2) L'absence d'efficacité du benfluorex sur l'hypertriglycéridémie du diabète est à noter alors que l'hypertriglycéridémie est une des indications actuelles du produit.

Note interne d'évaluation :

Les questions nécessitant des réponses et un avis complémentaire sont :

1/ sur le plan méthodologique et de la qualité de l'essai :
- le choix de l'intervalle de confiance à 95% pour la comparaison versus placebo ; à 90% pour la comparaison versus metformine ;
- le maintien de l'aveugle pendant la durée de l'essai ;
- la qualité des inclusions (certains patients inclus avaient une HbA_{1C} dans les limites de la normale) ; les causes de sortie pour inefficacité : l'ajustement thérapeutique dans le groupe metformine.

2/ concernant l'efficacité
- l'efficacité du benfluorex dans la réduction de l'HbA_{1c} est faible ;
- l'indication éventuelle se discute si la non-infériorité vs metformine est démontrée :
  - pour un sous-groupe défini de patients diabétiques ; les limites de l'HbA_{1c} seraient à définir :
  - en première intention ;
  - l'efficacité serait à évaluer à 6 mois et le traitement est arrêté s'il n'apporte pas de bénéfice (i.e normalisation de l'HbA_{1c})

Enfin, le benfluorex n'a pas apporté de preuve de diminution de l'incidence des complications à long-terme du diabète.

Annexe 2-38

Les données sont insuffisantes pour évaluer l'efficacité du benfluorex :
- dans les sous-groupes de patients qui ont un diabète plus sévère,
- en association avec d'autres thérapeutiques hypoglycémiantes
- en fonction du poids
- éventuellement chez les patients ayant une contre indication aux biguanides

enfin, l'absence d'effet sur les triglycérides est souligné

3/ D'autre part, la tolérance du benfluorex est remise en question en raison de la notification récente d'une hypertension artérielle pulmonaire d'allure primitive chez une patiente de 51 ans traitée par benfluorex depuis 4 à 5 ans.

Le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen de pharmacovigilance (Italie et France, rapporteurs).

Au total, une mise à jour des données de tolérance, des données de pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines ont été demandées à la firme.

AVIS DE LA COMMISSION N°289 DU 8 JUILLET 1999 : SURSIS A STATUER en l'attente

- des conclusions de l'inspection sur la qualité de l'essai ;
- de l'évaluation des données disponibles de pharmacovigilance.
- de l'avis de l'expert méthodologiste.

En tout état de cause le dossier actuel ne permettrait pas de donner l'indication "traitement du diabète de type II" en raison :
- de la faible efficacité hypoglycémiante observée,
- de l'absence de données suffisantes chez les diabétiques ayant une hémoglobine HbA1c élevée (supérieure à celle des patients de l'étude versée, soit en moyenne 7.48 - 7.79 %),
- de l'absence de données en association aux antidiabétiques,
- de l'absence de données à long terme ,
- de la difficulté de positionner le benfluorex dans la stratégie de prise en charge du diabète.

Des études chez les patients chez qui la metformine est contre-indiquée seraient utiles.

NOTE INTERNE D'ÉVALUATION :

• Au plan de la pharmacovigilance :

1 - Les notifications en France ont été de 350 effets indésirables (essentiellement, allergie-anaphylaxie, élévation des transaminases) ;

2 - 1 cas d'hypertension artérielle pulmonaire a été rapporté en France chez un patient traité uniquement par le Médiator ;

3 - Compte-tenu du métabolisme mal connu, des données complémentaires de pharmacocinétiques ont été demandées à la firme par la Commission Nationale de Pharmacovigilance ;

4 - les données à moyen et long terme (>6 mois) sont insuffisantes et nécessiterait également d'être complétées).

Néanmoins, le profil de tolérance est acceptable.

• Données d'inspection :

1 - Limites du protocole :

Le critère principal d'évaluation de l'efficacité était l'hémoglobine glyquée HbA1c. Les critères d'inclusion dans l'essai étaient une glycémie à jeun ≥ 1,40 g/l (7,8 mmol/l) et ≤ 2,50 g/l (13,9 mmol/l) à la visite d'inclusion (V0) *et/ou* une HbA1c ≥ 7,5 % et ≤ 10 % à la visite V-1. La présence d'une HbA1c élevée n'était donc pas un critère obligatoire pour l'inclusion. De ce fait, la valeur de base de l'HbA1c de **79** des 722 patients inclus dans l'essai était **inférieure ou égale** à **5,8 %**, valeur de référence du laboratoire ; **281 avaient une HbA1c inférieure à 7,5 %.**

2 - Résultats :

• *Limites de l'analyse des résultats :*

Ces limites ont été examinées principalement pour l'analyse d'efficacité entre les groupes benfluorex et metformine concernant le critère d'évaluation principal.
L'analyse statistique réalisée pour l'HbA1c a consisté principalement en une comparaison des moyennes des HbA1c à la dernière visite entre les différents groupes. Le rapport de l'essai et son annexe 16.4. (listing des analyses statistique) ne présentent pas clairement de comparaison statistique des groupes à l'inclusion pour ce paramètre ; les moyennes des HbA1c **à l'inclusion** dans la population ITT ayant au moins une valeur sous traitement présentent pourtant une **différence de 0,14 %** entre les groupes metformine (7,79 %) et benfluorex (7,65 %), en faveur du médicament à l'essai, alors que la limite d'équivalence thérapeutique était fixée à 0,50 %.

• *Erreur de calcul de l'HbA1c :*

L'HbA1c a été dosée par un **laboratoire centralisé**, l'Institut Pasteur de Lille, par chromatographie liquide haute performance par échange d'ions. L'inspection de ce laboratoire a montré que la **formule de calcul utilisée pour le dosage de l'HbA1c était erronée**. Au vu des résultats des deux séries de dosages examinées au cours de l'inspection, il semble que les résultats d'HbA1c calculés par le laboratoire soient légèrement surestimés pour les valeurs d'HbA1c inférieures à 8 % environ et sous-estimés pour les valeurs supérieures à 8 % environ.
Pour ces deux séries, l'écart entre la valeur calculée au cours de l'essai et la valeur réelle est cependant faible et ne dépasse pas 0,1 % d'HbA1c pour chaque patient.
Pour chaque patient, l'écart entre l'HbA1c à l'inclusion et à la dernière visite pourrait donc être sous-estimé au maximum de 0,2 %.
Cette erreur peut avoir des conséquences sur plusieurs points :

- inclusion à tort de patients : des patients ont pu être inclus à tort dans l'essai si leur glycémie était inférieure à 1,4 g/l (7,8 mmol/l) et si leur HbA1c a été calculée de manière erronée à 7,5 % au lieu de 7,4 %. Le nombre de patients concernés est cependant vraisemblablement faible ;

- comparaison benfluorex - placebo : la sous-estimation de la diminution de l'HbA1c sous benfluorex est en défaveur de ce médicament ;

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- **comparaison benfluorex - metformine** : la diminution de l'HbA1c est plus importante sous metformine que sous benfluorex. La sous-estimation de cette diminution serait donc en faveur du benfluorex. L'erreur maximale réalisée pour chaque patient (0,2 % pour les deux séries de dosages examinées) est à rapprocher de la limite d'équivalence entre les traitements fixée par le protocole de l'essai (0,5 %).

• Au plan méthodologique :

En résumé, l'étude comprenait 3 groupes : placebo, traitement par Benfluàrex, traitement par Metformine.

1) Une première analyse d'efficacité du Benflurorex contre placebo a montré une différence significative en faveur du Benfluorex.

2) analyse d'efficacité Benfluorex contre Metformine

Le type d'analyse choisi a été celui de la **non-infériorité**.
L'analyse en non-infériorité implique :
- le choix d'une zone d'équivalence ;
- la bonne qualité de l'étude (les écarts entrainant des biais vers la non-infériorité)
- une analyse perprotocole et en ITT

• concernant la zone d'équivalence : la borne supérieure choisie est de 50 % ; elle est acceptable mais correspond à la limite supérieure de la borne acceptable ;

• concernant la qualité de la réalisation de l'étude, différents commentaires peuvent être faits :
- inclusion : 722 patients ont été inclus (contre 500 prévus) ; 15,7 % sont des **déviations majeures** ; le dosage d'HbA_{1C} à S_{17} est connu pour 88.5 % des patients ; ce nombre n'est pas connu à S_{29} ni la répartition dans les 2 groupes de cet écart.

Il existe un **déséquilibre dans les taux d'HbA_{1C} à l'inclusion** : 7.5 % dans le groupe Benfluorex ; 7.9 % dans le groupe metformine.

• D'autre part, seuls **68 % des patients ont été inclus dans l'analyse per protocole**.
Résultats :

	Benfluorex	**Metformine**	IC 90 %	IC 95 %
HbA_{1C} (per protocole)	6.89 %	6.81 %		[0.12-0.29]
HbA_{1C} (ITT)	7.5 %	6.77 %	[0.07-0.48]	[0.04-0.52]
si l'analyse est réalisée avec la variation d'HbA_{1C} (ΔHbA_{1C}) :				
ΔHbA_{1C} per protocole			[0.20-0.66]	
ΔHbA_{1C} (ITT)			[0.21-0.61]	

Conclusions :
- l'étude ne conclut pas à la non infériorité du Benfluorex versus metformine ;
- le Benfluorex apparaît inférieur à la metformine.

D'autre part,
• l'analyse des profils de tolérance des deux produits n'a montré aucune différence significative entre les deux produits;
• enfin, aucun effet sur les triglycérides n'a été observé.

Annexe 2-38

AVIS DE LA COMMISSION N° 296 DU 09 DECEMBRE 1999 :

AVIS DEFAVORABLE à l'indication proposée :

1 - au plan de l'efficacité :

➜ il est noté une efficacité du Benfluorex comparé au placebo. Néanmoins, il n'est pas possible d'évaluer sur la taille de l'effet compte tenu des défauts de qualité de l'étude.

➜l'essai clinique fourni ne permet pas de conclure à la non infériorité du Benfluorex comparé à la Metformine.

En effet, la réalisation de l'étude n'est pas satisfaisante au plan méthodologique :
- 79/722 patients avaient une HbA_{1C} inférieure à 5.8 % donc normale, et 281/722 avaient une HbA_{1C} inférieure à 7.5 % ;
- il existe un déséquilibre dans les taux d'HbA_{1C} à l'inclusion : 7.5 % dans le groupe Benfluorex ; 7.9 % dans le groupe Metformine.
- la qualité de l'essai est mauvaise:
  - à l' inclusion : 722 patients ont été inclus (contre 500 prévus) ; 15,7 % sont des déviations majeures ; le dosage d'HbA_{1C} à S_{17} est connu pour 88.5 % des patients ; ce nombre n'est pas connu à S_{29} ni la répartition dans les 2 groupes de cet écart.
  - il existe un déséquilibre des taux d'HbA_{1C} à l'inclusion : 7.5 % en moyenne dans le groupe Benfluorex contre 7.9 % dans le groupe Metformine.
- l'analyse per protocole n'a inclus que 68 % des patients ;
- enfin, les résultats sur l'HbA_{1C} en analyse per protocole et en ITT ne sont pas concordants. En effet en analyse per protocole, l'intervalle de confiance à 95% est de [0.12-0.29] et permettrait de conclure à une non infériorité alors que l'intervalle de confiance à 95% en analyse ITT est de [0.04-0.52], la borne supérieure de l'intervalle de confiance dépassant la limite retenue de 0.50.

2 - au plan de la tolérance, l'analyse des profils de tolérance n'a pas montré pas de différence significative avec la Metformine.

3 - d'autre part, aucune efficacité sur les triglycérides n'a été montrée.

4 - les données cliniques sont insuffisantes pour :
- placer le benfluorex dans la stratégie thérapeutique du diabète de type 2 ;
- évaluer l'efficacité du benfluorex en association avec d'autres antidiabétiques oraux ;
- indiquer le benfluorex chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisant rénale, sujet âgé...).

Annexe 2-39

RÉPUBLIQUE FRANÇAISE

A G E N C E
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET DES
PRODUITS BIOLOGIQUES

Réf. à rappeler : VNL 10008
COM 296
LD/TD

DÉCISION DU DIRECTEUR GÉNÉRAL DE L'AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

du 25 AVR. 2000
refusant la modification
de l'autorisation de mise sur le marché de

MEDIATOR 150 mg, comprimé enrobé

LE DIRECTEUR GÉNÉRAL DE L'AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ,

Vu le livre V du code de la santé publique, notamment les articles L. 601, L. 605 3è, R. 5128 à R. 5140 ;

Vu la décision d'autorisation de mise sur le marché octroyée le 22 avril 1987 ;

Vu la demande de modification de l'autorisation de mise sur le marché présentée par les laboratoires SERVIER ;

pour **MEDIATOR 150 mg, comprimé enrobé ;**

et concernant la modification d'indication : *"Diabète de type II (non insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique"* ;

Vu l'avis de la Commission prévu à l'article R.5140 du code de la santé publique ;

Considérant que la démonstration de l'efficacité n'a pas été apportée.

En effet :

1 - sur le plan de l'efficacité :

- il est pris acte d'une efficacité du Benfluorex comparé au placebo. Néanmoins, il n'est pas possible d'évaluer la taille de l'effet compte tenu des défauts de qualité de l'étude ;

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

Annexe 2-39

- l'essai clinique fourni ne permet pas de conclure à la non infériorité du Benfluorex comparé à la Metformine.

En effet, la réalisation de l'étude n'est pas satisfaisante au plan méthodologique :

- 79/722 patients avaient une HbA_{1C} inférieure à 5.8 % donc normale, et 281/722 avaient une HbA_{1C} inférieure à 7.5 % ;
- il existe un déséquilibre dans les taux d'HbA_{1C} à l'inclusion : 7.5 % dans le groupe Benfluorex ; 7.9 % dans le groupe Metformine.
- la qualité de l'essai est mauvaise :
  . à l' inclusion : 722 patients ont été inclus (contre 500 prévus) ; 15,7 % sont des déviations majeures ; le dosage d'HbA_{1C} à S_{17} est connu pour 88.5 % des patients ; ce nombre n'est pas connu à S_{29} ni la répartition dans les 2 groupes de cet écart,
  . il existe un déséquilibre des taux d'HbA_{1C} à l'inclusion : 7.5 % en moyenne dans le groupe Benfluorex contre 7.9 % dans le groupe Metformine.

- l'analyse per protocole n'a inclus que 68 % des patients ;
- enfin, les résultats sur l'HbA_{1C} en analyse per protocole et en ITT ne sont pas concordants. En effet en analyse per protocole, l'intervalle de confiance à 95% est de [0.12-0.29] et permettrait de conclure à une non infériorité alors que l'intervalle de confiance à 95% en analyse ITT, est de [0.04-0.52], la borne supérieure de l'intervalle de confiance dépassant la limite retenue de 0.50.

2 - Les données cliniques sont insuffisantes pour :
- placer le benfluorex dans la stratégie thérapeutique du diabète de type 2 ;
- évaluer l'efficacité du benfluorex en association avec d'autres antidiabétiques oraux ;
- indiquer le benfluorex chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisant rénale, sujet âgé...).

DÉCIDE

Article 1er

La modification de l'autorisation de mise sur le marché est refusée au médicament :

MEDIATOR 150 mg, comprimé enrobé

des laboratoires SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE Cedex

Article 2

Le Directeur de l'évaluation des médicaments et des produits biologiques est chargé de l'exécution de la présente décision.

25 AVR. 2000

FAIT À SAINT-DENIS, le

LE DIRECTEUR GÉNÉRAL DE L'AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

Pour le Directeur Général
Par empêchement du Directeur de l'Évaluation des Médicaments et des Produits Biologiques
l'Adjoint au Directeur Chargé des Affaires Médicales

Dr François MEYER

Annexe 2-40

AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

143-147 boulevard Anatole France
93285 Saint-DENIS Cédex

Tél. : 01.55.87.30.00

EXPEDITEUR	DESTINATAIRE
Secrétariat du Prof. CAULIN : P. MOSSALA **DIRECTION** : DEV **UNITE** : G.A.R.E **TELEPHONE** : 01.55.87.33.44. **FAX:** 01.55.87.33.42	**Organisme** : LAB. SERVIER **A l'attention de** : **Mme de la BURGADE** **N° de fax** : 01.55.72.33.02

Date : 01 Mars 2000

salle 2B

Nombre de page : .....1..

OBJET : MEDIATOR (vnl10008)
V/réf. : IT/sp/00.0122

Madame,

Nous faisons suite à votre courrier du 9 Février 2000, et vous proposons la date du **24 Mars 2000 à 15 h 00** pour une réunion de concertation concernant la spécialité :

MEDIATOR ®, comprimés enrobés

Nous vous remercions par avance de bien vouloir nous confirmer votre accord.

Dans cette attente, nous vous prions d'agréer, Madame, l'expression de nos salutations distinguées.

Copie : Dr. Dorranteau
Dr. Rey-Quinio
Dr. ABADIE

Sincères salutations.

CKJ
EF

Dr Rey souhaite une réunion en interne pour statuer sur ce dossier (devalidation) avant le 24.03. Des dates vont être demandées

Annexe 2-40

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ
Direction de l'Evaluation du Médicament et des produits Biologiques
143 - 147 Boulevard Anatole France
93200 SAINT-DENIS

Neuilly-sur-Seine, le 09 février 2000

A l'attention de Monsieur le Docteur ABADIE
Département de l'Évaluation Pharmaco
Toxico Clinique des Médicaments

N/Réf. : IT/sp/00.0122
☎ 01 55 72 30 70
Fax 01 55 72 33 02
Mme A. de la BURGADE

Objet : **MEDIATOR®**
Dossier VNL 10008
Réunion de concertation

Monsieur,

Nous avons été informés de la décision prise en Commission d'A.M.M. du **27 janvier 2000** pour notre spécialité :

MEDIATOR®, *comprimés enrobés*

L'avis rendu dans le cadre de la Validation de l'indication **"Diabète"** étant **défavorable**, avant toute décision de votre part, nous sollicitons une réunion de concertation, notamment pour répondre aux critiques méthodologiques de l'étude clinique présentée.

Dans l'attente de votre réponse, nous vous prions d'agréer, Monsieur, l'expression de nos salutations distinguées.

Alain LE RIDANT
Pharmacien Responsable

Anne

Objet : MEDIATOR®

Réunion de concertation avec la firme et organisée par C. REY QUINIO :

Vendredi 24 mars 2000
à 15H00

Cette réunion fait suite au courrier du 18/02/00 (ci-joint).

Une réunion préparatoire devrait avoir lieu en interne d'ici là.
C. Rey Quinio nous tiendra informés.

Annexe 2-41

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Copie { LD CRA
J'ai signé le rectif. Si vous souhaitez les prévenir qu'ils vont le recevoir et que leur argumentaire sera examiné dans le cadre d'un recours gracieux.

Monsieur le Professeur Ch. CAULIN
Président de la Commision d'A.M.M.
Agence Française de Sécurité Sanitaire
des Produits de Santé
143 - 147 Boulevard Anatole France
93200 SAINT-DENIS

Neuilly sur Seine, le 31 mars 2000

LD Copie Mey

Direction de l'Evaluation du Médicament
et des produits Biologiques

N/Réf. : IT/sp/00.0365
☎ 01 55 72 65 34
Fax 01 55 72 33 02
Isabelle THUILLIER

Objet : **MEDIATOR® 150 mg**
Réunion de concertation du 24.03.2000

On ne pourrait différer davantage... François !

Monsieur le Président,

Je souhaite tout d'abord vous remercier de nous avoir reçus vendredi dernier, et de nous avoir permis de nous exprimer sur la taille de l'effet hypoglycémiant observé avec MEDIATOR® versus placebo dans l'étude CL3-780-144-FRA, la méthodologie de cet essai et la place de MEDIATOR® dans la stratégie thérapeutique du diabète.

Nous avons retenu le plan d'action suivant :

- Préparation d'une synthèse de l'ensemble des études cliniques réalisées dans le diabète ainsi que des éléments précliniques et de pharmacologie clinique sur le mode d'action insulinosensibilisateur de MEDIATOR®.
- Proposition d'un nouveau libellé d'indication mentionnant l'association aux autres thérapeutiques antidiabétiques existantes.

Comme convenu, nous nous engageons à vous transmettre ces éléments d'ici un mois et souhaitons qu'ils puissent être pris en considération avant toute décision.

Par ailleurs, nous avons bien compris le souhait de Madame CASTOT de recevoir une proposition de modification de R.C.P. sur la base des informations à notre disposition sans attendre le rapport du Ministère Italien (fax du 17/3 dernier). Cette Demande de Modification de l'Information vous est adressée aujourd'hui même.

Je vous prie d'agréer, Monsieur le Président, l'expression de ma haute considération.

Patricia MAILLERE
Directeur Général
Affaires Pharmaceutiques Mondiales

Copie : Dr ABADIE
Chef du Département de l'Évaluation Pharmaco
Toxico Clinique des Médicaments

Annexe 2-42

AGENCE FRANCAISE DE SECURITE SANITAIRE
DES PRODUITS DE SANTE

PRESENTATION POUR

INFORMATION
ACCORD
SIGNATURE

ORIGINE : DEMEB / GARE	PIECES A SIGNER :
OBJET : MEDIATOR 150 mg, comprimé enrobé VNL 10008	1 AD

	VISA	DATE	OBSERVATIONS
Responsable du dossier	TD	27/1	Corrections.
Chef d'Unité	AB	27/1	
Directeur Adjoint	LD	28/01	OK
Directeur →			
Directeur Général			

25 AVR. 2000

29/3

F. Noyer : ~~Accord~~
La rédaction doit être revue il ne s'agit pas d'une demande d'extension d'indication. A voir avec les A. Regl. et moi merci

→ TMA

F. Noyer le 6 avril
Vu avec EA
Notification avec avis favorable à l'indication diabète
Etes vous OK pour notification ce qui laisse la possibilité d'un recours gracieux qui devrait permettre un accord sur l'indication diabète

LD 13/04/00 + remarques dans le texte et corrections

OK le 14.04.00 MG.

Annexe 2-43

REUNION GT PTC2 N° 1 DU 21 SEPTEMBRE 2000

PROCEDURE NATIONALE

- **MEDIATOR 150**, comprimé

Dossier n° VNL 10008

Laboratoires SERVIER

Demande déposée le 29 Mai 1998

Principe actif :	Benfluorex chlorhydrate
Caractère d'originalité :	Extension d'A.M.M. (Modification de l'Annexe I).
Classe ATC :	Système cardio-vasculaire/ Hypolipidémiants (C10A : hypocholestérolémiants et hypotriglycéridémiants)

Le benfluorex chlorhydrate a depuis 1987 (date d'A.M.M : 22.04.1987) les indications suivantes :
"- adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours obligatoire.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée."

Pour information, une **enquête de Pharmacovigilance** concernant le benfluorex a été réalisée et présentée au Comité Technique de Pharmacovigilance le 10 Septembre 1997.
Cette mise au point s'était avérée nécessaire en raison de la nature de l'un des métabolites du benfluorex (norfenfluramine) et en raison de la constatation d'une dérive de prescription comme anorexigène.
Les conclusions ont été les suivantes :

- les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60ng/l).Mais à partir de la fenfluramine, la norfenfluramine produite n'est plus biotransformée et se retrouve dans les urines à 7.4%; à partir du Benfluorex, la norfenfluramine est transformée en un produit désaminé et oxydé et la dose excrétée ne serait que de 2%.
- la réévaluation n'a pas permis d'écarter un passage de la barrière hémato-méningée de la norfenfluramine produite par le benfluorex. Les études pharmacodynamiques n'ont cependant pas mis en évidence d'effet anorexigène du benfluorex.
- le Comité Technique a proposé que la firme fournisse rapidement (avant le 2 Octobre) une analyse précise des prescriptions de MEDIATOR (nouvelles prescriptions, renouvellements de prescriptions) à partir des panels de vente à leur disposition (DOREMA, IMS).

Annexe 2-43

En ce qui concerne le dossier actuel,

1. **TYPE DE DEMANDE :**
La firme souhaite une extention d'A.M.M dans l'indication suivante :

"Diabète de type II (non insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique".

Cette demande est étayée par une étude clinique de Phase III de *"l'efficacité du benfluorex (150 à 450 mg/j) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul".*

2. **PARTICULARITÉS DE CETTE DEMANDE :**
L'étude a été réalisée en réponse à la question de l'Agence du Médicament (lettre du 26 Janvier 1996) afin de valider l'efficacité du benfluorex (dépôt d'élément complémentaire, validation tranche N°8 : diabétologie) dans son indication.
Les résultats ont été soumis en deux étapes :
- analyse de l'efficacité du benfluorex versus placebo : 1ère analyse (décembre 97),
- analyse de l'efficacité du benfluorex versus metformine : 2ème analyse (mai 98).

3. **ETUDE BENFLUOREX VERSUS PLACEBO ET METFORMINE**
Méthodologie :
- Etude de phase III, randomisée en double insu versus placebo et versus chlorhydrate de metformine (850 mg à 2550 mg/j),
- Nombre de patients prévus : 500 (placebo : 100, benfluorex: 200, metformine : 200),
- Nombre de patients analysés :
  - **1ère phase** : analyse intermédiaire à 6 mois de l'efficacité du benfluorex versus placebo 195 patients (placebo : 67 et benfluorex : 128),
  - **2ème phase** : analyse finale de l'efficacité du benfluorex versus metformine Groupe benfluorex: 252 sujets; groupe metformine : 232 sujets,
- Critère principal d'efficacité: **HbA1c** centralisée mesurée à S0, S17 et S29,
- Critères d'efficacité secondaires : glycémie à jeun (S0, S17 et S29), arrêts de traitement pour inefficacité, insulinémie sérique centralisée, bilan lipidique centralisé (cholestérol, HDL-cholestérol, triglycérides), poids (S0,S3,S5,S13,S17 et S29), glycémie locale à jeun (mesurée tous les 3 mois)
- Tolérance : fréquence et nature des événements indésirables, pression artérielle et fréquence cardiaque à toutes les visites, dosage de la créatininémie (S0 et S17).

Résultats :
1. Phase 1 : EFFICACITE benfluorex versus placebo

HbA1c (en %)		**Placebo**		**Benfluorex**
Analyse en ITT	(n)	Moy+/-ds	(N)	Moy+/-ds
S0	127	7.43 +/- 1.48	258	7.65 +/- 1.58
Dernière valeur	128	7.91 +/- 1.86	259	7.05 +/- 1.46
Dernière valeur -S0	127	0.50 +/- 1.32	258	- 0.60 +/- 1.42

Différence des moyennes (se)	**- 0.86 (0.17)**	IC à 95 % (-1.20, - 0.52)
Effet traitement (p)	P < 0.001	
Effet temps (p)	< 0.001	< 0.001

Glycémie à jeun (mmol/L) Analyse en ITT	Placebo (n)	Moy+/-ds	Benfluorex (N)	Moy+/-ds
S0	123	9.74 +/- 2.28	253	10.04 +/- 2.01
Dernière valeur	124	10.13 +/- 3.11	256	8.80 +/- 2.29
Dernière valeur -S0	123	0.36 +/- 2.73	253	- 1.24 +/- 2.30
Différence des moyennes (se)		**- 1.33 (0.28)**	IC à 95 % de la différence (- 1.89, - 0.77)	
Effet traitement (p)		< 0.001		
Effet temps (p)		0.147		< 0.001

2. Phase II. EFFICACITE benfluorex versus metformine

HbA1c (en %) Analyse en ITT	Benfluorex (n)	Moy+/-ds	Metformine (N)	Moy+/-ds
S0	258	7.65 +/- 1.58	250	7.79 +/- 1.61
Dernière valeur	259	7.05 +/- 1.46	252	6.77 +/- 1.34
Dernière valeur -S0	258	- 0.60 +/- 1.42	250	- 1.01 +/- 1.38
Différence des moyennes (se)		**0.28 (0.212)**	90 % IC de la différence (0.07 - **0.48**)	
Test de non-infériorité (p)		P = 0.037		

Glycémie à jeun (mmol/L) Analyse en ITT	Benfluorex (n)	Moy+/-ds	Metformine (N)	Moy+/-ds
S0	253	10.04 +/- 2.01	246	10.15 +/- 2.47
Dernière valeur	256	8.80 +/- 2.29	248	8.16 +/- 1.90
Dernière valeur -S0	253	- 1.24 +/- 2.30	246	- 1.97 +/- 2.32
Différence des moyennes (se)		**0.64 (0.19)**		
90 % de l'IC de la différence		(0.33 , 0.95)		

Les résultats de la phase I de cette étude (benfluorex versus placebo) montrent qu'après 6 mois de traitement :

- l'évolution de l'HbA1c est *significativement différente entre les deux groupes de traitement (p<0.001)* avec un effet groupe significatif à S17 et S29 en faveur du benfluorex,
- la différence entre les deux groupes sur la valeur finale de la glycémie à jeun est de -1.32 mmol/l, p=0.007.

3.Tolérance

Au cours de l'étude (phase I + phase II), 28% des patients du groupe placebo et 38 % de ceux du groupe benfluorex ont rapporté au moins un événement indésirable concernant le système gastro-intestinal, des troubles de l'état général et le système respiratoire.
Dans le groupe benfluorex, les événements émergents les plus fréquemment rapportés ont été: asthénie (7), diarrhée (6), vertiges (5) et céphalées (4 patients).

Note interne d'évaluation : L'évaluation de l'étude a soulevé les commentaires suivants:

1. Commentaires concernant la METHODOLOGIE de l'essai (phase I + phase II).

Rappel de la méthodologie :

722 patients diabétiques âgés de 35 à 70 ans, traités par régime seul avec une glycémie comprise entre 7.8 et 13.8 mmol/l et/ou une HbA1c entre 7.5 et 10 % ont participé à cette étude.

Les *critères d'efficacité* ont été :
- l'HbA1c à 0, S17 et S29 (critère principal),
- la glycémie à jeun, l'insulinémie, les lipides, le poids (critères secondaires).

La *tolérance* a été évaluée sur l'incidence et la nature des événements indésirables, les chiffres de pression artérielle et de fréquence cardiaque, le taux de créatininémie (S0 et S17).

➪ *Commentaires :*

- le **nombre de sujets inclus** dépasse celui prévu initialement dans le protocole (722 au lieu de 500 patients) ce qui entraîne :
  * une augmentation de la puissance de l'essai,
  * une incidence bénéfique sur les résultats concernant les critères secondaires d'efficacité, (l'analyse des résultats en terme d'efficacité avec seulement 500 patients inclus n'est pas transmise).

- **l'analyse intermédiaire** de l'efficacité du benfluorex versus placebo n'était pas prévue dans le protocole de l'essai. Par ailleurs, aucun ajustement du seuil de significativité (valeur de p) n'a été effectué pour l'analyse finale.

- il manque de nombreuses valeurs, en particulier de l'HbA1c. 45.4 % (soit 328 cas) de **déviations majeures** ont été notifiées, ce qui pose un problème de qualité générale de l'essai.

- **Intervalle de confiance (IC)** à 95 % pour l'HbA1c et les critères secondaires dans la partie I de l'essai (benfluorex versus placebo) alors que l'IC est à 90 % dans la seconde partie (benfluorex versus metformine).

- analyse de l'efficacité benfluorex versus metformine : les résultats montrent une diminution de 0.28 % de l'HbA1c (IC à 90 % : 0.07-0.48). La borne supérieure de cet intervalle est en-dessous de celle de 0.50 %, valeur fixée dans le protocole comme seuil de significativité d'un antidiabétique oral pour une étude d'équivalence.

- pour les **"cas-complets"**, une analyse de l'évolution des moyennes de l'HbA1c des groupes placebo et benfluorex à S0, S17 et S29 serait souhaitable.

***2. Commentaires concernant les RESULTATS de l'essai* (phase I + phase II).**

➪ *Rappel des principaux résultats :*

1. Efficacité du **benfluorex versus placebo** (6 mois de traitement par benfluorex)
   - réduction de l'HBA1c de **0.86 % (IC à 95 % : - 1,89 ; - 0.52)**,
   - réduction de la valeur moyenne de la glycémie de **- 1.33 mmol/l (IC à 95 % : -1.98 ;-0.77)**,
   - pas d'effet sur l'insulinémie, les triglycérides ou le HDL-cholestérol,
   - diminution très modérée mais *significative* du poids sous benfluorex (- 1.96 kg +/- 3.13).

2. Efficacité de **benfluorex versus metformine**.
   - HbA1c :différence de **0.28 %** (IC à 90 % : 0.07; 0.48), soit benfluorex : 7.05 % et metformine : 6.77 %
   - glycémie à jeun : différence de **0.6 mmol/l** (IC à 90 % : 0.66 ; 0.94), soit benfluorex : 8.80 mmol/L et benfluorex : 8.16 mmol/L

3. En terme de **tolérance** :
   - le nombre total de patients ayant présenté des effets indésirables est réparti de la façon suivante :

   * placebo : 20.8 %
   * benfluorex : 24.8 %
   * metformine : 26.4 %

   - quel que soit le type d'événements indésirables, il n'y a pas de différence significative entre benfluorex et metformine.

   Les effets indésirables les plus fréquents sont de type **gastro-intestinal** (benfluorex : 5.1 % ; metformine : 13.7 %), nausées, douleurs abdominales. Les autres effets sont de type asthénie, vertige, myalgies et lombalgies.
   - les effets *indésirables émergents sévères* attribués à benfluorex sont :
     * 1 cas de trouble de l'équilibre,
     * 1 cas de vertige,
     * 2 cas de diarrhées,
     * 1 cas de ballonnement intestinal.

➪ *Commentaires :*

1. La présentation des résultats est ambiguë et les groupes concernés ne sont pas toujours définis.
   Les résultats donnés sont variables selon les tableaux (ex. : données en ITT du groupe Benfluorex versus placebo et versus metformine sur HbA1c).

2. **Concernant l'HbA1c. Bien que l'éventail des valeurs d'HbA1c soit large,** la valeur moyenne des taux **d'HbA1c est peu élevée (7.48-7.79 %),** et n'est pas représentative d'une population de sujets diabétiques. Les patients inclus sont en moyenne peu sévèrement atteints.
   La distribution est-elle Gaussienne? Comment évolue l'efficacité du benfluorex en fonction du déséquilibre du diabète?

3. Les **arrêts de traitements par manque d'efficacité (glycémie > 2.5 g/l)** ont été de 10.4% dans le groupe placebo, 6.8 % dans le groupe benfluorex et de 1 % dans le groupe metformine.

4. La comparaison de l'efficacité du benfluorex versus metformine ne tient pas compte des doses des deux traitements, en particulier **les posologies réelles de metformine utilisées ne sont pas précisées** (posologie minimale, maximale et moyenne).

5. Enfin, il est noté que dans cette étude **aucun effet sur les lipides, en particulier sur les triglycérides n'est mis en évidence** alors que l'A.M.M actuelle précise qu'il s'agit d'un traitement "adjuvant adapté dans les hypertriglycéridémies".

CONCLUSIONS :

Cette étude met en évidence une *action significative et favorable du benfluorex versus placebo sur le contrôle de la glycémie* de sujets diabétiques de type II.

Toutefois, l'évaluation globale de l'efficacité du benfluorex dans l'indication du diabète de type 2 devra tenir compte des réponses aux questions et commentaires soulevées par l'analyse de cette étude, tant sur le plan méthodologique que sur l'interprétation des résultats de l'essai (notamment versus metformine).

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Enfin, il serait important de prendre connaissance des données récentes de l'enquête de pharmacovigilance.

AVIS DE LA COMMISSION N° 273 DU 2 OCTOBRE 1998 : SURSIS A STATUER en l'attente d'une réévaluation du dossier au plan méthodologique, notamment afin de situer l'efficacité du benfluorex vis à vis de la metformine.

N.B. :

1) l'efficacité du benfluorex versus placebo sur la réduction de l'HbA1c paraît établie. Elle est de faible amplitude : 0,9 % et porte sur des patients initialement peu sévèrement atteints (HbA1c de 7,5 à 7,8 %).
2) L'absence d'efficacité du benfluorex sur l'hypertriglycéridémie du diabète est à noter alors que l'hypertriglycéridémie est une des indications actuelles du produit.

Note interne d'évaluation :

Les questions nécessitant des réponses et un avis complémentaire sont :

1/ sur le plan méthodologique et de la qualité de l'essai :
- le choix de l'intervalle de confiance à 95% pour la comparaison versus placebo ; à 90% pour la comparaison versus metformine ;
- le maintien de l'aveugle pendant la durée de l'essai ;
- la qualité des inclusions (certains patients inclus avaient une HbA_{1C} dans les limites de la normale) ; les causes de sortie pour inefficacité : l'ajustement thérapeutique dans le groupe metformine.

2/ concernant l'efficacité
- l'efficacité du benfluorex dans la réduction de l'HbA_{1c} est faible ;
- l'indication éventuelle se discute si la non-infériorité vs metformine est démontrée :
  - pour un sous-groupe défini de patients diabétiques ; les limites de l'HbA_{1c} seraient à définir :
  - en première intention ;
  - l'efficacité serait à évaluer à 6 mois et le traitement est arrêté s'il n'apporte pas de bénéfice (i.e normalisation de l'HbA_{1c})

Enfin, le benfluorex n'a pas apporté de preuve de diminution de l'incidence des complications à long-terme du diabète.

Les données sont insuffisantes pour évaluer l'efficacité du benfluorex :
- dans les sous-groupes de patients qui ont un diabète plus sévère,
- en association avec d'autres thérapeutiques hypoglycémiantes
- en fonction du poids
- éventuellement chez les patients ayant une contre indication aux biguanides

enfin, l'absence d'effet sur les triglycérides est souligné.

3/ D'autre part, la tolérance du benfluorex est remise en question en raison de la notification récente d'une hypertension artérielle pulmonaire d'allure primitive chez une patiente de 51 ans traitée par benfluorex depuis 4 à 5 ans.

Le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen de pharmacovigilance (Italie et France, rapporteurs).

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Au total, une mise à jour des données de tolérance, des données de pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines ont été demandées à la firme.

AVIS DE LA COMMISSION N°289 DU 8 JUILLET 1999 : SURSIS A STATUER en l'attente

- des conclusions de l'inspection sur la qualité de l'essai ;
- de l'évaluation des données disponibles de pharmacovigilance.
- de l'avis de l'expert méthodologiste.

En tout état de cause le dossier actuel ne permettrait pas de donner l'indication "traitement du diabète de type II" en raison :
- de la faible efficacité hypoglycémiante observée,
- de l'absence de données suffisantes chez les diabétiques ayant une hémoglobine HbA1c élevée (supérieure à celle des patients de l'étude versée, soit en moyenne 7.48 - 7.79 %),
- de l'absence de données en association aux antidiabétiques,
- de l'absence de données à long terme ,
- de la difficulté de positionner le benfluorex dans la stratégie de prise en charge du diabète.

Des études chez les patients chez qui la metformine est contre-indiquée seraient utiles.

NOTE INTERNE D'ÉVALUATION :

• Au plan de la pharmacovigilance :

1 - Les notifications en France ont été de 350 effets indésirables (essentiellement, allergie-anaphylaxie, élévation des transaminases) ;

2 - 1 cas d'hypertension artérielle pulmonaire a été rapporté en France chez un patient traité uniquement par le Médiator ;

3 - Compte-tenu du métabolisme mal connu, des données complémentaires de pharmacocinétiques ont été demandées à la firme par la Commission Nationale de Pharmacovigilance ;

4 - les données à moyen et long terme (>6 mois) sont insuffisantes et nécessiterait également d'être complétées).

Néanmoins, le profil de tolérance est acceptable.

• Données d'inspection :

1 - Limites du protocole :

Le critère principal d'évaluation de l'efficacité était l'hémoglobine glyquée HbA1c. Les critères d'inclusion dans l'essai étaient une glycémie à jeun ≥ 1,40 g/l (7,8 mmol/l) et ≤ 2,50 g/l (13,9 mmol/l) à la visite d'inclusion (V0) *et/ou* une HbA1c ≥ 7,5 % et ≤ 10 % à la visite V-1. La présence d'une HbA1c élevée n'était donc pas un critère obligatoire pour l'inclusion. De ce fait, la valeur de base de l'HbA1c de **79** des 722 patients inclus dans l'essai était **inférieure ou égale** à **5,8 %**, valeur de référence du laboratoire ; **281 avaient une HbA1c inférieure à 7,5 %.**

2 - Résultats :

• *Limites de l'analyse des résultats :*

Ces limites ont été examinées principalement pour l'analyse d'efficacité entre les groupes benfluorex et metformine concernant le critère d'évaluation principal.
L'analyse statistique réalisée pour l'HbA1c a consisté principalement en une comparaison des moyennes des HbA1c à la dernière visite entre les différents groupes. Le rapport de l'essai et son annexe 16.4. (listing des analyses statistique) ne présentent pas clairement de comparaison statistique des groupes à l'inclusion pour ce paramètre ; les moyennes des HbA1c **à l'inclusion** dans la population ITT ayant au moins une valeur sous traitement présentent pourtant une **différence de 0,14 %** entre les groupes metformine (7,79 %) et benfluorex (7,65 %), en faveur du médicament à l'essai, alors que la limite d'équivalence thérapeutique était fixée à 0,50 %.

• *Erreur de calcul de l'HbA1c :*

L'HbA1c a été dosée par un **laboratoire centralisé**, l'Institut Pasteur de Lille, par chromatographie liquide haute performance par échange d'ions. L'inspection de ce laboratoire a montré que la **formule de calcul utilisée pour le dosage de l'HbA1c était erronée**. Au vu des résultats des deux séries de dosages examinées au cours de l'inspection, il semble que les résultats d'HbA1c calculés par le laboratoire soient légèrement surestimés pour les valeurs d'HbA1c inférieures à 8 % environ et sous-estimés pour les valeurs supérieures à 8 % environ.
Pour ces deux séries, l'écart entre la valeur calculée au cours de l'essai et la valeur réelle est cependant faible et ne dépasse pas 0,1 % d'HbA1c pour chaque patient.
Pour chaque patient, l'écart entre l'HbA1c à l'inclusion et à la dernière visite pourrait donc être sous-estimé au maximum de 0,2 %.
Cette erreur peut avoir des conséquences sur plusieurs points :

- inclusion à tort de patients : des patients ont pu être inclus à tort dans l'essai si leur glycémie était inférieure à 1,4 g/l (7,8 mmol/l) et si leur HbA1c a été calculée de manière erronée à 7,5 % au lieu de 7,4 %. Le nombre de patients concernés est cependant vraisemblablement faible ;

- comparaison benfluorex - placebo : la sous-estimation de la diminution de l'HbA1c sous benfluorex est en défaveur de ce médicament ;

- **comparaison benfluorex - metformine** : la diminution de l'HbA1c est plus importante sous metformine que sous benfluorex. La sous-estimation de cette diminution serait donc en faveur du benfluorex. L'erreur maximale réalisée pour chaque patient (0,2 % pour les deux séries de dosages examinées) est à rapprocher de la limite d'équivalence entre les traitements fixée par le protocole de l'essai (0,5 %).

• Au plan méthodologique :

En résumé, l'étude comprenait 3 groupes : placebo, traitement par Benfluàrex, traitement par Metformine.

1) Une première analyse d'efficacité du Benflurorex contre placebo a montré une différence significative en faveur du Benfluorex.

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2) analyse d'efficacité Benfluorex contre Metformine

Le type d'analyse choisi a été celui de la **non-infériorité**.
L'analyse en non-infériorité implique :
- le choix d'une zone d'équivalence ;
- la bonne qualité de l'étude (les écarts entrainant des biais vers la non-infériorité)
- une analyse perprotocole et en ITT

• concernant la zone d'équivalence : la borne supérieure choisie est de 50 % ; elle est acceptable mais correspond à la limite supérieure de la borne acceptable ;

• concernant la qualité de la réalisation de l'étude, différents commentaires peuvent être faits :
- inclusion : 722 patients ont été inclus (contre 500 prévus) ; 15,7 % sont des **déviations majeures** ; le dosage d'HbA_{1C} à S_{17} est connu pour 88.5 % des patients ; ce nombre n'est pas connu à S_{29} ni la répartition dans les 2 groupes de cet écart.

Il existe un **déséquilibre dans les taux d'HbA_{1C} à l'inclusion** : 7.5 % dans le groupe Benfluorex ; 7.9 % dans le groupe metformine.

• D'autre part, seuls **68 % des patients ont été inclus dans l'analyse per protocole**.
Résultats :

	Benfluorex	**Metformine**	IC 90 %	IC 95 %
HbA_{1C} (per protocole)	6.89 %	6.81 %		[0.12-0.29]
HbA_{1C} (ITT)	7.5 %	6.77 %	[0.07-0.48]	[0.04-0.52]
si l'analyse est réalisée avec la variation d'HbA_{1C} (ΔHbA_{1C}) :				
ΔHbA_{1C} per protocole			[0.20-0.66]	
ΔHbA_{1C} (ITT)			[0.21-0.61]	

Conclusions :
- l'étude ne conclut pas à la non infériorité du Benfluorex versus metformine ;
- le Benfluorex apparaît inférieur à la metformine.

D'autre part,
• l'analyse des profils de tolérance des deux produits n'a montré aucune différence significative entre les deux produits;
•enfin, aucun effet sur les triglycérides n'a été observé.

AVIS DE LA COMMISSION N° 296 DU 09 DECEMBRE 1999 :

AVIS DEFAVORABLE à l'indication proposée :

1 - au plan de l'efficacité :

➜ il est noté une efficacité du Benfluorex comparé au placebo. Néanmoins, il n'est pas possible d'évaluer sur la taille de l'effet compte tenu des défauts de qualité de l'étude.

➜l'essai clinique fourni ne permet pas de conclure à la non infériorité du Benfluorex comparé à la Metformine.

En effet, la réalisation de l'étude n'est pas satisfaisante au plan méthodologique :
- 79/722 patients avaient une HbA_{1C} inférieure à 5.8 % donc normale, et 281/722 avaient une HbA_{1C} inférieure à 7.5 % ;
- il existe un déséquilibre dans les taux d'HbA_{1C} à l'inclusion : 7.5 % dans le groupe Benfluorex ; 7.9 % dans le groupe Metformine.
- la qualité de l'essai est mauvaise:
  - à l' inclusion : 722 patients ont été inclus (contre 500 prévus) ; 15,7 % sont des déviations majeures ; le dosage d'HbA_{1C} à S_{17} est connu pour 88.5 % des patients ; ce nombre n'est pas connu à S_{29} ni la répartition dans les 2 groupes de cet écart.
  - il existe un déséquilibre des taux d'HbA_{1C} à l'inclusion : 7.5 % en moyenne dans le groupe Benfluorex contre 7.9 % dans le groupe Metformine.
- l'analyse per protocole n'a inclus que 68 % des patients ;
- enfin, les résultats sur l'HbA_{1C} en analyse per protocole et en ITT ne sont pas concordants. En effet en analyse per protocole, l'intervalle de confiance à 95% est de [0.12-0.29] et permettrait de conclure à une non infériorité alors que l'intervalle de confiance à 95% en analyse ITT est de [0.04-0.52], la borne supérieure de l'intervalle de confiance dépassant la limite retenue de 0.50.

2 - au plan de la tolérance, l'analyse des profils de tolérance n'a pas montré pas de différence significative avec la Metformine.

3 - d'autre part, aucune efficacité sur les triglycérides n'a été montrée.

4 - les données cliniques sont insuffisantes pour :
- placer le benfluorex dans la stratégie thérapeutique du diabète de type 2 ;
- évaluer l'efficacité du benfluorex en association avec d'autres antidiabétiques oraux ;
- indiquer le benfluorex chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisant rénale, sujet âgé...).

Demande de recours grâcieux:

Suite à l'avis défavorable émis par la Commission d'AMM le 9 décembre 1999 concernant l'indication suivante :

"diabète de type 2 (non-insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique",

la firme dépose les éléments suivants:

1/ des analyses complémentaires en sous-groupes des données de l'étude de phase III de *"l'efficacité du Benfluorex (150 à 450 mg/jour) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul"*. A noter, ces analyses complémentaires ont été présentées lors d'une réunion à l'Agence le 14 mars 2000.

Le dossier comporte par ailleurs:

2/ une revue de la littérature sur les activités pharmacologiques de Médiator chez l'animal.

Annexe 2-43

3/ une revue de l'efficacité de Médiator à différents stades de la maladie.
Un programme d'études a été mis en place pour étudier le mécanisme d'action chez l'homme. Les populations suivantes ont été étudiées :

=> *patients insuffisamment contrôlés par régime seul* (Velussi et col., 196): comparaison de Médiator au placebo en monothérapie.

=> *patients insuffisamment contrôlés par un sulfonylurée en monothérapie* (2 études: Stucci et col., 1996, Louvet, rapport interne, 1995): comparaison de Médiator à un placebo en association à une traitement par sulfonylurée à dose maintenue constante pendant l'étude.

=> *patients insuffisamment contrôlés par une insulinothérapie* (2 études: Bianchi et col., 1996; Pontiroli et col., 1996): comparaison de Médiator à un traitement par placebo en association à l'insuine à dose maximale maintenue constante pendant la durée du traitement en double aveugle. Dans l'étude de Pontiroli, les patients étaient soumis à un régime à très basse calorie (800 Kcal /jour pendant la période de pré-inclusion et 1000 Kcal / jour pendant la période de traitement en double aveugle.

=> *patients insuffisamment contrôlés par metformine en monothérapie* (Pr Roger): comparaison de Médiator à un placebo en association à la metformine à dose maintenue constante pendant l'étude, après une période de pré-inclusion de 2 mois sous metformine seule.

=> *patients insulinorequérants* (Pr Leutenegger): comparaison de Médiator au placebo en association à l'insuline, dont la dose pouvait être modifiée au cours de l'étude.

NB. En parallèle, une demande de modification de l'information médicale concernant les effets cutanés et/ou allergiques (rubriques "*Contre-indications*" et "*Effets indésirables*") est examinée par l'Unité de Pharmacovigilance de l'Agence.

NOTE INTERNE D'ÉVALUATION :

- concernant le **mode d'action** du benfluorex,
  * les études de la sensibilité à l'insuline ne mettent pas toutes en évidence une augmentation de la sensibilité à l'insuline;
  * une augmentation de l'utilisation périphérique de glucose a été montrée dans 3 études utilisant des techniques de clamp euglycémique : R. Binachi, 1993; P. De Feo, 1993; et A. Ricchio, 1993)
  * études relatives à la production hépatique de glucose: les résultats sont contradictoires. Etude de De Feo: diminution de la production hépatique de glucose, non démontrée dans l'étude de Ricchio.
  * étude de la consommation périphérique de glucose sous benfluorex (Bianchi) non démontrée.

- concernant **l'efficacité du benfluorex à différents stades de la maladie**. Ces études ont permis d'explorer l'efficacité anti-diabétiques de Médiator, en monothérapie (Velussi) et en association, respectivement aux sulfonylurées (Stucci et Louvet), à la metformine (Roger), et à l'insuline (Bianchi, Leutenegegr et Pontiroli). L'étude du Pr Roger a été menée chez des médecins généralistes, celle de Leutenegger dans 7 centres hospitaliers français.
A noter, ces études ont toutes été réalisées selon le même schéma: études monocentriques en double aveugle, comparant Médiator à une placebo en groupes parallèles, pour une durée de traitement de trois mois.

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Remarques:
* la comparaison entre benfluorex et placebo est en faveur d'un effet positif mais modéré du produit.
* cependant, la taille réduite des effectifs est faible dans chaque étude, soit de 20 à 60 patients.
* dans les études multicentriques (Leutenegger), le dosage des paramètres principaux d'évaluation (glycémie à jeun et HbA1c) n'a pas été centralisé.
* aucune analyse de la perte de poids n'a été réalisée dans ces études. Il serait en effet intéressant de savoir si l'effet du Médiator n'est pas uniquement lié à son effet sur le poids (cf. études de pharmacologie et rapprochement avec les effets anorexigènes).
* l'étude réalisée chez les médecins généralistes (Roger) montre un effet significatif sur la glycémie à jeun; celle réalisée en milieu hospitalier (Leutenegger) ne montre pas d'effet sur l'HbA1c.
Au total, compte-tenu des critiques méthodologiques de ces études (défaut de centralisation des dosages), leur validité pour une demande d'AMM reste insuffisante.

- concernant les **analyses complémentaires en sous-groupes** de l'étude ce *"l'efficacité du Benfluorex (150 à 450 mg/jour) par voie orale chez 500 patients diabétiques de type 2 mal contrôlés par le régime seul"*.
Les principales critiques formulées lors de la 1ère analyse restent identiques:
* analyse effectuée chez 722 patients inclus contre 500 initialement prévus dans le protocole. Aucune présentation des résultats sur les 500 patients prévus n'a été effectuée par la firme.

* déséquilibre du taux d'HbA1c à l'inclusion, plus basse dans le groupe Benfluorex que dans le groupe metformine;
* il apparaît que 25 % des patients étaient des inclus à tort, avec un taux d'HbA1c normal (< 6.5%);
* l'analyse *per-protocol* n'inclut que 68 % des patients. Aucune explication n'est donnée sur les patients exclus de cette analyse;
* les doses maximales de metformine réellement reçues n'ont pas été précisées, les patients pouvant recevoir de 820 mg à 2250 mg. Il est donc pas possible de savoir si le Médiator a été comparé à des doses maximales de metformine et de connaître réellement son efficacité par rapport à ce traitement de référence.
* enfin, les critères utilisés en ITT et en analyse *per protocol* ne sont pas concordants: utilisation d'un IC à 95% dans l'étude versus placebo et à 90% versus metformine.

AVIS DU GT PTC2 N°1 DU 20 SEPTEMBRE 2000:

- Maintien de **l'AVIS DEFAVORABLE** à l 'indication proposée par la firme: 11/12/00 . *"diabète de type 2 (non-insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique"*.
En effet, compte-tenu des défauts méthodologiques de l'essai, aucune conclusion ne peut être formulée sur la taille de l'effet hypoglycémiant :
- du benfluorex comparé au placebo ;
- du benfluorex comparé à la metformine.
De plus le dossier ne permet pas de situer le benfluorex dans la stratégie de prise en charge des patients diabétiques.

En conséquence, le libellé de l'indication thérapeutique (rubrique 4.1. Indications thérapeutiques) retenu est le suivant:
"- adjuvant du régime adapté dans les hypertriglycéridémies;
- adjuvant du régime chez les diabétiques avec surcharge pondérale.
Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée."

L'information de l'ensemble des rubriques du RCP sera revue en fonction du nouveau libellé.

Enfin, en vue de l'obtention d'une indication dans le diabète de type 2, la firme devrait fournir des études évaluant l'efficacité du benfluorex en monothérapie et en association avec d'autres antidiabétiques oraux. L'efficacité devrait également être étudiée chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisant rénaux, sujets âgés).

RÉPUBLIQUE FRANÇAISE

AGENCE
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ
Direction de l'Evaluation des médicaments et des produits biologiques

Saint-Denis, le

11 DEC. 2000

Monsieur le Pharmacien Responsable
Laboratoires SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE CEDEX

Réf. à rappeler : VNL 10008
GTPTC2-1
CRQ/MG

Monsieur,

Par courrier du 29 mai 1998, concernant la spécialité :

MEDIATOR 150 mg, comprimé

vous avez sollicité une demande de modification d'indication au *"Diabète de type II (non insulino-dépendant), en association au régime adapté, lorsque ce régime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique".*

Une décision de refus à cette modification de l'autorisation de mise sur le marché vous a été notifiée le 25 avril 2000 pour insuffisance de données d'efficacité. Cette décision fait suite à l'avis défavorable rendu par la Commission mentionnée à l'article R. 5140 du code de la santé publique, en date du 27 janvier 2000.

Par courrier du 29 juin 2000, vous avez déposé un recours gracieux, suite à la décision défavorable sus-mentionnée, en apportant point par point les réponses aux objections émises par la Commission.

J'ai l'honneur de vous faire connaître qu'après avis de la Commission sus-citée, **je ne suis toujours pas en mesure de réserver une suite favorable** à votre demande d'extension d'indication pour insuffisance de données d'efficacité.

En effet, compte-tenu des défauts méthodologiques de l'essai, aucune conclusion ne peut être formulée sur la taille de l'effet hypoglycémiant :
- du benfluorex comparé au placebo ;
- du benfluorex comparé à la metformine.

Concernant les analyses complémentaires en sous-groupes de l'étude de *phase III "l'efficacité du Benfluorex (150 à 450 mg/jour) par voie orale chez 500 patients*

143/147 Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

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diabétiques de type 2 mal contrôlés par le régime seul", les principales critiques formulées lors de la première analyse restent identiques :

* l'analyse a été effectuée chez 722 patients inclus contre 500 initialement prévus dans le protocole. Aucune présentation des résultats sur les 500 patients prévus n'a été effectuée ;

* il y a un déséquilibre du taux d'HbA1c à l'inclusion, plus basse dans le groupe benfluorex que dans le groupe metformine ;

* il apparaît que 25 % des patients étaient des inclus à tort, avec un taux d'HbA1c normal (< 6.5%) ;

* l'analyse *per-protocol* n'inclut que 68 % des patients. Aucune explication n'est donnée sur les patients exclus de cette analyse ;

* les doses maximales de metformine réellement reçues n'ont pas été précisées, les patients pouvant recevoir de 820 mg à 2250 mg. Il est donc pas possible de savoir si le MEDIATOR a été comparé à des doses maximales de metformine et de connaître réellement son efficacité par rapport à ce traitement de référence ;

* enfin, les critères utilisés en intention de traiter et en analyse *per protocol* ne sont pas concordants: utilisation d'un intervalle de confiance à 95% dans l'étude versus placebo et à 90% dans l'étude versus metformine.

De plus le dossier ne permet pas de situer le benfluorex dans la stratégie de prise en charge des patients diabétiques.

En vue de l'obtention d'une indication dans le diabète de type 2, des études évaluant l'efficacité du benfluorex en monothérapie et en association avec d'autres antidiabétiques oraux devraient être fournies. L'efficacité devrait également être étudiée chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisant rénaux, sujets âgés).

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation
Par empêchement du Directeur de l'Évaluation des
Médicaments et des Produits Biologiques
l'Adjoint au Directeur Chargé des Affaires Médicales

Dr François MEYER

A G E-N C E
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

RÉPUBLIQUE FRANÇAISE

12 JUIN 2001

Direction de l'Evaluation des
Médicaments et des
Produits Biologiques

SAINT DENIS, le

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
Les Laboratoires SERVIER
22 rue Garnier
92200 NEUILLY SUR SEINE
Cedex

Dossier suivi par : Madame le Dr. Catherine REY QUINIO
Madame Florence MONTANIER

Réf. à rappeler : VNL10008
GT PTC2 N°1 - COM 311
CRQ/FMM/DN

Monsieur,

J'ai l'honneur de vous faire parvenir, ci-joint, l'ampliation de la décision portant modification de l'autorisation de mise sur le marché du médicament :

- MEDIATOR 150 mg, comprimé enrobé

que vous avez sollicité le 9 juin 1998.

Je vous informe que le pictogramme mentionné à l'avant dernier alinéa de l'article R 5143 du code de la santé publique tel qu'issu du décret N°99-338 du 3 mai 1999 doit être apposé sur le conditionnement extérieur de votre spécialité, celle-ci ayant des effets sur la capacité de conduire des véhicules ou d'utiliser des machines mentionnés dans la rubrique du résumé des caractéristiques du produit prévue à cet effet.

Le modèle de pictogramme devant être utilisé et libre de droit, est disponible sur le site internet de l'Agence Française de Sécurité Sanitaire des Produits de Santé: http://agprod.sante.fr.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation
Par empêchement du Directeur de l'Évaluation
des Médicaments et des Produits Biologiques
L'Adjointe au Directeur Chargée des Affaires Réglementaires
Fabienne [illegible]

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AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

DIRECTION DE L'EVALUATION DES MEDICAMENTS ET DES PRODUITS BIOLOGIQUES

Références à rappeler : VNL10008
GT PTC2 N°1 - COM 311
CRQ/FMM/DN

DÉCISION DU DIRECTEUR GÉNÉRAL DE L'AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

du .....

portant modification
de l'autorisation de mise sur le marché du médicament

MEDIATOR 150 mg, comprimé enrobé

VU le livre V du code de la santé publique, notamment les articles L.601 et R.5128 à R.5140 et R.5143-5-1 à R.5143-5-5 ;

VU l'autorisation de mise sur le marché validée octroyée le **22 avril 1987** ;

Vu la demande de modification de l'autorisation de mise sur le marché présentée par LES LABORATOIRES SERVIER ;

le 9 juin 1998 ;

pour le médicament :

MEDIATOR 150 mg, comprimé enrobé

et concernant dans :

- les rubriques de l'annexe I (résumé des caractéristiques du produit)
  4.1 Indications thérapeutiques
  4.6. Grossesse et allaitement

Les annexes I (RCP), IIIA (Etyiquetage) et IIIB (Notice) sont modifiées en conséquence ;

Vu la décision de refus de modification notifiée le 25 avril 2000 ;

Vu la demande de recours gracieux en date du 29 juin 2000, suite à l'avis défavorable sus-cité ;

Annexe 2-45

VU l'avis de la commission prévu à l'article R. 5140 du code de la santé publique ;

DÉCIDE

Article 1er

La demande de modification du dossier d'autorisation de mise sur le marché est acceptée et les annexes I, II, III_A, et III_B de la présente décision remplacent les dispositions prévues par les annexes I, II et III de l'Autorisation de Mise sur le Marché susvisée modifiée.

Article 2

Les Laboratoires SERVIER
22 rue Garnier
92200 NEUILLY SUR SEINE Cedex
sont destinataires de la présente décision.

FAIT A SAINT DENIS, le 12 JUIN 2001

LE DIRECTEUR GENERAL DE L'AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Pour ampliation
L'Adjointe au Directeur de l'Évaluation
des Médicaments et des Produits Biologiques

France ROUSSELLE

Pour le Directeur Général
et par délégation
Pour empêchement du Directeur de l'Évaluation
des Médicaments et des Produits Biologiques
Adjoint au Directeur Chargée des Affaires Réglementaires
[illegible]

Pièces Jointes : 4 annexes

Annexe 2-45

ANNEXE I

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION

12 JUIN 2001

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé de 700 mg

Pour les excipients, voir rubrique 6.1..

3. FORME PHARMACEUTIQUE

Comprimé enrobé

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

- Adjuvant du régime adapté dans les hypertriglycéridémies;
- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque : L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

4.2 Posologie et mode d'administration

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:
- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.

En association à un régime adapté, Médiator constitue un traitement *adjuvant* : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

4.3 Contre-indications

- Hypersensibilité au chlorydrate de benfluorex ou à l'un des constituants ;
- Pancréatites chroniques avérées.

4.4 Mises en garde et précautions particulières d'emploi

Les troubles métaboliques relevant d'un traitement par Médiator sont essentiellement observés chez l'adulte. La prescription de Médiator n'est donc pas justifiée chez l'enfant.

Si, après une période d'administration de quelques mois (3 à 6 mois), une diminution satisfaisante de concentrations sériques de lipides ou de glucose n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase.

4.5 Interactions avec d'autres médicaments et autres formes d'interactions

4.6 Grossesse et allaitement

Grossesse:
Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.
En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.
En conséquence, par mesure de prudence, il est préférable de ne pas utiliser ce médicament pendant la grossesse. En cas d'exposition fortuite, il conviendra d'interrompre ce traitement.

Allaitement
En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement.

4.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

L'attention des conducteurs est attirée sur la somnolence pouvant survenir lors de l'utilisation de ce médicament.

Annexe 2-45

4.8 Effets indésirables

Les effets secondaires suivants ont été observés :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée) ;
- asthénie ;
- somnolence ;
- état vertigineux.

Toutefois, ces effets s'observent plus particulièrement à des posologies élevées. Une susceptibilité individuelle a également été observée.

4.9 Surdosage

En cas d'absorption massive, le traitement sera uniquement symptomatique: lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience ainsi que des fonctions respiratoire et cardiaque.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

HYPOCHOLESTROLEMIANT ET HYPOTRIGLYCERIDEMIANT
Code ATC : C10AX04

Actions de Médiator sur le métabolisme lipidique:
Chez l'animal (rat), Médiator diminue l'absorption intestinale des triglycérides.
Cet effet a été également observé chez l'homme en pharmacologie clinique et serait dû à une diminution de l'activité de la lipase pancréatique.

Les effets suivants ont été également observés chez l'animal:
- diminution de la synthèse hépatique des triglycérides et du cholestérol, *in vitro* et *in vivo* (rat);
- diminution de la stéatose hépatique induite par des régimes riches en lipides, riches en glucides (rat obèse) ainsi qu'au cours du diabète expérimental (rat);
- limitation de l'incorporation du cholestérol dans la paroi artérielle (lapin).

Ces différents mécanismes pourraient expliquer en partie la diminution du cholestérol et des triglycérides observée chez l'homme.

Actions de Médiator sur le métabolisme glucidique:
Chez l'animal, les effets suivants ont été observés:
- facilitation de la pénétration et de l'utilisation cellulaire du glucose (rat);
- diminution de l'hyperglycémie chez le rat diabétique (insulinoprive ou non), diminution de l'hyperglycémie (mesurée par l'aire d'HPO) chez le lapin.

Médiator n'a pas d'action sur l'insulino-sécrétion; la survenue d'hypoglycémie est peu probable.

Effet complémentaire de Médiator:
Une baisse de l'uricémie d'environ 14 % a été observée chez des patients obèses hyperuricémiques traités par Médiator en association à un régime adapté.

Annexe 2-45

7

5.2 Propriétés pharmacocinétiques

L'absorption gastro-intestinale est rapide et totale.
Après administration orale, le pic de concentration plasmatique est maximal entre 1 et 2 heures.

L'élimination est rapide et totale par voie urinaire. Huit heures après l'absorption, 74 % de la dose administrée est éliminée dans les urines.

L'élimination se fait en 2 phases :
- une première phase rapide (60 % en 3 ou 4 heures);
- une seconde phase lente, de 36 heures environ.

5.3 Données de sécurité précliniques

Sans objet.

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane (E 171), éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

6.2. Incompatibilités

Sans objet.

6.3. Durée de conservation

3 ans

6.4. Précautions particulières de conservation

Pas de précautions particulières de conservation.

6.5. Nature et contenu de l'emballage extérieur

Plaquettes thermoformées (PVC-Aluminium)

6.6. Instructions pour l'utilisation et la manipulation

(Cf. 4.2.Posologie et mode d'administration)

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE Cedex

Annexe 2-45

8. PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE

317 553-3 :10 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 555-6 : 20 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 556-2 : 24 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 557-9 : 30 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 558-5 : 60 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 559-1 : 100 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

10. DATE DE MISE A JOUR DU TEXTE

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste I

ANNEXE II

A- TITULAIRE DE L'AUTORISATION(S) DE FABRICATION RESPONSABLE DE LA LIBERATION DES LOTS ET NOM ET ADRESSE DU PRODUCTEUR DE SUBSTANCE ACTIVE BIOLOGIQUE

LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

B- CONDITIONS LIEES A L'AUTORISATION DE MISE SUR LE MARCHE

CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I

AUTRES CONDITIONS

Sans objet.

C- ENGAGEMENTS DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

Sans objet.

Annexe 2-45

ANNEXE IIIA
ETIQUETAGE

MENTIONS DEVANT FIGURER SUR L'EMBALLAGE EXTÉRIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTÉRIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION EN SUBSTANCES ACTIVES

Chlorhydrate de benfluorex ..... 150,00 mg

pour un comprimé enrobé

3. LISTE DES EXCIPIENTS

Excipient à effet notoire : saccharose

4. FORME PHARMACEUTIQUE ET CONTENU

Comprimé enrobé.
Boîte de 10, 20, 24, 30, 60 et 100 comprimés.

5. MODE ET VOIE(S) D'ADMINISTRATION, SI NÉCESSAIRE

Voie orale.

6. MISE EN GARDE SPÉCIALE INDIQUANT QUE LE MÉDICAMENT DOIT ÊTRE CONSERVÉ HORS DE PORTÉE ET DE VUE DES ENFANTS

Ne laisser ni à la portée, ni à la vue des enfants.

7. AUTRE(S) MISE(S) EN GARDE SPÉCIALE(S)

Lire attentivement la notice avant utilisation.

8. DATE DE PÉREMPTION

9. PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

Pas de précautions particulières de conservation.

10. PRÉCAUTIONS PARTICULIÈRES D'ÉLIMINATION DES MÉDICAMENTS NON UTILISÉS OU DES DÉCHETS PROVENANT DE CES MÉDICAMENTS S'IL Y A LIEU

Sans objet

11. NOM ET ADRESSE DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

Titulaire/Exploitant :
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Fabricant :
LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

12. NUMÉRO D'IDENTIFICATION ADMINISTRATIVE

13. NUMÉRO DU LOT DE FABRICATION

14. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I

15. INDICATIONS THÉRAPEUTIQUES

Sans objet

PICTOGRAMME DEVANT FIGURER SUR L'EMBALLAGE EXTERIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTERIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

Le pictogramme doit être conforme à l'arrêté du 3 mai 1999 pris en application de l'article R 5143 du code de la santé publique et relatif à l'apposition d'un pictogramme. Celui-ci précise que le pictogramme a la forme d'un triangle équilatéral rouge sur fond blanc dans lequel se trouve une voiture noire. Ses dimensions sont adaptées à la taille du conditionnement extérieur.

MENTIONS DEVANT FIGURER À TITRE MINIMAL SUR LES PLAQUETTES THERMOFORMEES OU LES FILMS THERMOSOUDEES

1. **DÉNOMINATION DU MÉDICAMENT**

MEDIATOR 150 mg, comprimé enrobé

2. **NOM DU TITULAIRE DE L'A.M.M**

Les Laboratoires SERVIER

3. **DATE DE PÉREMPTION**

4. **NUMÉRO DE LOT**

ANNEXE III B

NOTICE

Lisez attentivement l'intégralité de cette notice avant de prendre ce médicament.
Elle contient des informations importantes sur votre traitement.
Si vous avez d'autres questions, si vous avez un doute, demandez plus d'informations à votre médecin ou à votre pharmacien.
Ce médicament vous a été personnellement prescrit. Ne le donnez jamais à quelqu'un d'autre, même en cas de symptômes identiques, car cela pourrait lui être nocif.
Gardez cette notice, vous pourriez avoir besoin de la relire.

MEDIATOR 150 mg, comprimé enrobé

La substance active est :

Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé

Les autres composants sont : amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane (E 171), éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

Titulaire/Exploitant :
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Fabricant :
LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

1. QU'EST-CE QUE MEDIATOR 150 mg, comprimé enrobé ET DANS QUEL CAS EST-IL UTILISÉ ?

MEDIATOR 150 mg, comprimé enrobé contient du chlorhydrate de benfluorex.
MEDIATOR 150 mg se présente sous la forme de comprimés enrobés.
Boîtes de 10, 20, 24, 30, 60 et 100 comprimés.

Ce traitement est en préconisé comme adjuvant à un régime adapté :
- dans les hypertriglycéridémies *(taux de lipides élevés dans le sang)* ;
- chez les diabétiques avec surcharge pondérale *(taux de sucre élevé dans le sang)*.

2. INFORMATIONS NÉCESSAIRES AVANT D'UTILISER MEDIATOR 150 mg, comprimé enrobé

MEDIATOR 150 mg, comprimé enrobé NE DOIT JAMAIS ETRE UTILISE dans les cas suivants :
- allergie au chlorhydrate de benfluorex ou à l'un des composants du produit;
- en cas de pancréatite chronique *(insuffisance du pancréas)*.

MISES en GARDE et PRECAUTIONS PARTICULIERES D'EMPLOI avec MEDIATOR 150 mg, comprimé enrobé:

Un régime alimentaire adapté doit être poursuivi pendant toute la durée du traitement.

Si après une période de plusieurs mois (3 à 6 mois), une diminution des concentrations de lipides ou de glucose (sucre) dans le sang n'est pas obtenue, votre médecin pourra envisager d'autres moyens thérapeutiques adaptés à votre cas.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase *(maladies métaboliques rares)*.

Grossesse/Allaitement:
Il est préférable de ne pas utiliser ce médicament pendant la grossesse ou au cours de l'allaitement.
Si vous découvrez que vous êtes enceinte pendant le traitement, consultez votre médecin car lui seul peut juger de la nécessité de le poursuivre.

Conduite de véhicules et utilisation de machines:
L'attention est attirée sur le risque de somnolence pouvant survenir avec ce médicament.

Sportifs:
Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

Liste des excipients à effet notoire:
Saccharose.

Prise ou utilisation d'autres médicaments:
Sans objet.

3. COMMENT PRENDRE MEDIATOR 150 mg, comprimé enrobé ?

Posologie:
RESERVE A L'ADULTE

Voie orale.
La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:
- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

La posologie peut-être ramenée à 2 comprimés par jour, voire 1 comprimé par jour, en fonction des résultats biologiques.

DANS TOUS LES CAS, SE CONFORMER STRICTEMENT A L'ORDONNANCE DE VOTRE MEDECIN.

Si vous avez pris plus de MEDIATOR 150 mg, comprimé enrobé que vous n'auriez dû:
Les signes de surdosage peuvent être des troubles digestifs (nausées, vomissements, diarrhée), une sensation vertigineuse voire une somnolence. En cas d'apparition de ces troubles, consultez votre médecin ou votre pharmacien.

Si vous oubliez de prendre MEDIATOR 150 mg, comprimé enrobé:
Ne prenez pas de double dose pour compenser la dose simple que vous avez oubliée de prendre.

Effets pouvant apparaître lorsque le traitement par MEDIATOR 150 mg, comprimé enrobé est arrêté :
Sans objet.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS avec MEDIATOR 150 mg, comprimé enrobé ?

Comme tous les médicaments, MEDIATOR 150 mg, comprimé enrobé est susceptible d'avoir des effets indésirables :

- troubles digestifs: nausées, vomissements, diarrhée, maux d'estomac ;
- sensation de fatigue, voire somnolence;
- sensations vertigineuses.

Ces effets ont été observés à des posologies élevées.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

5. COMMENT CONSERVER MEDIATOR 150 mg, comprimé enrobé ?

Pas de précautions particulières de conservation.

Ne laisser ni à la portée ni à la vue des enfants.

Ne pas utiliser après la date de péremption figurant sur la boîte.

La dernière date à laquelle cette notice a été approuvée est le (date).

ANNEXE I

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé de 700 mg

Pour les excipients, voir rubrique 6.1..

3. FORME PHARMACEUTIQUE

Comprimé enrobé

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

- Adjuvant du régime adapté dans les hypertriglycéridémies;
- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque : L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

4.2 Posologie et mode d'administration

Voie orale.

habituellement (Cohérence avec la description du schéma posologique ci-dessous).

La posologie est ~~en moyenne~~ de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:
- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.

(Conformité au libellé d'indications thérapeutiques)

En association à un régime adapté, Médiator ~~ne~~ constitue ~~qu'~~un traitement *adjuvant*; une surveillance régulière clinique et biologique de chaque patient sera instaurée.

4.3 Contre-indications

- Hypersensibilité au chlorydrate de benfluorex ou à l'un des constituants ;
- Pancréatites chroniques avérées.

Annexe 2-46

× Cohérence avec le libellé de la rubrique "Indications thérapeutiques" et celui de la rubrique "Posologie et mode d'administration".

22-12-2010
Projet de rectificatif d'AMM
envoyé à la firme
et retourné avec annotations
des Affaires réglementaires (Seven)
en charge de ce dossier.
C REY-QUINIO

× Grossesse :
- Cohérence avec la première phrase introductive :
"Ce médicament <u>ne doit pas être utilisé</u> pendant la grossesse et l'allaitement"
- l'allusion à des propriétés amphétaminiques ne se justifie pas :
  - propriétés non retrouvées avec Benfluorex,
  - classification ATC différente de Benfluorex,
  - ne correspond pas à la réalité clinique,
  - pourrait, en outre, susciter des déviations d'usage.

4.4 Mises en garde et précautions particulières d'emploi

Les troubles métaboliques relevant d'un traitement par Médiator sont essentiellement observés chez l'adulte. La prescription de Médiator n'est donc pas justifiée chez l'enfant.

Si, après une période d'administration de quelques mois (3 à 6 mois), une diminution satisfaisante de concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

ou de glucose OK

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase.

4.5 Interactions avec d'autres médicaments et autres formes d'interactions

4.6 Grossesse et allaitement

~~Ce médicament ne doit pas être utilisé pendant la grossesse et l'allaitement.~~

Grossesse:
Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.
En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.

PROJET

En cas d'exposition fortuite, il conviendra d'interrompre ce traitement ~~dont la prescription du fait des propriétés amphétaminiques est déconseillée au cours de la grossesse~~.

ajout ↓
(1) En conseq, par mesure de prudence, il est préf de ne pas utiliser ce medic pdt la grossesse OK

Allaitement
En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement.

4.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

L'attention des conducteurs est attirée sur la somnolence pouvant survenir lors de l'utilisation de ce médicament.

4.8 Effets indésirables

Les effets secondaires suivants ont été observés :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée) ;
- asthénie ;
- somnolence ;

Annexe 2-46

Non
Le résumé d'avis ne mentionne
pas cela en conclusion
L'étude ne permet pas de conclure

non

x Chez le diabétique avec surcharge pondérale, en association à un régime adapté, on observe une baisse de l'hémoglobine glyquée supérieure à celle que l'on obtient avec un régime identique associé à un placebo.

(cf: décision de l'AFSSAPS du 25 avril 2000)

- état vertigineux.

X Toutefois, ces effets s'observent plus particulièrement à ~~la posologie de 3 comprimés par jour~~ des posologies élevées. Une susceptibilité individuelle a également été observée. OK

4.9 Surdosage

En cas d'absorption massive, le traitement sera uniquement symptomatique: lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience ainsi que des fonctions respiratoire et cardiaque.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

Actions de Médiator sur le métabolisme lipidique:
Chez l'animal (rat), Médiator diminue l'absorption intestinale des triglycérides.
Cet effet a été également observé chez l'homme en pharmacologie clinique et serait dû à une diminution de l'activité de la lipase pancréatique.

Les effets suivants ont été également observés chez l'animal:
- diminution de la synthèse hépatique des triglycérides et du cholestérol, *in vitro* et *in vivo* (rat);
- diminution de la stéatose hépatique induite par des régimes riches en lipides, riches en glucides (rat obèse) ainsi qu'au cours du diabète expérimental (rat);
- limitation de l'incorporation du cholestérol dans la paroi artérielle (lapin).
Ces différents mécanismes pourraient expliquer en partie la diminution du cholestérol et des triglycérides observée chez l'homme.

Actions de Médiator sur le métabolisme glucidique:
Chez l'animal, les effets suivants ont été observés:
- facilitation de la pénétration et de l'utilisation cellulaire du glucose (rat);
- diminution de l'hyperglycémie chez le rat diabétique (insulinoprive ou non), diminution de l'hyperglycémie (mesurée par l'aire d'HPO) chez le lapin.

X ← Médiator n'a pas d'action sur l'insulino-sécrétion; la survenue d'hypoglycémie est peu probable.

Effet complémentaire de Médiator:
Une baisse de l'uricémie d'environ 14 % a été observée chez des patients obèses hyperuricémiques traités par Médiator en association à un régime adapté.

5.2 Propriétés pharmacocinétiques

L'absorption gastro-intestinale est rapide et totale.
Après administration orale, le pic de concentration plasmatique est maximal entre 1 et 2 heures.

L'élimination est rapide et totale par voie urinaire. Huit heures après l'absorption, 74 % de la dose administrée est éliminée dans les urines.

L'élimination se fait en 2 phases :
- une première phase rapide (60 % en 3 ou 4 heures);
- une seconde phase lente, de 36 heures environ.

5.3 Données de sécurité précliniques

Sans objet.

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane, éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

6.2. Incompatibilités

Sans objet.

6.3. Durée de conservation

3 ans

6.4. Précautions particulières de conservation

6.5. Nature et contenu de l'emballage extérieur

Plaquettes thermoformées (PVC-Aluminium)

6.6. Instructions pour l'utilisation et la manipulation

(Cf. 4.2.Posologie et mode d'administration)

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

8. PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE

317 553-3 :10 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 555-6 : 20 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 556-2 : 24 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 557-9 : 30 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 558-5 : 60 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 559-1 : 100 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

10. DATE DE MISE A JOUR DU TEXTE

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

PROJET

Liste I

ANNEXE II

A- TITULAIRE DE L'AUTORISATION(S) DE FABRICATION RESPONSABLE DE LA LIBERATION DES LOTS ET NOM ET ADRESSE DU PRODUCTEUR DE SUBSTANCE ACTIVE BIOLOGIQUE

LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

B- CONDITIONS LIEES A L'AUTORISATION DE MISE SUR LE MARCHE

CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I

AUTRES CONDITIONS

Sans objet.

PROJET

C- ENGAGEMENTS DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

Sans objet.

ANNEXE IIIA
ETIQUETAGE

MENTIONS DEVANT FIGURER SUR L'EMBALLAGE EXTÉRIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTÉRIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION EN SUBSTANCES ACTIVES

Chlorydrate de benfluorex ..... 150,00 mg

pour un comprimé enrobé

3. LISTE DES EXCIPIENTS

Excipient à effet notoire : saccharose

4. FORME PHARMACEUTIQUE ET CONTENU

Comprimé enrobé.
Boîte de 10, 20, 24, 30, 60 et 100 comprimés.

PROJET

5. MODE ET VOIE(S) D'ADMINISTRATION, SI NÉCESSAIRE

Voie orale.

6. MISE EN GARDE SPÉCIALE INDIQUANT QUE LE MÉDICAMENT DOIT ÊTRE CONSERVÉ HORS DE PORTÉE ET DE VUE DES ENFANTS

Ne laisser ni à la portée, ni à la vue des enfants.

7. AUTRE(S) MISE(S) EN GARDE SPÉCIALE(S)

Lire attentivement la notice avant utilisation.

8. DATE DE PÉREMPTION

9. PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

10. PRÉCAUTIONS PARTICULIÈRES D'ÉLIMINATION DES MÉDICAMENTS NON UTILISÉS OU DES DÉCHETS PROVENANT DE CES MÉDICAMENTS S'IL Y A LIEU

Sans objet

11. NOM ET ADRESSE DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

Titulaire/Exploitant :
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Fabricant :
LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

12. NUMÉRO D'IDENTIFICATION ADMINISTRATIVE

317 553-3
317 555-6
317 556-2
317 557-9
317 558-5
317 559-1

13. NUMÉRO DU LOT DE FABRICATION

PROJET

14. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I

15. INDICATIONS THÉRAPEUTIQUES

Sans objet

PICTOGRAMME DEVANT FIGURER SUR L'EMBALLAGE EXTERIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTERIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

Le pictogramme doit être conforme à l'arrêté du 3 mai 1999 pris en application de l'article R 5143 du code de la santé publique et relatif à l'apposition d'un pictogramme. Celui-ci précise que le pictogramme a la forme d'un triangle équilatéral rouge sur fond blanc dans lequel se trouve une voiture noire. Ses dimensions sont adaptées à la taille du conditionnement extérieur.

MENTIONS DEVANT FIGURER À TITRE MINIMAL SUR LES ~~PETITS CONDITIONNEMENTS PRIMAIRES~~ PLAQUETTES THERMOFORMEES OU LES FILMS THERMOSOUDÉS

1. DÉNOMINATION DU MÉDICAMENT ET, SI NÉCESSAIRE, VOIE (S) D'ADMINISTRATION

MEDIATOR 150 mg, comprimé enrobé

2. MODE D'ADMINISTRATION

Voie orale

3. DATE DE PÉREMPTION

4. NUMÉRO DE LOT

5. CONTENU EN POIDS, VOLUME OU UNITÉ

Boîtes de 10, 20, 24, 30, 60 et 100 comprimés enrobés.

PROJET

ANNEXE III B

NOTICE

Lisez attentivement l'intégralité de cette notice avant de prendre ce médicament.
Elle contient des informations importantes sur votre traitement.
Si vous avez d'autres questions, si vous avez un doute, demandez plus d'informations à votre médecin ou à votre pharmacien.
Ce médicament vous a été personnellement prescrit. Ne le donnez jamais à quelqu'un d'autre, même en cas de symptômes identiques, car cela pourrait lui être nocif.
Gardez cette notice, vous pourriez avoir besoin de la relire.

MEDIATOR 150 mg, comprimé enrobé

La substance active est :

Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé

Les autres composants sont : amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane, éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

PROJET

Titulaire/Exploitant :
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Fabricant :
LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

1. QU'EST-CE QUE MEDIATOR 150 mg, comprimé enrobé ET DANS QUEL CAS EST-IL UTILISÉ ?

MEDIATOR 150 mg, comprimé enrobé contient du chlorhydrate de benfluorex.
MEDIATOR 150 mg se présente sous la forme de comprimés enrobés.
Boîtes de 10, 20, 24, 30, 60 et 100 comprimés.

Code ATC: A (Appareil Digestif et métabolisme).

Ce traitement est en préconisé comme adjuvant à un régime adapté :
- dans les hypertriglycéridémies (pour diminuer le taux de lipides dans le sang),
- chez les diabétiques avec surcharge pondérale (pour diminuer le taux de sucre dans le sang).

Annexe 2-46

Il est préférable de ne pas utiliser ce médic pendant ce t -
-Si vous découvrez que vous êtes enceinte pendant le traitement, consultez votre médecin car lui seul peut juger de la nécessité de le

X Grossesse / Allaitement : Selon la terminologie habituelle de cette rubrique dans l'Annexe III B : poursuivre ?

" L'utilisation de ce médicament est déconseillé pendant la grossesse ou chez la femme qui allaite

Demandez conseil à votre médecin ou à votre pharmacien avant de prendre tout médicament

2. INFORMATIONS NÉCESSAIRES AVANT D'UTILISER MEDIATOR 150 mg, comprimé enrobé

MEDIATOR 150 mg, comprimé enrobé NE DOIT JAMAIS ETRE UTILISE dans les cas suivants : chlorhydrate OK
- allergie au ~~chlorure de~~ benfluorex ou à l'un des composants du produit;
- en cas de pancréatite chronique *(insuffisance du pancréas)*.

MISES en GARDE et PRECAUTIONS PARTICULIERES D'EMPLOI avec MEDIATOR 150 mg, comprimé enrobé:

Un régime alimentaire adapté doit être poursuivi pendant toute la durée du traitement.

Si après une période de plusieurs mois (3 à 6 mois), une diminution des concentrations de lipides (glucides, urines) dans le sang n'est pas obtenue, votre médecin pourra envisager d'autres moyens thérapeutiques adaptés à votre cas.
ou du sucre (Conformité à Annexe I)

~~L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.~~
(mention à faire figurer au paragraphe "Sportifs") OK

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase *(maladies métaboliques rares)*.

Grossesse/Allaitement :

~~Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu.~~
~~En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.~~
~~En cas d'exposition fortuite, il conviendra d'interrompre ce traitement dont la prescription du fait des propriété amphétaminiques est déconseillée au cours de la grossesse.~~
~~En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement.~~

PROJET

Conduite de véhicules et utilisation de machines :
L'attention est attirée sur le risque de somnolence pouvant survenir avec ce médicament.

Sportifs :
~~Sans objet.~~ Attention, cette spécialité contient un principe actif pouvant induire une réaction des tests pratiqués lors des contrôles antidopages.

Liste des excipients à effet notoire :
Saccharose. OK

Prise ou utilisation d'autres médicaments :
Sans objet.

x La posologie peut être ramenée à 2 comprimés par jour, voire 1 comprimé par jour, en fonction des résultats biologiques (dosages réguliers des lipides et du taux de sucre dans le sang)

(Conformité à Annexe I)

Annexe 2-46

3. COMMENT PRENDRE MEDIATOR 150 mg, comprimé enrobé ?

ok

Posologie:
RESERVE A L'ADULTE

X Voie orale. habituellement (conformité à Annexe I)
La posologie est ~~en moyenne~~ en de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:
- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

X ← ok En fonction des résultats biologiques, la posologie peut être ramenée à 2 comprimés par jour, voire 1 comprimé par jour.

DANS TOUS LES CAS, SE CONFORMER STRICTEMENT A L'ORDONNANCE DE VOTRE MEDECIN.

Si vous avez pris plus de MEDIATOR 150 mg, comprimé enrobé que vous n'auriez dû :
Les signes de surdosage peuvent être des troubles digestifs (nausées, vomissements, diarrhée), une sensation vertigineuse voire une somnolence. En cas d'apparition de ces troubles, consultez votre médecin ou votre pharmacien.

Si vous oubliez de prendre MEDIATOR 150 mg, comprimé enrobé :
Ne prenez pas de double dose pour compenser la dose simple que vous avez oubliée de prendre.

Effets pouvant apparaître lorsque le traitement par MEDIATOR 150 mg, comprimé enrobé est arrêté :
Sans objet.

PROJET

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS avec MEDIATOR 150 mg, comprimé enrobé ?

Comme tous les médicaments, MEDIATOR 150 mg, comprimé enrobé est susceptible d'avoir des effets indésirables :

ok

- troubles digestifs (nausées, vomissements, diarrhée, ~~douleurs abdominales~~); maux d'estomac);
- sensation de fatigue, voire somnolence;
- sensations vertigineuses.

(terminologie habituelle pour le grand public - Annexe I)

Ces effets ont été observés à des posologies supérieures à ~~la posologie journalière recommandée~~ des posologies élevées (conformité à Annexe I)
de 3 comprimés.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

ok

5. COMMENT CONSERVER MEDIATOR 150 mg, comprimé enrobé ?

Ne laisser ni à la portée ni à la vue des enfants.

Ne pas utiliser après la date de péremption figurant sur la boîte.

La dernière date à laquelle cette notice a été trouvée est le (date).

PROJET

Annexe 2-47

RÉPUBLIQUE FRANÇAISE

AGENCE
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ

DIRECTION DES ÉTUDES MÉDICO-ÉCONOMIQUES
ET DE L'INFORMATION SCIENTIFIQUE

DÉPARTEMENT PUBLICITÉ ET BON USAGE
DES PRODUITS DE SANTÉ
Unité Publicité des médicaments pour les professionnels

Saint-Denis, le 28 NOV. 2002

DÉCISION

Interdisant une publicité pour un médicament, mentionnée à l'article L.5122-1, premier alinéa du code de la santé publique, destinée aux personnes habilitées à prescrire ou délivrer ces médicaments ou à les utiliser dans l'exercice de leur art.

LE DIRECTEUR DE L'AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

Vu le code de la santé publique et notamment les articles L.5122-1 à L.5122-3, L.5122-9, L.5422-1, R.5045, R.5047 à R.5047-2, R.5047-5, R.5054 à R.5054-4 ;

Vu l'avis de la Commission chargée du contrôle de la publicité et de la diffusion de recommandations sur le bon usage des médicaments réunie le 15 octobre 2002.

Considérant que les Laboratoires SERVIER, 22 rue Garnier, 92 200 Neuilly-sur-Seine, ont diffusé une publicité relative à la spécialité MEDIATOR – tiré-à-part.

Considérant que

Ce document présente les résultats d'un résumé de communication de congrès relatif à une étude évaluant l'efficacité et la tolérance de MEDIATOR versus metformine et placebo chez des patients diabétiques sur une durée de six mois, avec notamment les allégations " efficacité antidiabétique sur l'HbA1c après 6 mois de traitement ", " versus metformine : MEDIATOR s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c " et la mise en exergue des conclusions des auteurs " 1) MEDIATOR réduit significativement l'HbA1c et la glycémie à jeun, en comparaison au placebo ; 2) MEDIATOR est bien toléré ; 3) MEDIATOR s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c. Cette baisse apparaît néanmoins un peu plus importante, dans cette étude, sous metformine ".

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Cette étude a été examinée par la Commission d'Autorisation de Mise sur le Marché des médicaments dans le cadre d'une demande d'extension d'indication de MEDIATOR au traitement du diabète de type 2 après échec des mesures hygiéno-diététiques seules.

Or, cette étude présente des faiblesses méthodologiques, avec notamment :

- des patients inclus qui sont en moyenne peu sévèrement atteints ;
- un déséquilibre dans les taux d'HbA1c à l'inclusion, plus bas dans le groupe MEDIATOR que dans le groupe metformine ;
- une analyse statistique de la comparaison de l'efficacité de MEDIATOR versus metformine réalisée avec un intervalle de confiance à 90 % (soit un risque d'erreur de 10 %), alors que la comparaison de MEDIATOR versus placebo a été analysée avec un intervalle de confiance à 95 % (soit un risque d'erreur de 5 %). Ainsi, l'analyse réalisée avec un intervalle de confiance à 90 % présentée dans le document promotionnel montre une non infériorité de MEDIATOR par rapport à la metformine, tandis que celle réalisée avec un intervalle de confiance à 95 % en intention de traiter ne permet pas de conclure à la non infériorité du benfluorex comparé à la metformine ;
- une analyse en per protocole qui n'a inclus que 68 % des patients.

Ainsi, cette extension d'indication a été refusée par la Commission d'autorisation de mise sur le marché, considérant que la démonstration d'efficacité n'a pas été apportée, notamment dans la mesure où l'essai clinique fourni ne permet pas de conclure à la non infériorité du benfluorex par rapport à la metformine compte tenu des faiblesses méthodologiques de l'étude.

Par ailleurs, la mise en exergue d'une non infériorité de MEDIATOR sur la diminution de l'HbA1c est associée en dernière page du document à la mise en exergue de résultats de tolérance gastro-intestinale en faveur de MEDIATOR : 13 % dans le bras traité par MEDIATOR versus 25 % pour la metformine, sans précision d'un degré de significativité pour interpréter cette différence et sans que soient mentionnés les autres effets indésirables. Or, cette présentation tend à établir une comparaison du rapport bénéfice/risque de ces deux spécialités et à générer une prescription préférentielle de MEDIATOR chez certains diabétiques de type 2 sur la base d'un profil de tolérance plus favorable pour une efficacité non inférieure, ce qui ne favorise pas le bon usage de MEDIATOR dans la mesure où les indications validées par les autorisations de mise sur le marché de MEDIATOR et de la metformine ne sont pas superposables concernant leur place dans la prise en charge du diabète de type 2. En effet, MEDIATOR est indiqué comme « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » tandis que la metformine est indiquée dans le « traitement du diabète de type 2 de l'adulte, en particulier en cas de surcharge pondérale, lorsque le régime alimentaire et l'exercice physique ne sont pas suffisants pour rétablir l'équilibre glycémique ». Ainsi, cette présentation d'une efficacité antidiabétique non inférieure à la metformine associée à une meilleure tolérance gastro-intestinale tend à positionner MEDIATOR au même niveau de la stratégie thérapeutique du traitement du diabète de type 2, c'est-à-dire après échec des mesures hygiéno-diététiques, ce qui ne correspond pas à l'indication validée par l'autorisation de mise sur le marché de MEDIATOR.

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Considérant qu'

En conséquence, la présentation des résultats de l'étude précitée comparant l'efficacité et la tolérance de MEDIATOR versus metformine et la conclusion " efficacité antidiabétique sur l'HbA1c après 6 mois de traitement : versus metformine, MEDIATOR s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c " sont contraires à l'article L.5122-2 du code de la santé publique, qui dispose que la publicité doit respecter les dispositions de l'autorisation de mise sur le marché, présenter le médicament de façon objective et favoriser son bon usage.

DÉCIDE

ARTICLE 1er.

Les publicités, sous quelque forme que ce soit, pour la spécialité pharmaceutique *MEDIATOR* reprenant les allégations mentionnées ci-dessus sont interdites.

ARTICLE 2.

Le Directeur des Etudes Médico-économiques et de l'Information Scientifique est chargé de l'exécution de la présente décision, qui sera publiée par extrait au Journal officiel de la République française.

Fait à Saint-Denis, le 28 NOV. 2002

Le Directeur Général de l'~~Agence~~ Française
de Sécurité Sanitaire des Produits de Santé

Annexe 2-47

RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

DÉCISION

interdisant une publicité pour un médicament mentionnée à l'article L.5122-1, premier alinéa du code de la santé publique, destinée aux personnes habilitées à prescrire ou délivrer ces médicaments, ou à les utiliser dans l'exercice de leur art.

-:-:-:-:-:-:-:-:-:-:-:-:-

Par décision du Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé en date du 28 NOV. 2002
Considérant que les Laboratoires SERVIER, 22 rue Garnier, 92 200 Neuilly-sur-Seine, ont diffusé une publicité relative à la spécialité MEDIATOR – tiré-à-part.
Considérant que ce document présente les résultats d'un résumé de communication de congrès relatif à une étude évaluant l'efficacité et la tolérance de MEDIATOR versus metformine et placebo chez des patients diabétiques sur une durée de six mois, avec notamment les allégations " efficacité antidiabétique sur l'HbA1c après 6 mois de traitement ", " versus metformine : MEDIATOR s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c " et la mise en exergue des conclusions des auteurs " 1) MEDIATOR réduit significativement l'HbA1c et la glycémie à jeun, en comparaison au placebo ; 2) MEDIATOR est bien toléré ; 3) MEDIATOR s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c. Cette baisse apparaît néanmoins un peu plus importante, dans cette étude, sous metformine ".

Cette étude a été examinée par la Commission d'Autorisation de Mise sur le Marché des médicaments dans le cadre d'une demande d'extension d'indication de MEDIATOR au traitement du diabète de type 2 après échec des mesures hygiéno-diététiques seules.

Or, cette étude présente des faiblesses méthodologiques, avec notamment :
- des patients inclus qui sont en moyenne peu sévèrement atteints ;
- un déséquilibre dans les taux d'HbA1c à l'inclusion, plus bas dans le groupe MEDIATOR que dans le groupe metformine ;
- une analyse statistique de la comparaison de l'efficacité de MEDIATOR versus metformine réalisée avec un intervalle de confiance à 90 % (soit un risque d'erreur de 10 %), alors que la comparaison de MEDIATOR versus placebo a été analysée avec un intervalle de confiance à 95 % (soit un risque d'erreur de 5 %). Ainsi, l'analyse réalisée avec un intervalle de confiance à 90 % présentée dans le document promotionnel montre une non infériorité de MEDIATOR par rapport à la metformine, tandis que celle réalisée avec un intervalle de confiance à 95 % en intention de traiter ne permet pas de conclure à la non infériorité du benfluorex comparé à la metformine ;
- une analyse en per protocole qui n'a inclus que 68 % des patients.

Ainsi, cette extension d'indication a été refusée par la Commission d'autorisation de mise sur le marché, considérant que la démonstration d'efficacité n'a pas été apportée, notamment dans la mesure où l'essai clinique fourni ne permet pas de conclure à la non

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infériorité du benfluorex par rapport à la metformine compte tenu des faiblesses méthodologiques de l'étude.

Par ailleurs, la mise en exergue d'une non infériorité de MEDIATOR sur la diminution de l'HbA1c est associée en dernière page du document à la mise en exergue de résultats de tolérance gastro-intestinale en faveur de MEDIATOR : 13 % dans le bras traité par MEDIATOR versus 25 % pour la metformine, sans précision d'un degré de significativité pour interpréter cette différence et sans que soient mentionnés les autres effets indésirables. Or, cette présentation tend à établir une comparaison du rapport bénéfice/ risque de ces deux spécialités et à générer une prescription préférentielle de MEDIATOR chez certains diabétiques de type 2 sur la base d'un profil de tolérance plus favorable pour une efficacité non inférieure, ce qui ne favorise pas le bon usage de MEDIATOR dans la mesure où les indications validées par les autorisations de mise sur le marché de MEDIATOR et de la metformine ne sont pas superposables concernant leur place dans la prise en charge du diabète de type 2. En effet, MEDIATOR est indiqué comme « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » tandis que la metformine est indiquée dans le « traitement du diabète de type 2 de l'adulte, en particulier en cas de surcharge pondérale, lorsque le régime alimentaire et l'exercice physique ne sont pas suffisants pour rétablir l'équilibre glycémique ». Ainsi, cette présentation d'une efficacité antidiabétique non inférieure à la metformine associée à une meilleure tolérance gastro-intestinale tend à positionner MEDIATOR au même niveau de la stratégie thérapeutique du traitement du diabète de type 2, c'est-à-dire après échec des mesures hygiéno-diététiques, ce qui ne correspond pas à l'indication validée par l'autorisation de mise sur le marché de MEDIATOR.

Considérant qu'en conséquence, la présentation des résultats de l'étude précitée comparant l'efficacité et la tolérance de MEDIATOR versus metformine et la conclusion " efficacité antidiabétique sur l'HbA1c après 6 mois de traitement : versus metformine, MEDIATOR s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c " sont contraires à l'article L.5122-2 du code de la santé publique, qui dispose que la publicité doit respecter les dispositions de l'autorisation de mise sur le marché, présenter le médicament de façon objective et favoriser son bon usage.
Les publicités, sous quelque forme que ce soit, pour la spécialité pharmaceutique MEDIATOR reprenant les allégations mentionnées ci-dessus sont interdites.

siège social se situe à Paris (15e), 6, rue Vandrezanne, est agréée pour pratiquer les opérations relevant des branches ou sous-branches suivantes mentionnées à l'article R. 211-2 du code précité :

1 Accidents (y compris les accidents du travail et les maladies professionnelles) ;
2 Maladie ;
20 Vie-décès.

Art. 2. – Le directeur de la sécurité sociale est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 13 décembre 2002.

Le ministre de la santé, de la famille et des personnes handicapées,
Pour le ministre et par délégation :
Par empêchement du directeur de la sécurité sociale :
Le sous-directeur des retraites et des institutions de la protection sociale complémentaire,
F. LE MORVAN

Le ministre des affaires sociales, du travail et de la solidarité,
Pour le ministre et par délégation :
Par empêchement du directeur de la sécurité sociale :
Le sous-directeur des retraites et des institutions de la protection sociale complémentaire,
F. LE MORVAN

Arrêté du 16 décembre 2002 relatif au budget pour 2002 de l'agence régionale de l'hospitalisation de Languedoc-Roussillon

NOR : *SANG0224184A*

Par arrêté du ministre de la santé, de la famille et des personnes handicapées et du ministre délégué au budget et à la réforme budgétaire en date du 16 décembre 2002, le montant du budget primitif pour 2002 de l'agence régionale de l'hospitalisation de Languedoc-Roussillon est majoré de la somme nette de 22 904,43 € (décision modificative n° 1).

Arrêté du 18 décembre 2002 portant prorogation du mandat des membres des commissions administratives paritaires de l'Assistance publique-hôpitaux de Paris

NOR : *SANH0224208A*

Par arrêté du ministre de la santé, de la famille et des personnes handicapées en date du 18 décembre 2002, le mandat des membres des commissions administratives paritaires propres à l'Assistance publique-hôpitaux de Paris est prorogé d'un *an* à compter du 1er janvier 2003.

Décision du 28 novembre 2002 interdisant des publicités pour des médicaments mentionnées à l'article L. 5122-1, premier alinéa, du code de la santé publique, destinées aux personnes habilitées à prescrire ou à délivrer ces médicaments ou à les utiliser dans l'exercice de leur art

NOR : *SANM0239953S*

Par décision du directeur général de l'Agence française de sécurité sanitaire des produits de santé en date du 28 novembre 2002 :

Considérant que les laboratoires Servier, 22, rue Garnier, 92200 Neuilly-sur-Seine, ont diffusé une publicité relative à la spécialité Mediator (tiré à part) ;

Considérant que ce document présente les résultats d'un résumé de communication de congrès relatif à une étude évaluant l'efficacité et la tolérance de Mediator *versus* metformine et placebo chez des patients diabétiques sur une durée de six mois, avec notamment les allégations « efficacité antidiabétique sur l'HbA1c après six mois de traitement », « *versus* metformine : Mediator s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c » et la mise en exergue des conclusions des auteurs :

« 1. Mediator réduit significativement l'HbA1c et la glycémie à jeun, en comparaison au placebo ;

2. Mediator est bien toléré ;

3. Mediator s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c. Cette baisse apparaît néanmoins un peu plus importante, dans cette étude, sous metformine. »

Cette étude a été examinée par la commission d'autorisation de mise sur le marché des médicaments dans le cadre d'une demande d'extension d'indication de Mediator au traitement du diabète de type 2 après échec des mesures hygiéno-diététiques seules.

Or, cette étude présente des faiblesses méthodologiques, avec notamment :

- des patients inclus qui sont en moyenne peu sévèrement atteints ;
- un déséquilibre dans les taux d'HbA1c à l'inclusion, plus bas dans le groupe Mediator que dans le groupe metformine ;
- une analyse statistique de la comparaison de l'efficacité de Mediator *versus* metformine réalisée avec un intervalle de confiance à 90 % (soit un risque d'erreur de 10 %), alors que la comparaison de Mediator *versus* placebo a été analysée avec un intervalle de confiance à 95 % (soit un risque d'erreur de 5 %). Ainsi, l'analyse réalisée avec un intervalle de confiance à 90 % présentée dans le document promotionnel montre une non-infériorité de Mediator par rapport à la metformine, tandis que celle réalisée avec un intervalle de confiance à 95 % en intention de traiter ne permet pas de conclure à la non-infériorité du benfluorex comparé à la metformine ;
- une analyse en per protocole qui n'a inclus que 68 % des patients.

Ainsi, cette extension d'indication a été refusée par la commission d'autorisation de mise sur le marché, considérant que la démonstration d'efficacité n'a pas été apportée, notamment dans la mesure où l'essai clinique fourni ne permet pas de conclure à la non-infériorité du benfluorex par rapport à la metformine, compte tenu des faiblesses méthodologiques de l'étude.

Par ailleurs, la mise en exergue d'une non-infériorité de Mediator sur la diminution de l'HbA1c est associée en dernière page du document à la mise en exergue de résultats de tolérance gastro-intestinale en faveur de Mediator : 13 % dans le bras traité par Mediator *versus* 25 % pour la metformine, sans précision d'un degré de significativité pour interpréter cette différence et sans que soient mentionnés les autres effets indésirables. Or, cette présentation tend à établir une comparaison du rapport bénéfice/risque de ces deux spécialités et à générer une prescription préférentielle de Mediator chez certains diabétiques de type 2 sur la base d'un profil de tolérance plus favorable pour une efficacité non inférieure, ce qui ne favorise pas le bon usage de Mediator dans la mesure où les indications validées par les autorisations de mise sur le marché de Mediator et de la metformine ne sont pas superposables concernant leur place dans la prise en charge du diabète de type 2. En effet, Mediator est indiqué comme « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale », tandis que la metformine est indiquée dans le « traitement du diabète de type 2 de l'adulte, en particulier en cas de surcharge pondérale, lorsque le régime alimentaire et l'exercice physique ne sont pas suffisants pour rétablir l'équilibre glycémique ». Ainsi, cette présentation d'une efficacité antidiabétique non inférieure à la metformine associée à une meilleure tolérance gastro-intestinale tend à positionner Mediator au même niveau de la stratégie thérapeutique du traitement du diabète de type 2, c'est-à-dire après l'échec des mesures hygiéno-diététiques, ce qui ne correspond pas à l'indication validée par l'autorisation de mise sur le marché de Mediator ;

Considérant qu'en conséquence la présentation des résultats de l'étude précitée comparant l'efficacité et la tolérance de Mediator *versus* metformine et la conclusion efficacité antidiabétique sur l'HbA1c après six mois de traitement, *versus* metformine Mediator s'est montré statistiquement non inférieur à la metformine sur la baisse de l'HbA1c sont contraires à l'article L. 5122-2 du code de la santé publique, qui dispose que la publicité doit respecter les dispositions de l'autorisation de mise sur le marché, présenter le médicament de façon objective et favoriser son bon usage,

les publicités, sous quelque forme que ce soit, pour la spécialité pharmaceutique Mediator reprenant les allégations mentionnées ci-dessus sont interdites.

Liste des postes à recrutement prioritaire vacants de praticien hospitalier à temps partiel pour l'année 2002 pour la région Bourgogne

NOR : *SANH0224102K*

En application de l'article 3-1 du décret n° 85-384 du 29 mars 1985 modifié portant statut des praticiens exerçant leur activité à temps partiel dans les établissements d'hospitalisation publics, la liste des postes à recrutement prioritaire vacants est établie pour l'année 2002 ainsi qu'il est mentionné dans les tableaux ci-dessous.

Les conditions et les modalités de dépôt des candidatures sur ces postes vacants à recrutement prioritaire sont identiques à celles définies dans l'avis précédent de vacance de postes de praticien des hôpitaux à temps partiel (postes vacants ou susceptibles de l'être).

* * *

Les tableaux suivants dressent la liste de ces postes à recrutement prioritaire vacants dans les établissements publics de santé hors centres hospitaliers universitaires et dans les hôpitaux locaux ou dans les centres hospitaliers universitaires, dans les services placés hors de l'application de l'ordonnance du 30 décembre 1958 :

Annexe 2-47

RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

DIRECTION DES ETUDES MEDICO-ECONOMIQUES
ET DE L'INFORMATION SCIENTIFIQUE

Saint Denis, le 28 NOV. 2002

DEPARTEMENT PUBLICITE ET BON USAGE
DES PRODUITS DE SANTE
Unité Publicité des médicaments pour les professionnels

Personne chargée du dossier :
Raphaële HENNEQUIN
Tél. : 01.55.87.38.91
Fax : 01.55.87.38.82

Réf. : 363mar02
CP n° 119

Laboratoires **SERVIER**
A l'attention de
Monsieur Pierre MONTES
Pharmacien Responsable
22, rue Garnier
92 200 NEUILLY-sur-SEINE

Lettre avec Accusé de Réception

Monsieur,

Je vous informe qu'en application des dispositions des articles L.5122-9 et R.5047-5-II du code de la santé publique, et après avis de la Commission chargée du contrôle de la publicité et de la diffusion de recommandations sur le bon usage des médicaments réunie le 15 octobre 2002, la poursuite de la diffusion de votre publicité concernant la spécialité MEDIATOR – tiré-à-part, est interdite par décision du 28 NOV. 2002 dont vous trouverez ci-joint une copie.

Cette interdiction, qui sera publiée au Journal Officiel de la République Française, prend effet à compter de la date de réception de ce courrier par vos services.

Toute diffusion qui se poursuivrait après cette date constituerait une infraction aux articles précités, passible des peines énumérées à l'article L.5422-1 du code de la santé publique.

Dans le cas où vous désireriez contester cette décision, un recours contentieux pourra être engagé devant le Tribunal administratif compétent dans un délai de deux mois à compter de la présente notification.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Le Directeur Général

Annexe 3-1

Pharmacovigilance AFSSAPS

Organisation de la pharmacovigilance

La pharmacovigilance est la surveillance et la prévention du risque d'effet indésirable, que ce risque soit potentiel ou avéré, des médicaments lorsqu'ils sont consommés largement dans le cadre de leur commercialisation.

Elle comprend :

- Le recueil basé sur la notification spontanée des effets indésirables par les professionnels de santé et les industriels avec l'appui du réseau des 31 centres régionaux de pharmacovigilance
- L'enregistrement et l'évaluation de ces informations
- La mise en place d'enquêtes ou d'études pour analyser les risques, la participation à la mise en place et au suivi des plans de gestion des risques
- L'appréciation du profil de sécurité d'emploi du médicament en fonction des données recueillies
- La prise de mesures correctives (précautions ou restriction d'emploi, contre-indications, voire retrait du produit) et la communication vers les professionnels de santé et le public
- La communication et la diffusion de toute information relative à la sécurité d'emploi du médicament
- La participation à la politique de santé publique de lutte contre la iatrogénie médicamenteuse

La pharmacovigilance s'appuie sur une base réglementaire nationale et européenne : lois, décrets, directives, bonnes pratiques de pharmacovigilance publiées par arrêté.

Le système national de pharmacovigilance comprend :

Un échelon national

- L'Afssaps (département de pharmacovigilance)
- La Commission nationale de pharmacovigilance et de son comité technique

Un échelon régional

- Les centres régionaux de pharmacovigilance (CRPV)

Autres acteurs

- Les professionnels de santé
- Les patients et/ou les associations de patients
- Les entreprises du médicament

Ce système s'intègre dans une organisation européenne de la pharmacovigilance (groupe de travail européen de pharmacovigilance/eudravigilance) et de l'évaluation du médicament (agence européenne du médicament : EMEA) dans le respect du contexte réglementaire européen

Le département de pharmacovigilance échange avec des institutions internationales telles que l'OMS qui dispose d'un centre collaborateur de référence en pharmacovigilance (Uppsala Monitoring Center) ou avec d'autres autorités de santé (aux USA, au Japon) ...

Lire aussi

- Actualité sur la pharmacovigilance des médicaments - Ateliers du MEDEC (11/03/2009) (310 ko)
- Rapport d'activité Pharmacovigilance 2008 (29/07/2008) (135 ko)

Pharmacovigilance européenne

Il existe une **organisation européenne** pour l'autorisation et la surveillance des médicaments. La création le 1er janvier 1995 de l'Agence européenne des médicaments : EMEA (European Médicines Evaluation Agency) implantée à Londres a permis d'organiser et de structurer un système de pharmacovigilance au niveau communautaire. Cette structure reproduit l'organisation française : recueil et validation décentralisés au niveau de chaque état membre, évaluation et avis et/ou décision centralisés au niveau européen à l'EMEA par l'intermédiaire du comité des médicaments à usage humain (CHMP) et de son **groupe de travail** européen de pharmacovigilance.

Ce groupe de travail (dit « **pharmacovigilance working party** ») réunit les responsables des départements de pharmacovigilance de chacun des 27 états membres ainsi qu'un représentant de la commission européenne et du secrétariat de l'EMEA. Il s'agit d'un véritable forum européen de discussion et d'échanges en pharmacovigilance qui peut être saisi à la demande du CHMP ou des états membres. Il peut aussi bien aborder les problèmes de sécurité d'emploi rencontrés après l'AMM qu'en cours d'évaluation des dossiers d'AMM si besoin. Il permet aussi des échanges réguliers avec la FDA.

Ce système européen permet :

- Une identification/communication rapide et efficace sur les problèmes de pharmacovigilance
- Une coopération dans l'évaluation des risques liés à l'utilisation des médicaments
- La prise de mesures pour répondre à un problème de pharmacovigilance
- Et une information commune sur les médicaments

Il existe une base de données européenne de Pharmacovigilance EudraVigilance dont l'objectif est de :

- Développer les outils permettant le traitement et la transmission électronique d'observations individuelles de pharmacovigilance

- Et d'améliorer la communication et faciliter la collaboration en pharmacovigilance entre les autorités compétentes

Champ d'application

La pharmacovigilance repose avant tout sur le signalement, par les professionnels de santé, des effets indésirables susceptibles d'être dus aux médicaments ou produits. Ces déclarations sont ensuite validées, évaluées et enregistrées par les centres régionaux de pharmacovigilance (CRPV) dans une base informatique située à l'Afssaps qui coordonne l'ensemble du système.

Ces trois activités : signalement, évaluation, et transmission des effets indésirables, permettent d'identifier les risques médicamenteux.

Si nécessaire, des études complémentaires sont réalisées et le cas échéant des mesures correctives sont mises en place afin de réduire ces risques.

Dans quelle cadre d'utilisation du médicament le dispositif de pharmacovigilance s'applique t-il ?

La pharmacovigilance s'exerce sur les médicaments et produits à finalité sanitaire à usage humain lors d'une utilisation « conforme » mais aussi lors d'une utilisation non conforme. Cependant en cas d'abus de médicament contenant des substances psychoactives, la surveillance est effectuée par le système national de pharmacodépendance (addictovigilance).

Il est important de préciser que ce dispositif permet aussi de recueillir les effets indésirables résultant :

- D'une utilisation au cours de la grossesse ou de l'allaitement
- D'une interaction médicamenteuse
- D'une perte d'efficacité
- D'un défaut de qualité
- **Une fiche** permettant de signaler un défaut de qualité en dehors de la survenue d'un effet indésirable .

A quels produits?

La pharmacovigilance s'exerce sur les médicaments et produits à usage humain mentionnés à l'article L.2121-1.

Ces médicaments sont distribué par une pharmacie (avec ou sans ordonnance).

De façon explicite, il s'agit des produits suivants :

> Spécialité pharmaceutique ayant fait l'objet d'une AMM (autorisation de mise sur le marché)

La règlementation ayant évolué au fil du temps, il est important de préciser que cela comprend bien :

- Le médicament immunologique : allergène, vaccin, toxine, ou sérum
- Le produit de thérapie cellulaire lorsqu'il est soumis à une AMM
- Le produit de thérapie génique
- Le médicament radiopharmaceutique
- Le produit présenté comme supprimant l'envie de fumer ou réduisant l'accoutumance au tabac
- Le médicament dérivé du sang (produit stable préparé à partir du sang ou de ses composants)
  (Remarque : c'est le dispositif d'hémovigilance qui surveille le produit sanguin labile)
- Les insecticides et acaricides destinés à être appliqués sur l'homme
- Les produits contraceptifs

> Spécialité pharmaceutique faisant l'objet d'une ATU

Lire aussi :

Pharmacovigilance des médicaments en ATU :

- Avis aux demandeurs d'Autorisation Temporaire d'Utilisation (ATU) (15/11/2007) (345 ko) chapitre VIII

- Notice to applicants for Temporary Authorisation for Use (ATU) (15/11/2007) (735 ko) chapter VIII

> Le médicament homéopathique,

Remarques

- La pharmacovigilance des médicaments utilisés dans le cadre des essais cliniques est soumise à un autre dispositif décrit dans des textes réglementaires nationaux et européens distincts
- Les aliments diététiques destinés à des fins médicales spéciales ne sont pas des médicaments

Rôle de l'Afssaps

L'Afssaps est l'autorité compétente en matière de pharmacovigilance. En vertu des missions qui lui sont dévolues, elle veille à la sécurité de l'emploi des médicaments et contribue à leur bon usage. L'Afssaps assure la mise en œuvre et coordonne le système national de pharmacovigilance. Ce système national s'intègre dans une organisation européenne pour l'autorisation et la surveillance des médicaments (lien avec la pharmacovigilance européenne).

Cette veille sanitaire repose sur :

- Le signalement des effets indésirables par les professionnels de santé et les industriels
- Le recueil, l'exploitation et l'évaluation de toute information concernant le risque d'effets indésirables
- La réalisation d'études ou de travaux concernant la sécurité d'emploi des médicaments
- La mise en place d'actions nécessaires à l'exercice de la pharmacovigilance.
- La prise de mesures correctives ou préventives

En pratique, ces missions sont assurées, au sein de l'Afssaps, par l'Unité de pharmacovigilance qui est rattachée au Département de l'évaluation thérapeutique de la Direction de l'évaluation des médicaments et des produits biologiques (DEMEB).

Mise en place pour animer le système national de pharmacovigilance, son rôle consiste notamment à :

- Évaluer toutes les déclarations d'effets indésirables qui lui parviennent
- Informer les professionnels de santé des procédures et des recommandations établies
- Coordonner l'activité des centres régionaux de pharmacovigilance
- Mettre en place des groupes de réflexion scientifique et méthodologique
- Assurer le secrétariat du Comité technique et de la Commission nationale de pharmacovigilance
- Etre en liaison permanente avec les autres directions de l'Afssaps et, en particulier, le Comité de coordination des vigilances, les autres Unités de vigilance (matériovigilance, hémovigilance, réactovigilance, biovigilance...).

Rôle de la Commission nationale de pharmacovigilance et son comité technique

La Commission nationale de pharmacovigilance est une commission composée de 6 membres de droit (présidents de la DGS, DHOS, Afssaps, INSERM, Commission nationale de pharmacovigilance vétérinaire et Commission nationale des stupéfiants et psychotropes) et de 33 membres nommés. Ces derniers sont des médecins ou des pharmaciens choisis en fonction de leurs compétences dans les différents domaines d'activité ayant trait à la pharmacovigilance (médecins cliniciens, pharmaciens, pharmacologues ou toxicologues, pharmaco-épidémiologistes) mais aussi des personnes représentant différentes instances (le comité technique de toxicovigilance, les associations de personnes malades et d'usagers du système de santé, associations de consommateurs, les entreprises exploitant des médicaments). Cette commission est nommée après un appel à candidature par le ministre chargé de la santé pour 3 ans. Elle se réunit tous les 2 mois.

Elle a pour missions :

- D'évaluer les informations sur les médicaments et produits à usage humain ;
- De proposer les enquêtes et travaux utiles à l'exercice de la pharmacovigilance ;
- De donner un avis au directeur général de l'Afssaps sur les mesures à prendre pour faire cesser les incidents et accidents liés à l'emploi des médicaments et produits.

Le Ministre chargé de la santé a la possibilité de saisir la Commission nationale de pharmacovigilance sur toute question ayant trait à son domaine de compétence pour recueillir son avis.
Un règlement intérieur permet de préciser toutes les modalités de fonctionnement de la dite commission.
Les comptes rendus des réunions sont mis en ligne.

Le **Comité technique de pharmacovigilance**, composé des membres de droit de la Commission nationale de pharmacovigilance et d'un représentant de chaque centre régional de pharmacovigilance est chargé de préparer les travaux de la Commission nationale de pharmacovigilance.

Il a pour missions :

- De coordonner et évaluer les informations relatives aux effets indésirables des médicaments et produits ;
- De proposer, mettre en place et évaluer les enquêtes demandées aux centres régionaux de pharmacovigilance et aux industriels.

Rôle des centres régionaux de pharmacovigilance

La mission générale des **centres régionaux de pharmacovigilance**(CRPV) est de surveiller, d'évaluer et de prévenir les risques médicamenteux potentiels ou avérés et de promouvoir le bon usage du médicament.

Il existe 31 CRPV répartis sur toute la France.

Les CRPV sont au cœur du système de déclaration puisque qu'ils assurent le recueil et la transmission des effets indésirables à l'Afssaps. Ils sont chargés de remplir une mission d'expertise au sein du système national de pharmacovigilance en conduisant les enquêtes de pharmacovigilance et/ou en assurant une évaluation de dossiers (demande d'AMM, demande de modification de l'information…).

Ils assurent également une mission d'information en matière de pharmacovigilance, notamment en renseignant les professionnels de santé et en participant à leur formation et en faisant remonter les informations portées à leur connaissance au niveau de l'Afssaps (usage abusif, mésusage, produit défectueux…).

Rôle des professionnels de santé

Comme pour les autres systèmes de vigilances déjà opérationnels et coordonnés par l'Afssaps, les professionnels de santé jouent un rôle fondamental dans le système national de pharmacovigilance. En effet, ce sont eux qui sont habilités, d'une part à prescrire les

médicaments, à les administrer ou à les délivrer et, d'autre part, à assurer le suivi médical des patients.

La pharmacovigilance repose sur le signalement, sans délai, par les professionnels de santé, des effets indésirables graves susceptibles d'être dus à un médicament. Dès qu'ils soupçonnent un lien, même s'il n'est pas certain, une déclaration peut être effectuée auprès du centre régional de pharmacovigilance.

Rôle des entreprises du médicament

Toute entreprise ou organisme exploitant un médicament ou produit à usage humain doit mettre en place un service de pharmacovigilance dans le but d'assurer le recueil, l'enregistrement et l'évaluation des informations relatives aux effets indésirables susceptibles d'être dus à des médicaments. Ce service est placé sous la responsabilité d'un médecin ou pharmacien justifiant d'une expérience en matière de pharmacovigilance.. Le responsable de pharmacovigilance doit veiller au respect des obligations de déclaration de pharmacovigilance auprès de l'Afssaps :

> Déclaration immédiate des effets indésirables graves

- Information destinée aux entreprises pharmaceutiques concernant la transmission électronique des observations individuelles de pharmacovigilance (18/06/2009) (91 ko)
- Electronic exchanges of individual case safety reports (ICSRs) with Afssaps (30/06/2009) (72 ko)

> Envoi de rapports périodiques actualisés de pharmacovigilance appelés PSUR (Periodic Safety Update Report) contenant l'ensemble des données de pharmacovigilance recueillies sur le plan national et international par le laboratoire pendant la période considérée.

- Avis aux demandeurs d'autorisation de mise sur le marché des médicaments à usage humain (20/10/2009) (551 ko) (voir partie concernée pour les PSURs)
- Avis aux demandeurs d'autorisation de mise sur le marché des médicaments à usage humain (02/11/2010) (1041 ko) (voir partie concernée pour les PSURs)

> Réponse aux demandes du directeur général de l'Afssaps

> Transmission de toute autre information présentant un intérêt pour l'évaluation du rapport bénéfice/risque d'un médicament

> Demande de modification de l'information

- Avis aux demandeurs d'autorisation de mise sur le marché des médicaments à usage humain (20/10/2009) (551 ko) (voir partie concernée pour les DMI et variations)
- Avis aux demandeurs d'autorisation de mise sur le marché des médicaments à usage humain (02/11/2010) (1041 ko) (voir partie concernée pour les DMI et variations)

> Proposition de plan de gestion des risques

Les entreprises du médicament travaillent avec l'Afssaps et les centres régionaux de pharmacovigilance dans le cadre des enquêtes de pharmacovigilance relatives aux médicaments ou produits qu'ils exploitent.

Rôle des patients et des associations de patients

La loi du 4 mars 2002 relative au droit des malades et à la qualité du système de santé confère aux malades un rôle actif en les associant au fonctionnement du système de santé.

Actuellement, les dispositions de pharmacovigilance ne prévoient pas de déclaration directe d'un effet indésirable par un patient ou ses proches. Cependant, il arrive de plus en plus fréquemment qu'un patient ou une association de patients contacte directement un CRPV ou un laboratoire pharmaceutique pour les informer d'un problème lié à la survenue d'un effet indésirable médicamenteux. Ils sont alors invités à se diriger vers un professionnel de santé afin de procéder à la déclaration de l'effet indésirable conformément aux bonnes pratiques de pharmacovigilance.

L'Afssaps s'est engagée, depuis 2002, dans une réflexion sur leur éventuelle participation au système de pharmacovigilance. Plusieurs expériences pilotes de signalement direct des effets indésirables par les patients ont été réalisées, en collaboration avec des associations de patients, ou sont en cours.

Partenariat Afssaps /Associations de patients

- Partenariat Afssaps/Associations de patients et de consommateurs : lancement d'une étude sur les déclarations des événements indésirables par les patients - 07/06/2006 - communiqué

Déclaration des effets indésirables

Que déclarer?

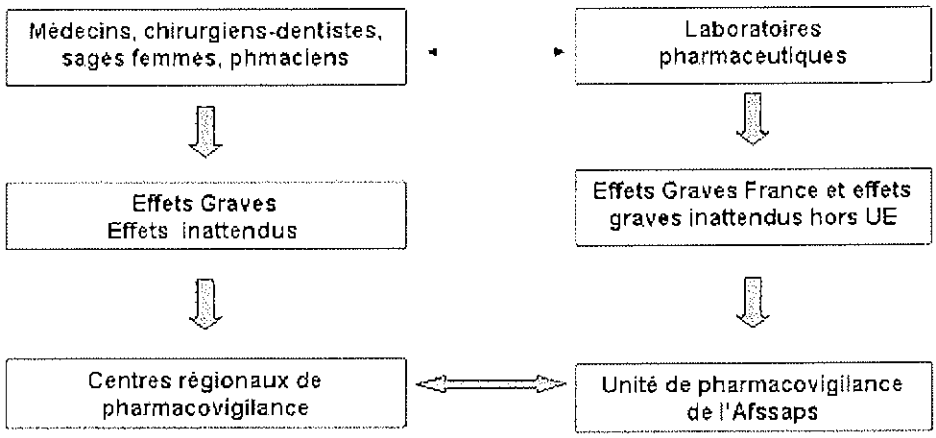
- **Tout effet indésirable grave** (létal, ou susceptible de mettre la vie en danger, ou entraînant une invalidité ou une incapacité importantes ou durables, ou provoquant ou prolongeant une hospitalisation ou se manifestant par une anomalie ou une malformation congénitale).
- **Tout effet inattendu** (dont la nature, la sévérité ou l'évolution ne correspondent pas aux informations contenues dans le RCP).
- Mais aussi tout effet que vous jugez pertinent de déclarer en dehors de ces définitions

Qui doit déclarer?

Les professionnels de santé

Les patients doivent s'adresser à leur médecin ou à leur pharmacien qui a délivré les médicaments ou produits.

Cependant tout autre professionnel de santé ayant observé un effet indésirable susceptible d'être dû à un médicament ou produit peut également en faire la déclaration auprès du centre régional de pharmacovigilance dont il dépend



A qui déclarer?

A un centre régional de pharmacovigilance

Quand déclarer?

Immédiatement pour les effets graves ou inattendus ; pas de délai défini pour les autres.

Comment déclarer

A l'aide de la **fiche de pharmacovigilance** par courrier postal ou électronique.

Une déclaration doit comporter au minimum les informations suivantes :

- Une source identifiable (le notificateur)
- Un patient identifiable
- Le nom du produit suspecté et le numéro de lot (indispensable pour la traçabilité du médicament dérivé du sang)
- La nature de l'effet indésirable.

Il est recommandé de transmettre ces informations par écrit ou au moyen du après contact téléphonique préalable le cas échéant.

En pratique, pour être évalué correctement, le dossier comprendra des informations sur le patient (sexe, âge, poids, taille, département de résidence, antécédents, profession, etc.), les médicaments pris (dénomination, numéro de lot, posologie, voies d'administration, date de début et de fin de traitement, indication etc.), l'effet indésirable (description, date d'apparition, évolution etc.).

Il peut comprendre des copies de compte-rendus d'hospitalisation, de courriers médicaux et d'examens complémentaires.

Le notificateur pourra être recontacté si un suivi est nécessaire ou pour obtenir des informations complémentaires. A tout moment, après obtention de nouvelles informations, la déclaration initiale pourra être complétée.

Il s'agit d'un dossier évolutif dans le temps.

- Signalement de pharmacovigilance - Cerfa N°10011*02

Centres régionaux de pharmacovigilance

Coordonnées et territoire géographique d'intervention

Le réseau est constitué de 31 centres répartis de façon à favoriser les échanges de proximité avec les professionnels de santé.

Parmi leurs missions, ils sont notamment chargés de :

- Recueillir les déclarations d'effet indésirable que doivent leur adresser les médecins, chirurgiens-dentistes, les sages-femmes et les pharmaciens,
- Renseigner les professionnels de santé sur leur territoire d'intervention.

Les professionnels de santé sont incités à contacter les centres régionaux de leur lieu d'exercice dont ils trouveront les coordonnées et les zones d'intervention dans la liste suivante

[1] xxxtableauxxx

Annexe 3-2

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Jean Minjoz 25030 BESANCON Cedex

MEDIATOR (benfluorex)

ENQUETE OFFICIELLE

(Mise à jour du rapport de décembre 1998)

Comité Technique du 20 Juillet 1999

Confidentiel

M.DAVID-LAROCHE
P.BECHTEL

Annexe 3-2

Le MEDIATOR (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par le laboratoire BIOPHARMA, sous forme de comprimés, dosés à 150 mgL
La posologie recommandée est de 3 comprimés par jour.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène.
(Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Une enquête officieuse a été ouverte, suite à la première mise au point des effets indésirables du benfluorex, présentée lors du Comité Technique du 11 juillet 1995.
Deux mises au point ont été faites :
-le 30 Avril 1998 sur les effets indésiirables du benfluorex, rapportés aux CRPV
-le 10 Septembre 1998 sur le métabolisme et les chiffres de vente du benfluorex.

Le rapport a été présenté au Comité Technique du 17 décembre 1998.

Ce présent rapport est une mise à jour du rapport précédent (du 17 décembre 1998) avec les nouvelles notifications des CRPV jusqu'au 30 juin 1999.
(Tous les changements par rapport à décembre 1998 sont inscrits en italique)

Les effets indésirables rapportés dans les RCP sont :

- effets digestifs : nausées, vomissements, gastralgies, diarrhée
- asthénie
- somnolence
- état vertigineux

Annexe 3-2

A. BILAN GLOBAL :

279 notifications validées ont été rapportées :

177 aux Centres Régionaux de Pharmacovigilance, 105 au laboratoire.(dont 3 doublons)

Elles concernent *100* hommes et *178* femmes (1 sexe non précisé), dont l'age moyen est de :

Répartition par classe-organe des effets indésirables notifiés :

APPAREIL	Nombre de Notifications CRPV	Nombre de Notifications Laboratoire	TOTAL	Nombre de doublons
FOIE	***20***	9	***28***	1
APP. DIGESTIF (sauf foie)	***17***	5	***23***	-
HEMATOLOGIE	8	6	14	-
APPAREIL RESPIRATOIRE	***11***	11	***21***	1
CARDIO-VASCULAIRE	***14***	6	***20***	-
APPAREIL URINAIRE	9	4	13	-
PEAU - ALLERGIE	***43***	23	***66***	-
NEURO-PSYCHIATRIE	***31***	18	***49***	-
VERTIGES	***20***	5	***24***	1
METABOLISME	3	18	21	-
APPAREIL SENSORIEL	1	-	-	-
TOTAL	***177***	105	***279***	3

N.B : les nouvelles notifications par rapport à la mise au point de Juillet 1995, sont imprimées **«en gras »** dans les tableaux suivants.
Dans la colonne, « traitement associé », le médicament est souligné, lorsque l'imputabilité bibliographique est supérieure au MEDIATOR.

Annexe 3-2

I. ATTEINTES HEPATIQUES :

26 cas d'hépatites ou de perturbations de la biologie hépatique ont été notifiés : (le benfluorex est le seul suspect ou d'imputabilité égale ou supérieure aux médicaments associés)

-*18* aux CRPV, 9 au laboratoire (dont 1 doublon) .

Elles concernent *16* femmes (âge moyen : *55,2* ans) et *10* hommes (âge moyen: 59.9 ans)

Dans *8* cas le benfluorex a une imputation plausible:

DJ9300271 : Femme de 50 ans , traitée pendant 2 semaines par MEDIATOR, une préparation d'aubépine, 200mg, et amfépramone 35 mg ,citrarginine, Veinobiase et depuis 1 mois et demi par AXONYL.
ALAT = 625 UI/L, ASAT : 303 UI/L, γGT: 656 UI/L, Ph.Alc. : 198 UI/L.
Evolution favorable 2 semaines après l'arrêt du traitement ,sauf les γGT qui sont encore à 171 UI/L

NY8804047=060K94 (doublon) : homme de 47 ans, traité par MEDIATOR, pendant 6 mois, puis 3 mois (après un arrêt de 3 mois)
ALAT : 375 UI/L , ASAT : 105 UI/L, γGT : 182 UI/L
L'évolution est lentement favorable dans un délai de 2 mois.

DJ9100164 : homme de 61 ans, éthylique chronique, traité depuis 4 ans par RENITEC, DOGMATIL, LASILIX, depuis 1 an par RYHMODAN et depuis 3 ans par MEDIATOR.
ALAT : 1350 UI/L, ASAT : 410 UI/L, γGT : 280 UI/L
La régression de l'hépatite est partielle à l'arrêt de toutes les thérapeutiques, chez ce patient éthylique.

NC9600020 :Femme de 39 ans, traitée par MEDIATOR depuis 8 mois.
ALAT: 205 UI/L (4N), ASAT : 89 UI/L (2N), γGT: 134 UI/L
L'évolution est favorable à l'arrêt du MEDIATOR.

NY9608618 : Femme de 36 ans, traité par MEDIATOR, pour cure d'amaigrissement pendant 4 mois.
ALAT : 126 UI/L, ASAT : 41UI/L, γGT : 110 UI/L
L'évolution est favorable à l'arrêt du MEDIATOR.

BX9700024 : Femme de 59 ans, apparition d'un ictère avec prurit, après 4 semaines de traitement par MEDIATOR. (LOXEN et ACUILIX sont pris au long cours)
ALAT: 1017 UI/L (30N), ASAT : 391 UI/L (10N), γGT : 1042 UI/L, Ph. alc. : 907 UI/L (4N)

10010325 : Homme de 42 ans présentant une cytolyse modére et une cholestase discrète 3 semaines après le début d'un traitement par MEDIATOR, pour hypertriglycéridémie et diabète modéré.
L'évolution est favorable à l'arrêt du MEDIATOR.

LY9900193 : *Femme de 57 ans, hospitalisée pour décompensation respiratoire et cytolyse hépatique,qui prenait MEDIATOR, XANAX, depuis 6 mois, AVLOCARDYL, DEROXAT, depuis 1 an et TOPALGIC depuis 2 mois et SOLUPRED, 1 mois*

Dans 1 cas, l'imputation est vraisemblable :

Observation 120O39 : observation très succinte du laboratoire, concernant une augmentation des γGT (169 UI/L) , chez une femme de 70 ans, qui était traitée par ailleurs par Diamicron, Icaz et Hypérium. La réintroduction a été positive.

Dans *17* cas, l'imputation est douteuse : dont 10 C2,S1, *7* C1,S1

Annexe 3-2

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
Hépatite mixte						
RE8660098	M,82	1 mois	C2,S1	CORVASAL, DIAMICRON TADENAN	A	
DJ9300271	F,50	2 sem.	C2,S2	Amfépramone, C2,S2	A	γGT↑
10060607	M,61	15 j	C2,S1	GLUCOPHAGE RETARD, C1,S1 DIAMICRON, C1,S1 SECTRAL, C1,S1 RISORDAN, C1,S1	A	
Hépatite cytolytique						
NY8804047 = 060K94	M,47	3 mois	C2,S2		A	γGT↑
DJ9100164	M,61	3 ans	C2,S2	RENITEC, C2,S2 DOGMATIL	A	γGT↑
LY9900193	***F, 57***	***6 mois***	***C2,S2***	***TOPALGIC, C2,S2*** ***SOLUPRED, C2,S2***	***A***	
MP9902037	***M, 73***	***2 ans***	***C1,S1***	***ELISOR, C1,S1*** ***ZESTRIL, C1,S1*** ***ZYLORIC, C1,S1*** ***BURINEX, C1,S1*** ***KARDEGIC, C1,S1***	***D***	***+ Ins. rénale*** ***+ rhabdo-myolyse***
Hépatite cholostatique						
NC9200360	F,85	3 mois	C2,S1	TENSTATEN, C2,S1	A	
Biologie hépatique perturbée						
NC9600020	**F,39**	**8 mois**	**C2,S2**		**A**	**ALAT↑**
MA9700402	**F,47**	**12 sem.**	**C2,S1**		**A**	**ALAT↑**
MA9400451	F,57	3 mois	C1,S1	Amfépramone, C1,S1	U	ALAT↑
BX9700611	**F,51**	**6 j**	**C2,S1**	**LUTERAN, C2,S1** **LEVOTHYROX , C2,S1** **TENORMINE, C2,S1**	F	**ALAT↑**
PA9803765	**F,66**	**3 mois**	**C1,S1**	**LAROXYL** **GLUCOR** **TEATROIS** **TEALINE...**	**U**	**ALAT↑** **Prep.Magistr.**
PB9300028	M,60	15 j	C1,S1	Prep. magistrale: 15 j Yohimbine Dexfenfluramine Metformine, 2 ans ANAFRANIL, 2 ans	A	ALAT↑
NY9608618	**F,36**	**4 mois**	**C2,S2**		**A**	**ALAT+Bil↑**
PA8851623	M,61	3 ans	C2,S1	(MYOCORIL,C1,S1)	F	ALAT+P.A↑
BX9700024	**F,59**	**4sem.**	**C2,S2**	**LOXEN,C2,S2** **ACUILIX, C2,S2**	**A**	**ALAT+P.A↑** **+γGT↑**
10010325	M,42	3 sem.	C2,S2	(éthylisme)	A	ALAT+P.A↑
10060020	M,55	3 mois	C2,S1		A	ALAT ↑
10060A69	M,?	50 j	C2,S1		A	ALAT ↑ (1,5N)
10540L94	F,48	20 mois	C2,S1	MADECASSOL (C1,S1)	A	ALAT + γGT↑
MP9800161	**F,51**	**5 mois**	**C1,S1**	**ESTREVA, C1,S1** **GESTORAL, C1,S1**	**A**	**ALAT + γGT↑**
10060498	F,50	3 ans	C1,S1		U	γGT↑ dossier succinct
10060038	F,62	> 3 mois	C2,S1		A	γGT↑
120O39	**F,70**	**?**	**C3,S1**	**DIAMICRON** **ICAZ** **HYPERIUM**		γGT↑
NC9900122	***M,56***	***6 ans***	***C1,S1***	***ALDACTONE*** ***DAONIL*** ***LUBENTYL***	***F***	*γGT↑*

Conclusion : Plusieurs cas d' augmentations de transaminases et/ou de γGT ont été rapportés.
La plupart du temps, le MEDIATOR est en association avec d'autres médicaments qui ont la même imputabilité.
Dans quelques cas, le MEDIATOR est le seul médicament pris par le ou la patiente.
Dans la majorité des dossiers, le délai de survenue est de ≅ 3 mois.

Cet effet indésirable n'est pas mentionné dans les RCP

- **AUTRES ATTEINTES HEPATIQUES**

2 observations d'imputabilité douteuse ont été rapportées:

- BX88003099, patient de 53 ans, éthylique, traité depuis 13 ans par MEDIATOR, ZYLORIC et VISKEN . L'évolution n'est pas connue.

-LY9500598 , femme de 59 ans, hospitalisée pour tentative d'autolyse, traitée par de nombreux médicaments: évolution inconnue, dossier très succinct.

CIRRHOSE						
BX8800309	M,57	13 ans	C1,S1	ZYLORIC,13 ans, C1,S1 VISKEN,13 ans,C1,S1	U	autre étiologie
STEATOSE						
LY9500598	**F,59**			**EQUANIL** **LEVOTHYROX** **LOXAPAC** **ANAFRANIL** **ROHYPNOL**	**U**	**dossier succinct**

II. AUTRES ATTEINTES DIGESTIVES :

Elles concernent *15* femmes (âge moyen : *60,1* ans) et 7 hommes (âge moyen : 61,7 ans)

- Dans les 14 cas de diarrhée rapportés, (10 femmes et 4 hommes), le MEDIATOR est utilisé en monothérapie, ou son imputabilité est supérieure aux médicaments associés.

Cet effet indésirable est mentionné dans les RCP.

- *4* cas d'ulcères ont été rapportés (3 par le laboratoire, *1* par le CRPV) :

- 10060052 : homme de 74 ans, reçoit MEDIATOR, depuis 6 à 8 mois, LIPANTHYL depuis 10 ans , TANAKAN et des AINS. Une fibroscopie montre des ulcères multiples qui nécessitent non seulement l'arrêt des AINS mais de toute thérapeutique.
L'évolution est favorable après prescription d'antiulcéreux. (C1,S1)

- 10540930 : Femme de 64 ans, hospitalisée pour ulcère gastrique, après 3 mois de traitement par MEDIATOR et après 1 an de GLUCOPHAGE RETARD, EUGLUCAN, ZESTRIL, LIPUR.
Le MEDIATOR est arrêté.
L'évolution est favorable après traitement par anti-acide, pansement gastrique et perfusion. (C1,S1)

--10060587 : Femme de 72 ans, avec diabète, HTA, traitée par MODURETIC et ALDOMET depuis plusieurs années et MEDIATOR depuis 3 jours. Apparition de gastralgies intenses après prise de MEDIATOR, avec réadministration positive. (C3,S1)
L'évolution est favorable à l'arrêt du MEDIATOR.
Une fibroscopie ultérieure met en évidence un ulcère duodénal.

Annexe 3-2

- TO990455 : *Femme de 53 ans, traitée depuis 2 semaines par MEDIATOR et XENICAL , d écouverte d'un ulcère gastrique, traité par MOPRAL. (C1,S1)*

- 1 cas de rectocolite hémorragique : (1054P69) chez une femme de 46 ans traitée au long cours par DAONIL, GLUCOPHAGE RETARD, INSULINE, LEVOTHYROX et ELISOR, apparition d'une diarrhée aigue, sanglante et colite inflammatoire ressemblant à une colite hémorragique après 1 cp de MEDIATOR.

L'évolution est favorable après administration de PENTASA. (C2,S1)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DIARRHEE						
LY8600250	F,70	6 j	C2,S1		A	
MP8600156	M,60	2 mois	C3,S2	MODUCREN, C1,S1	A	
LY8700109	M,71	21 j	C2,S2	DIGOXINE	A	
BX8800223	M,40	3 j	C3,S2		A	
LY8800383	F,72	10 mois	C1,S1		F	
LY8800202	F,58	18 j	C2,S1		A	
MA9000721	F,29	3 j	C2,S2	DININTEL,C1,S2	A	
NC9200041	F,42	3 ans	C2,S2		A	
BR9300084	F,63	1 j	C2,S1	ZOCOR,C1,S1 ZYLORIC, C1,S1 ARMOPHYLLINE, C1,S1 DIAMICRON, C1,S1 BRICANYL, C1,S1	A	
NC9300212	M,75	47 j	C2,S2	DIACTANE, C1,S1	A	
DJ9400277	F,81	7 mois	C1,S2		U	
NC9500365	**F,70**	**2 sem.**	**C2,S2**	**BEFIZAL, C1,S2**	**A**	
CF9700156	**F,62**	**3 sem.**	**C2,S1**		**A**	
540V43	**F,66**	**45 j**	**C2,S1**	**ELISOR VEINAMITOL TEMESTA, C1,S1**	**A**	**selles molles anorexie dyspepsie**
PANCREATITE						
MA9000382	M,40	6m	C2,S1	ISOMERIDE ,C2,S1	A	
MA9700296	**F,54**	**8j**	**C2,S1**		**A**	**autre étiologie!**
EPIGASTRALGIE						
LY8600060	M,72	13j	C2,S1		A	
ULCERE DUODENAL						
10060587	F,72	3 j	C3,S1	MODURETIC, C1,S1 ALDOMET, C1,S1	A	
ULCERE GASTRIQUE						
10540930	F,64	3 mois	C1,S1	GLUCOPHAGE RETARD, C1,S1 EUGLUCAN, C1,S1 ZESTRIL, C1,S1 LIPUR, C1,S1	A	
TO990455	***F, 53***	***?***	***C1,S1***	***XENICAL, C1,S1 ROCEPHINE MOPRAL***	***F***	
ULCERE						
10060052	M,74		C2,S1	AINS, C2,S1 TANAKAN, C2,S1 LIPANTHYL, C1,S1	A	ulcères multiples
RECTOCOLITE HEMORRAGIQUE						
10540P69	F,46	1 j	C1,S1	DAONIL, C1,S1 GLUCOPHAGE RETARD , C1,S1 INSULINE , C1,S1 LEVOTHYROX, C1,S1 ELISOR, C1,S1	F	

Annexe 3-2

III. ATTEINTES HEMATOLOGIQUES

14 observations (8 CRPV, 6 laboratoire) ont été rapportées.

Elles concernent 5 hommes (âge moyen : 62,2 ans) et 9 femmes (âge moyen : 57 ans) .

- Aucun nouveau cas n'a été rapporté depuis la mise au point de Juillet 1995

- L'imputabilité est douteuse dans tous les cas : 11 C1,S1
3 C2,S1

Dans la plupart des observations, il existe un traitement associé, qui peut être responsable de l'effet indésirable

-Dans l'observation 10050F09 : (C2,S1) il s'agit d'1 femme de 70 ans, avec HTA, hyperlipémie, angor et antécédents d'ulcère gastrique, traitée par MEDIATOR depuis 3 semaines:
apparition de purpura et d'hémorragie digestive : plaquettes<5000/mm3 et hémoglobine à 9g/l
La recherche d'anticorps antiplaquettes est positive.
L'évolution est favorable après arrêt du MEDIATOR

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol	
THROMBOPENIE						
LY8500365	M,51	3 mois	C1,S1	RISORDAN, 4 ans, C1,S1 SECTRAL, 4 ans, C1, S1 TILDIEM, 7 mois, C1S1	U	
SE9100183	F,64	2 mois	C1,S1	TENSTATEN, 2m, C1S1 EFFERALGAN, C1S1	U	
PS9400301	F,61	?	C1,S1	GERIMAX, C1,S1 OROCAL, C1,S1 LEVOTHYROX, C1,S1	A	
NC9400153	F,19	2 mois	C2,S1	DOXYCLINE, 5j, C2,S1 ALDACTONE, 2m, C2,S1	A	
LEUCOPENIE						
MA8801234	F,58	2 mois	C1,S1	LIPUR, 2ans, C2,S1	A	
10060617	M,60	4 ans	C1,S1		F	
LYMPHOPENIE						
DJ8800131	F,76	6 j	C1,S1	DIGOXINE, C1,S1 CALCIPARINE, C1,S1 RYTHMODAN, C1,S1	A	somnolence
MA9100793	M,59	8 j	C1,S1		A	hyperthermie
NEUTROPENIE + THROMBOPENIE						
NC8900022	M,72	2 ans	C1,S1	HEMIDAONIL, 6 ans, C1S1	A	
10060073	F,40	+ mois	C1,S1	DIAMICRON, C1,S1 GLUCOPHAGE, C1,S1	F	
10060050	M,69	3 ans	C1,S1	LEGALON	F	
ANEMIE + THROMBOPENIE						
10050F09	F,70	3 sem	C2,S1		A	
HYPERLYMPHOCYTOSE						
10060311	F,56	3-6 mois	C1,S1		U	dossier succinct
HYPEREOSINOPHILIE						
10540640	F,69	3 ans	C2,S1	LOPRIL, C1,S1 FLUDEX, C1,S1	F	

21 notifications (*11* CRPV et 11 laboratoire) dont 1 doublon ont été rapportées, concernant

- *12* hypertensions pulmonaires:.9 dossiers ont été expertisés par le Professeur WEITZENBLUM , 6 ont été classés en HTA P d'allure primitive lors de l'enquête « anorexigènes et HTAPP», 3 en hypertensions pulmonaires post-embolique(1) et post-capillaire(2).
Elles concernent ***10*** femmes (âge moyen : *544* ans) et 2 hommes (âge moyen : 48 ans)

Le MEDIATOR n'est jamais prescrit seul : il est présent en association à un ou plusieurs anorexigènes (ISOMERIDE : 10 fois, PONDERAL : 2 fois)
Ces cas font partie de l'enquête concernant les anorexigènes

Dans 1 cas, ***(PS9900385),*** *chez une femme de 50 ans, ayant une HTA et une hypercholestérolémie, traitée par LOGIRENE, TRIATEC, Fenofibrate et MEDIATOR, découverte en décembre 1998 d'une HTAP.*

La durée de traitement par MEDIATOR est imprécise dans 5 cas sur 12.
Dans les 6 autres cas, la durée de traitement va de plusieurs mois à 4 ans.

La prise de MEDIATOR et d'anorexigènes est concommitante dans 5 cas, antérieure dans 2 cas, postérieure dans 3 cas, imprécise dans 1 cas.

-- 5 cas de toux, après des traitements allant de 8 à 34 mois. L'évolution est inconnue dans 2 cas.

Dans 1 observation (541078), dont l'imputabilité est vraisemblable, chez une femme de 70 ans, traitée par MEDIATOR pour un diabète et AMLOR pour HTA depuis 2 mois, apparition d'une toux sèche qui disparait à l'arrêt du MEDIATOR.
Les dates de prise de MEDIATOR ne sont pas précisées: seul un rechallenge positif est noté. (C3,S1),

- des cas de syndrome hémorragique intra-alvéolaire (MP9500482), tuberculome (SE9400175), pneumopathies interstitielles (LM9800297 et NT9800036) ont tous une imputabilité douteuse: soit une autre étiologie est fortement évoquée, soit l'évolution est inconnue.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION PULMONAIRE						
PP8990081	F,42	1 an	C1,S1	DININTEL, 5ans, C1,S1 Tenuate Dospan,5ans,C1,S1 FRINGANOR, 5ans, C1,S1	U	
NC9300007 = 052454	M,48	4 ans	C1,S1	ISOMERIDE, 3 ans, C1,S1 ZYLORIC, 6 ans, C1,S1 LIPANTHYL	D	
10052455	F,46	25 mois	C1,S1	ISOMERIDE CORGARD BUSPAR VELITEN ALDACTONE	F	
10052733	F,71	60 mois	C1,S1	ISOMERIDE	F	HTAP post-capillaire
10840193	F,47	?	C1,S1	ISOMERIDE COVERSYL LASILIX GLUCOPHAGE	F	
10840255	F,57	?	C1,S1	ISOMERIDE PONDERAL STILNOX XANAX VEINOBIASE	F	

10840663	M,48	+ mois	C1,S1	ISOMERIDE FLUDEX	F	
10840770	F,66		C1,S1	ISOMERIDE FENPROPOREX	F	HTAP post-embolique
10840954	F,54		C1,S1	ISOMERIDE STAGID DIAMICRON	A	HTAP post-capillaire
10840B19	**F,51**		**C1,S1**	**ISOMERIDE SECTRAL MODURETIC KALEORID LEXOMIL RANIPLEX PREPULSID**	**F**	
10840D01	**F,59**	**4 ans**	**C1,S1**	**ISOMERIDE PONDERAL ZOCOR PROGESTOGEL SPIROCTAN**	**D**	
PS9900385	***F, 50***	***?***	***C1,S1***	***LOGIRENE TRIATEC Fenofibrate***	***U***	
			TOUX			
MA9000654	F,60	2 ans	C1,S1	ARTEX, 1 an, C1,S1 GLUCINAN, 2 ans,C1,S1	U	
NC9500265	**F,48**	**10mois**	**C1,S1**	**EUTHYRAL, 2mois, C1,S1**	**A**	
MA9600518	**F,63**	**8 mois**	**C1,S1**	**MONOTILDIEM, 1 an, C1,S1 KARDEGIC, 1 an, C1,S1 ADANCOR, 1 an, C1,S1**	**U**	
541078	**F,70**	**?**	**C3,S1**	**AMLOR, C1,S1**	**A**	
NC9800121	**F,71**	**34 mois**	**C2,S1**	**FLUDEX TENORMINE FONZYLANE ROHYPNOL**	**A**	
			SYNDROME HEMORRAGIQUE INTRA-ALVEOLAIRE			
MP9500482	**F,45**	**1 mois**	**C1,S1**	**PONDERAL, 1 mois, C1,S1**	**A**	
			TUBERCULOME			
SE9400175	F,46	2 mois	C1,S1	ISOMERIDE, 2 mois, C1,S1 DININTEL, 2 mois, C1,S1	A	autre étiologie !
			PNEUMOPATHIE INTERSTITIELLE			
LM9800297	**M,75**	**?**	**C1,S1**	**AMAREL, C1,S1**	**U**	
NT9800036	**M,69**	**10 ans**	**C1,S1**	**DETENSIEL, C1,S1 JOSIR, C1,S1 LEXOMIL, C1,S1**	**F**	**fibrose interstitielle**

V. ATTEINTES CARDIOVASCULAIRES :

20 notifications ont été rapportées : *14* par les CRPV, 6 par le laboratoire

Elles concernent *5* hommes (âge moyen : *50.8* ans) et 15 femmes (âge moyen : 48,3 ans)

Annexe 3-2

- 3 cas d'hypertension artérielle : dont une observation plausible :

NC9100093 : chez une femme de 51 ans, hypertendue traitée par LOPRESSOR depuis 5 ans, la tension est montée progressivement de 150/90 à 180/110 après introduction de MEDIATOR, malgré l'ajout de RENITEC. La tension a diminué lorsque le MEDIATOR a été arrêté.

- 2 cas de tachycardie : dont 1 plausible

NC8900097 : chez une patiente de 60 ans, qui a pris 3 comprimés de MEDIATOR, le soir. Apparition 3 heures plus tard de vertiges, puis d'angoisse, tachycardie et prurit généralisé. L'évolution est favorable.

- une fibrillation auriculaire (C2,S2) chez une femme de 25 ans après 9 mois de MEDIATOR, CANOL et TEALINE et 6 mois de MODERATAN. Evolution favorable à l'arrêt de tout le traitement.

- 3 syndromes de Raynaud dont un plausible C2,S2 et 2 douteux (C2,S1 et C1,S1)

- une insuffisance aortique *découverte chez un homme de 43 ans, ayant des antécédents d'infarctus du myocarde, d'insuffisance mitrale, d'hypercholestérolémie, de tabagisme, et qui était traité par MEDIATOR, VASTEN, TENORMINE depuis 6 ans*

- les autres notifications sont isolées et d'imputabilité douteuse

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION ARTERIELLE						
NC9100093	F,51	1an	C2,S2	RENITEC, C1S1 LOPRESSOR, C1S1	A	
CF9300241	F,73	6j	C2,S1		A	
120S330	**F,43**	**15 mois**	**C1,S1**	**SURGESTONE** **PROZAC**	**U**	
HYPOTENSION ARTERIELLE						
10060039	M,52	?	C1,S1		A	R -
SYNCOPE						
PP9010597	F,37	1j	C1,S2	Amfepramone, C1,S2 LUMITENS, C1,S2	A	
MALAISE						
10540A46	F,43	8 mois	C1,S1		A	R -
BRADYCARDIE						
120E93	**M,38**	**1 sem**	**C1,S1**		**A**	
CF9900109	***M, 58***	***3 sem***	***C1,S1***	***RISORDAN*** ***SOPROL*** ***ASPEGIC***	***U***	***+ hypotension + arythmie + céphalées***
TACHYCARDIE						
GR9500235	**F,52**	**?**	**C1,S1**	**SOTALEX, C1,S1**	**A**	
NC8900097	F,60	1j	C2,S2	CERVOXAN, C1,S1 DIGOXINE, C1,S1	A	
FIBRILLATION AURICULAIRE						
LY9700643	**F,25**	**9 m**	**C2,S2**	**MODERATAN ,C2,S2** **CANOL, C2,S2** **TEALINE, C2,S2**	**A**	**Terrain dépressif**
EXTRASYSTOLES VENTRICULAIRES						
CN9500150	**F,?**		**C2,S1**		**A**	**dossier succinct**
CN9500151	**F,?**		**C1,S1**		**U**	**dossier succinct**

Annexe 3-2

ACCIDENT VASCULAIRE CEREBRAL						
LL9700372	**F,39**	**3 mois**	**C2,S1**	**SPIRONONE, 3 mois, C2,S1** ***Tabagisme***	A	
PB9800124	**F,72**	**2 ans**	**C1,S1**	**GLIBENESE** **GLUCOR**	F	
SYNDROME DE RAYNAUD						
PC9300059	M,63	3 mois	C1,S1	MINIDIAB, 2ans, C1,S1	F	
PC9700170	**F,30**	**2 sem.**	**C2,S2**		A	
124U10	**F,30**		**C2,S1**	**FONZYLANE**	A	
OEDEMES DES MEMBRES INFERIEURS						
10060561	F,73	1 mois	C2,S1	GLUTRIL, C1,S1 CORDARONE, C1,S1	A	
INSUFFISANCE AORTIQUE						
MA9900176	***M, 43***	***6 ans***	***C2,S2***	***VASTEN*** ***TENORMINE*** ***ASPIRINE***	***F***	***ATCD : infarctus du myocarde***

VI. ATTEINTES RENALES :

13 notifications ont été rapportées , 9 par les CRPV et 4 par le laboratoire

Elles concernent 5 hommes (âge moyen : 66,6 ans) et 8 femmes (âge moyen : 55,2 ans)

-3 cas de dysurie, d'imputation :
C3,S1 : réadministration positive mais durée de traitement inconnu
C2,S2 : apparition après 5 mois de MEDIATOR, évolution favorable à l'arrêt de celui-ci
C2,S1 : apparition après 48 h de traitement par MEDIATOR (cystite concommitante)

- 4 cas de pollakurie :
- en début de traitement 1j,2j et 16j
- ou réadministration positive après 4 mois de traitement

-1 cas de cystalgie (C2,S1) chez une femme de 33 ans après 8 jours de traitement.
L'évolution est favorable à l'arrêt de MEDIATOR

- les autres dossiers ont tous une imputabilité douteuse:
- anurie (MA8900044)
- glomérulonéphrite (LY8700356),
- syndrome néphrotique (BX9700689),
- créatininémie augmentée(10060463)
- soit le dossier est succinct
- soit l'évolution est inconnue ou l'évolution n'est pas favorable à l'arrêt du traitement:
- soit une autre étiologie est possible

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DYSURIE						
BR9100053	F,42	?	C3,S1	VARNOLINE,C1,S1	A	
NC9300208	M,78	5 mois	C2,S2	GLUTRIL, C1,S1 ZYLORIC, C1,S1 PREPULSID, C1,S1	A	
SE9700347	**F,?**	**2 j**	**C2,S1**		**A**	

Annexe 3-2

POLYURIE						
BX8700115	F,40	7 mois	C2,S1		A	
POLLAKIURIE						
NC8800144	M,62	4 mois	C3,S1		A	
NC9300297	F,67	16 j	C2,S2		A	
10060O44	F,56	1 j	C2,S1		A	
10060O45	M,62	2 j	C2,S1	GLUCOPHAGE RETARD, C1,S1	A	
ANURIE						
MA8900044	M,79	2 mois	C1,S1	ARTEX, 2mois, C1,S1 ZYLORIC, 2 mois, C1,S1 HEMIDAONIL, 2 mois, C1,S1 ALDACTAZINE, 2 mois,C1,S1	N	dossier succinct, non informatif
GLOMERULONEPHRITE						
LY8700356	M,52	5 mois	C1,S1	ZYLORIC, C1,S1 DIAMICRON, C1,S1	U	
SYNDROME NEPHROTIQUE						
BX 9700689	**F,71**	**?**	**C1,S1**	**TROLOVOL, C1,S1 LASILIX,C1,S1 MONOTILDIEM, C1,S1 TRINITRINE, C1,S1 GLUCOPHAGE, C1,S1 DAONIL, C1,S1 VOLTARENE, C1,S1 CYTOTEC, C1,S1 AZANTAC, C1,S1**	F	
CREATININEMIE AUGMENTEE						
10060463	F,78	9 mois	C1,S1	ALDOMET, C1,S1 ALDACTAZINE, C1,S1 LIPANTHYL, C1,S1	F	
CYSTALGIES						
10540F68	F,33	8 j	C2,S1		A	

VII. ATTEINTES METABOLIQUES :

21 Notifications ont été rapportées , 18 par le laboratoire, 3 par les CRPV.

Elles concernent 11 hommes (âge moyen : 58,7 ans) et 10 femmes (âge moyen : 56,7 ans)

Dans 13 cas, c'est 1 effet lié à aux propriétés pharmacologiques du médicament lui-même:

- hypoglycémie : 6 cas
- malaise hypoglycémique : 1 cas
- hyperglycémie : 2 cas

- hyperlipémie : 2 cas
- augmentation des triglycérides : 2 cas

-3 cas de lactacidémie d'imputabilité douteuse

-dans 1 cas (10060F73), chez un homme de 68 ans, la lactacidémie est à 4.13mmol/l (normale 0.55-2.20) après un traitement de 37 jours par MEDIATOR. Un mois après de MEDIATOR, elle est de 2.27mmol/l.

Annexe 3-2

-2 dossiers succincts: pas de précision sur l'arrêt du MEDIATOR (10060683)
évolution inconnue (10060356)

- 2 cas de goutte chez 2 hommes de 61 et 71 ans (LASILIX est associé dans les 2 cas : C3,S2,B3 et C1,S1,B3)

- 2 cas d 'amaigrissement déclaré par un médecin au laboratoire (10060446 et 10060447) : perte de 5 Kg chez un homme de 36 ans après 1 mois de traitement, perte de 8 Kg chez une femme de 67 ans après 2 mois de traitement pour hypercholestérolémie.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERLIPEMIE						
BX8600168	?,55	15j	C1,S1		U	
HYPERLIPIDEMIE + HYPERCHOLESTEROLEMIE						
10051346	F,47	?	C1,S1	ECAZIDE, C1,S1	A	
TRIGLYCERIDES AUGMENTES						
10051289	M,59	8 mois	C1,S1		U	dossier succinct
10060J12	F,38	2 mois	C1,S1	TARDYFERON CALCIUM DEDROGYL	U	
HYPOTHYROIDIE						
BS9600267	**F,86**	**?**	**C1,S1**	**DAONIL, C1,S1** **SERMION, C1, S1** **LIPANTHYL,C1,S1** **VASTAREL, C1,S1**	**A**	
GOUTTE						
LY8500568	M,71	8 j	C2,S1	LASILIX, C3,S2	U	
10060F04	M,61	11 j	C2,S1	LASILIX, C1,S1 LOPRIL, C1,S1 ADALATE, C1,S1	A	
LACTACIDEMIE						
10060683	M,41	?	C1,S1	DAONIL ALDACTAZINE VASTAREL	A	dossier succinct
10060356	M,76	6 mois	C1,S1	DIGOXINE ADALATE SERMION AVLOCARDYL	U	
10060F73	M,68	37 j	C2,S1	TILDIEM SERMION	A	
HYPOGLYCEMIE						
10540J00	M,35	5 mois	C1,S1	TENSTATEN, C1,S1 BEFIZAL, C1,S1 ZYLORIC, C1,S1	U	
10060166	F,28	2 mois	C1,S1	GLUCOPHAGE	U	
10060O87	M,63	?	C2,S1	LIPANOR CERVOXAN LURSELLE	A	
10540P03	F,60	15 j	C2,S1	BEFIZAL PROZAC ETIOVEN	A	malaise *DNID*
10060449	F, 60	90 j	C3,S1	ZYLORIC LOPRIL	A	*DNID*
121U61	**F,44**	**110 j**	**C2,S2**	**CIBACENE** **LASILIX** **UTROGESTAN**	**A**	
MALAISE HYPOGLYCEMIQUE						
10060062	M,74	qq j	C2,S1	RENITEC	A	

Annexe 3-2

HYPERGLYCEMIE						
10060488	F,80	6 mois	C1,S1	CATAPRESSAN, C1,S1	F	
10060487	M,62	2 ans	C1,S1	CEBUTID VISKALDIX	A	*DNID*
AMAIGRISSEMENT						
10060446	M,36	1 mois	C2,S1		A	
10060447	F,67	2 mois	C1,S1		A	

VIII. DIVERS : Diminution de l'acuité visuelle

NY9810174	F,67	5 sem	C1,S1		F	

IX. ATTEINTES CUTANEES et REACTIONS ALLERGIQUES :

Elles concernent 20 hommes (Age moyen = 51,5 ans) et 46 femmes (Age moyen = *50,5* ans)

1 . Allergie, eczema :

Parmi les 29 réactions allergiques, on note:

- 14 cas d'urticaire dont 5 cas d'urticaires géantes ou généralisées
- 4 oedèmes de Quincke ou oedème laryngé
- 6 chocs anaphylactiques
- 5 allergies

Le délai de survenue est le plus souvent très rapide (1 jour), l'imputation sera donc souvent vraisemblable (15 fois) ou plausible (3 fois).
Elle est douteuse dans les cas où il y a eu un traitement correcteur : 9 fois

Parmi les 6 cas d'eczéma, d'imputabilité douteuse, l'évolution est favorable dans 4 cas.
L'eczéma n'est pas guéri dans 2 cas. (NC9300394 etNY9809751)
Dans l'observation 540W61, le délai d'apparition est long (2 ans) et la crème cosmétique semble être en cause.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
URTICAIRE						
CF8500013	M,50		C1,S2	LEXOMIL, C1,S2	A	
LY8700092	F,69	15 j	C3,S1		A	
TO9100366	M,34	7 j	C2,S2		A	
NC9400046	F,38	1 j	C3,S2		A	
MA9500024	M,45	3 mois	C3,S1	MAXEPA, C3,S1	U	
NY9507878	**M,61**	**2 mois**	**C2,S1**		**A**	
MA9700146	**F,50**	**1 j**	**C2,S2**		**A**	
10060I28	F,54	2 mois	C3,S1		A	
10540989	F,31	4 j	C3,S1	DI-ANTALVIC, FELDENE TRANCOPAL	A	
10540D65	F,48	3 sem	C1,S1		A	urticaire géante
10060H11	F,60	+ mois	C3,S1		A	urticaire géante
SE9800159	**F,32**	**9 j**	**C1,S1**	**PROZAC STRESAM CANOL**	**A**	**urticaire géante**
120T66	**F,59**	**1 j**	**C3,S1**	**ART 50, C1,S1**	**A**	**urticaire généralisée**
121D94	**F,60**	**1 j**	**C3,S1**		**A**	**urticaire généralisée + bronchospasme**

Annexe 3-2

OEDEME LARYNGE						
BX9800738	**F,?**	**3 j**	**C1,S1**		**A**	***autre cause!***
OEDEME DE QUINCKE						
PA9200399	F,41	1 j	C2,S1	GLUCINAN, C2,S1	A	
MA9500231	F,56	1 j	C3,S1		A	
10060K99	F,49	3 mois + 9 j	C3,S1		F	
CHOC ANAPHYLACTIQUE						
DJ9200119	F,73	2 j	C3,S2		A	
MA9300967	F,50	8 j	C3,S2		A	
MA9400018	F,?	1 j	C3,S2		A	
MA9700036	**F,60**	**1j**	**C2,S2**		**A**	
123K59	**F,38**	**1 j**	**C1,S1**	**BRONCHOKOD**	**A**	
LY9800499	**M,36**	**1 j**	**C3,S1**		**A**	
ALLERGIE						
LY9300329	F,53	12j	C3,S2		A	
10060500	M,64	3 j	C1,S1		A	oedème face et lèvres
121A605	**F,?**	**20 j**	**C2,S1**	**FLOXYFRAL PROTHIADEN NOCTRAN**	**A**	**flush**
NC9800400	***F, 36***	***1 j***	***C3,S2***		***A***	***urticaire hypotension oedeme de la langue***
BX9900286	***F, 30***	***1 j***	***C3,S2***		***A***	***malaise vomissement hypotension***
ECZEMA						
NC9300394	F,?	3 ans	C1,S2		F	
MA9500621	**F,68**	**2 ans**	**C2,S2**		**A**	
NY9809751	**M,70**	**10 mois**	**C1,S1**	**MOPRAL, C1,S1 GLUCOR, C1,S1**	**F**	
10840104	M,40	35 j	C1,S1		A	éruption eczématiforme photosensibilité
10060G65	F,64	1 mois	C1,S1	CATAPRESSAN VASTAREL DAFLON FONZYLANE	A	eczéma des membres oed. du visage prurit
540W61	**F,67**	**2 ans**	**C1,S1**	**Crème cosmétique**	**A**	éruption eczématiforme
SUDATION EXCESSIVE						
PA9240186	F,79		C1,S2	DIAMICRON, C1,S2 MEDIATENSYL, C1,S2 BRUFEN, C1,S2	A	

2. Eruption, vascularite, purpura

30 notifications ont été rapportées : 20 par les CRPV, 10 par le laboratoire

Elles concernent 18 femmes agées de 47,7 ans et 12 hommes agés de 52,6 ans

Les éruptions cutanées sont variées:

- 16 cas de prurit, d' éruptions érythèmateuse, maculeuse, papuleuse ou maculopapuleuse dont 6 cas d'imputabilité vraisemblable (réadministration positive)

Annexe 3-2

- 3 cas d'érythème polymorphe, avec une évolution favorable à l'arrêt du MEDIATOR, chez 2 hommes agés de 60 et 68 ans. Le délai d'apparition est respectivement de 15 jours et de 6 mois (!).
Dans le 3° cas, (MA9700614) l'évolution est inconnue et le TANAKAN a une imputabilité bibliographique supérieure au MEDIATOR.

- 3 notifications de vascularite aigue leucocytoclasique:
- dans 1 cas, l'évolution est favorable à l'arrêt du MEDIATOR (RE9420042)
- dans 1 cas, l'évolution est favorable sans arrêt du MEDIATOR , mais avec un traitement corticoïde (lorsque la corticothérapie est arrêtée, 4 mois plus tard, survient un érythème polymorphe :MA9700957)
- dans le troisième cas (MP9700134), l'évolution n'est pas complète malgré l'arrêt du MEDIATOR et une corticothérapie.

- 3 cas de purpura:
- purpura des membres inférieurs avec un oedème apparu une semaine après le début du traitement par MEDIATOR (PP8990384)
- purpura des membres inférieurs, s'étendant aux membres supérieurs, disparaissant 1 semaine après l'arrêt du traitement (CF9200106)
- purpura rhumatoïde survenant après 2 semaines de traitement, l' évolution est inconnue (PO9700410)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Ev.	
ERUPTION						
DJ9100155	M,31	10j	C3,S2		A	éruption érythémateuse
MP9300201	F,36	1 mois	C1,S1	DOLIPRANE, 1j,C1,S1 CLARADOL, 1j, C1,S1	A	éruption érythémateuse, prurit
540V73	**F,49**	**1 j**	**C3,S1**	**MEDIATENSYL**	**A**	**éruption + oedème**
PA9333879	F,54	5 sem.	C1,S1	GLUCOPHAGE,3 sem,C1,S1	U	prurit
10060913	F,65	qq j	C2,S1		A	prurit
10060161	M,40	3-4 j	C3,S1	LIPANTHYL	A	prurit
10060F71	F,47	?	C2,S1	TAGAMET, C1,S1 JONCTUM, C1,S1 LEXOMIL, C1,S1	A	prurit + érythème + vertiges
MA9500227	**M,38**	**16j**	**C3,S1**		**A**	**éruption prurigineuse**
10010408	M,72	7 j	C2,S1	ALDACTAZINE CORDITRINE PERSANTINE ZYLORIC	A	éruption prurigineuse
LY9700381	**F,56**	**11 sem.**	**C2,S1**	**LIPANTHYL, 11 SEM, C2S1**	**A**	**éruption**
MA9300723	F,41	1 cp	C2,S1	HEXALYSE,1cp, C2,S1	A	éruption maculopapul.
LY9400078	F,46	1 mois	C2,S1	TOCO 500, C1,S1 CYCLO 3, C1S1 CONFLICTAN, C1,S1 LEXOMIL, C1,S1	A	éruption maculeuse, prurit
1050S90	M,41		C3,S1	amfépramone phénobarbital	A	éruption papuleuse prurit
122X95	**F,32**	**1 mois**	**C3,S1**	**NIDREL FRACTAL AZANTAC**	**A**	**rash maculo-papuleux**
LM9100055	M,56	1 an	C1,S1	DETENSIEL, C1,S2 DIDRONEL, C1,S1	U	prurigo
NC9100505	F,48	1 mois	C2,S2	SOPROL, 1 mois, C2S2	A	éruption pustuleuse

Annexe 3-2

NC9100194	M,60	15 j	C2,S1	EUPRESSYL, C2,S1	A	érythème polymorphe
NY9300951	M,68	6 mois	C2,S1		A	érythème polymorphe
MA9700614	**F,50**	**3 mois**	**C1,S2**	**TANAKAN, C1,S2** **MEGAMAG, C1,S2**	U	**érythème polymorphe**
MP9700134	**F,58**	**6 j**	**C1,S1**	**SECTRAL** **BOP** **LEVOTHYROX**	F	**vascularite**
RE9420042	M,41	4 j	C1,S1	SORBITOL	A	vascularite
MA9700957	**F,50**	**8 ans**	**C1,S1**	**STAGID, 8 ANS, C1,S1**	A	**vascularite**
PP8990384	F,75	3 sem.	C2,S1	DAONIL, C1,S1 STAGID, C1,S1 TILDIEM, C1,S1 NATIROSE, C1,S1	A	purpura
CF9200106	F,67		C2,S2	VASTAREL, C2,S2 DAFALGAN, C2,S2 ELISOR, C2,S2	A	purpura
PO9700410	**M,47**	**2 sem.**	**C1,S1**	**ATHYMIL,C1,S1**	F	**purpura rhumatoide**
PA9739366	**M,65**	**8 mois**	**C1,S1**	**COZAAR, 5 j, C1,S1** **DAONIL, 8 mois, C1,S1** **GLUCOPHAGE, 8 m., C1,S1** **ZYLORIC, 33 mois, C1,S1** **LOXEN, 33 mois, C1,S1**	A	**lichen plan**
NC9400417	F,20	1 mois	C1,S2		F	acné
10540911	F,45	15 j	C2,S1	ASPIRINE	A	pustulose exanthématique
10540F26	F,20	2 mois	C1,S1		F	alopécie
10840616	M,72	7 mois	C2,S1	NIDREL ZYLORIC LASILIX ZOCOR ARTEX	F	colororation noire de la langue

Les effets indésirables cutanés et/ou allergiques ne sont pas mentionnés dans les RCP

X. ATTEINTES NEURO-PSYCHIATRIQUES :

49 notifications ont été rapportées, *31* par les CRPV, 18 par le laboratoire :

Elles concernent *24* hommes (Age moyen : *52,9* ans) , 25 femmes (Age moyen : 58,8 ans)

1. Asthénie, Somnolence, Impuissance :

Dans certaines observations:

- soit le délai de survenue semble long : 2ans (LM8600219) ou inconnu (DJ8800131)
- soit le traitement associé peut être responsable de tels effets: PROZAC, GLUCOPHAGE...

Asthénie et somnolence sont mentionnés dans les RCP.

Annexe 3-2

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
ASTHENIE						
LM8600219	M,56	2 ans	C2,S2		A	
TO8900326	M,49	1 mois	C1,S1		F	
MA9300480	F,45	6 mois	C2,S1	PRAXINOR, 1 mois, C2,S1 PONDERAL, C1,S1	A	
LY9600435	**F,53**	**8 sem.**	**C2,S1**	**GLUCOPHAGE, 8 sem., C2,S1** **PROZAC**	A	
123F40	**M,48**	**1 an**	**C1,S1**	**BEFIZAL**	U	
SOMNOLENCE						
DJ8800131	F,76	?	C2,S2		A	+ lymphopénie
TO9200397	F,64	6 j	C3,S2		A	
MA9300577	F,42			ISOMERIDE		
RE9510102	**F,69**	**4 j**	**C2,S1**	**LASILIX, C1,S1** **PREVISCAN, C1,S1** **COVERSYL, C1,S1** **INSULATARD, C1,S1**	A	
10060074	F,56	1 mois	C3,S1	FONLIPOL DIGOXINE CORDARONE Antivitamines K	A	
10060150	F,70	4-5 j	C2,S1	GLUCOPHAGE Retard, C1,S1 LIPANTHYL, C1,S1	A	
MA9900607	***M, 32***	***1 j***	***C3,S1***		***A***	
TROUBLE DE LA VIGILANCE						
10010335	F,72	3 j	C2,S1	TENORMINE SERESTA CYCLOTERIAM	A	
NC9500466	**M,55**	**3 j**	**C3,S2**		A	impuissance
10051460	M,45	1 mois	C2,S1	DESATURA DAFLON 500	A	trouble de l'érection

2. Troubles psychiatriques :

Elles concernent 13 hommes (âge moyen :53,2 ans) et 14 femmes (âge moyen : 60,4 ans)

Les troubles psychiatriques sont divers : agressivité, nervosité, confusion, délire

La responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue

3 cas sont imputés « vraisemblable » :

- NC9500171 : nervosité et nausées chez une femme de 50 ans, 1 à 2 h après la prise d'1 cp de MEDIATOR

- 10010345 : désorientation et obnubilation, chez une femme de 80 ans. Le traitement a été arrêté après 13 j. Une réadministration ultérieure a été positive. (traitement associé : KERLONE et MOGADON)

- PA97355052 : syndrome de sevrage avec excitation, chez un homme de 27 ans, sportif, qui avait pris 9 cp/j de MEDIATOR, comme « dopant ».

5 cas sont imputés « plausible » :

- NC9700094 : accès d'agitation et agressivité, chez une femme de 74 ans, pendant la prise de MEDIATOR, pendant 6 j. Disparition des symptômes 12 h après l'arrêt du MEDIATOR.

Annexe 3-2

- NC9300347 : irritabilité chez un homme de 39 ans, traité pendant 11 mois par MEDIATOR. L'évolution est favorable à l'arrêt du médicament.

- NC9300349 : dépression, chez un homme de 50 ans, traité pendant 9 mois par MEDIATOR. L'évolution est favorable à l'arrêt du médicament.

- MA9100069 : angoisse et palpitation, chez un homme de 40 ans, 2h après avoir ingéré 4 cp de MEDIATOR.

- CF9000137 : désorientation chez une femme de 79 ans, traitée par MEDIATOR, HALDOL, SERESTA, ZESTRIL, CATAPRESSAN, PRAXILENE, SERMION. L'évolution est favorable à l'arrêt de tous les médicaments.

19 ont été imputés « douteux » : (8 C1,S1, 10 C2,S1, 1 C1,S2)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
TROUBLES PSYCHIATRIQUES						
LY9600963	**M,45**	**1 mois**	**C1,S1**	**LEXOMIL, C2,S1**	**A**	**agressivité**
NC9700094	**F,74**	**6 j**	**C2,S2**		**A**	**agressivité**
541173	**F,45**	**8 j**	**C2,S1**	**CORENITEC, C1,S1**	**A**	**agressivité + hallucination**
MA8900523	F,40		C1,S1	ISOMERIDE, 1j, C2,S1	A	agitation
DJ9800349	**M,74**	**3 mois**	**C2,S1**		**A**	**agitation**
NC9300347	M,39	11 mois	C2,S2		A	irritabilité
NC9500171	F,50	1 cp	C3,S2		A	nervosité
MP9800179	**F,47**	**11 j**	**C2,S1**	**LIPANOR, C1,S1**	**A**	**nervosité**
124G84	**F,35**	**20 j**	**C2,S1**	**MAXEPA LEVOTHYROX HYDROCORTISONE**	**A**	**nervosité + excitation**
NC9300349	M,50	9 mois	C2,S2	LOPRIL, C1,S1	A	dépression
MA9100069	M,40	1 j	C2,S2		A	angoisse
TS9500338	**F,69**	**8 j**	**C2,S1**	**DAONIL, C1,S1 ALPRESS BITILDIEM DIAMICRON...**	**A**	**stupeur**
LY8900392	M,52	20 j	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1	A	cauchemars
10540O46	M,?	qq semaines	C1,S1	ZOCOR, C1,S1 PERSANTINE MAXEPA TILDIEM DAONIL	A	cauchemars
SE9500017	F,41	84 j	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1	A	confusion
10010326	M,61	?	C1,S1	FONZYLANE, C1,S1 SINTROM, C1,S1	A	confusion *autre cause !*
120M85	**M,70**	**11 j**	**C2,S1**	**PREVISCAN, C1,S1 CORDARONE, C1,S1**	**A**	**confusion troubles de la mémoire**
CF9000137	F,79		C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2 SERMION, C2,S2	A	désorientation
10010345	F,80	13 j	C3,S1	MOGADON, C1,S1 KERLONE, C1,S1	A	désorientation obnubilation

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10060J96	F,80	?	C1,S1	RENITEC ADALATE HEMIDAONIL TILDIEM	A	désorientation
10060J13	F,82	1 mois	C2,S1	DAONIL	A	désorientation
120M52	**M,60**	**2 j**	**C2,S1**	**LIPANTHYL, C1,S1** **ASPEGIC, C1,S1**	**A**	**désorientation sommnolence**
10060560	M,75	plusieurs mois	C2,S1	DAONIL	A	trouble du comportement
RN9500096	**F,59**	**73 j**	**C1,S2**	**LIPANTHYL, C1,S2** **PILOSURYL, C1,S2** **CANOL, C1,S2** **OLIVIASE, C1,S2** **Amfépramone, C1,S2**	**A**	**délire**
GR8700216	M,45	16 j	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1	A	délire
10060219	F,65	2 ans	C1,S1		A	bouffées d'angoisse au sevrage
PA9735052	**M,27**	**6 mois**	**C3,S1**	***« 9 cp/j (dopant!) »***	**U**	**excitation au sevrage**

3. Troubles neurologiques :

7 notifications d'imputabilité douteuse ont été rapportées (5 CRPV, 2 laboratoire)

Elles concernent 5 hommes (âge moyen : 59 ans) et 2 femmes (âge moyen : 39 ans)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
CONVULSION						
PA9223988	M,60	?	C2,S1	TENSIONORME, C2,S1 DIFFU K	A	
10060J47	F,36	2 mois	C1,S1	DAONIL	A	crise comitiale
NEUROPATHIE						
MA8700716	M,73	9 ans	C1,S1	HEMOCLAR TORENTAL	U	autre étiologie!
PARESTHESIE						
BX8800193	M,36	8 j	C1,S1	PRAXINOR, 8j, C1,S1	F	
LM9500090	M,61	4 j	C2,S1		A	
MA9700170	**F,42**	**1 j**	**C2,S2**	**TAMIK, C1,S1**	**U**	
10051683	M,65		C2,S1	DAONIL GLUCOPHAGE LIPANOR ANGIOXINE	A	

Annexe 3-2

XI. TROUBLES DE L'EQUILIBRE, VERTIGES :

Ils concernent *7* hommes (Age moyen: *66.4* ans) et *17* femmes (Age moyen : *63,9* ans)

Il s 'agit de patients agés, en général, avec une pathologie lourde : diabète, HTA, insuffisance cardiaque, pontage coronarien, cirrhose ...

6 cas rapportés par le CRPV de BORDEAUX ont été à l'origine d'une nouvelle mise au point des effets indésirables du MEDIATOR lors du Comité Technique du 30 avril 1998.

- BX9701040 : chez un homme de 74 ans, apparition d'une difficulté à la marche pendant un traitement de 4 semaines par MEDIATOR, les troubles sont apparus au bout de 3 semaines.
ATCD et terrain :HTA, DNID, double pontage coronarien
Traitement associé : PREVISCAN, DAONIL, CAPTOLANE, GLUCOPHAGE
Evolution favorable à l'arrêt de MEDIATOR

- BX9701041 : chez un homme de 78 ans, apparition d'un trouble de l'équilibre pendant un traitement de 10 j par MEDIATOR.
ATCD et terrain : DNID, Infarctus du myocarde,3 pontages coronariens, gastrectomie, anévrisme de l'aorte abdominale, ACFA
Traitement associé : DAONIL, CORDARONE, ASPEGIC, GLUCOR
Evolution favorable à l'arrêt de MEDIATOR

- BX9701023 : chez une femme de 63 ans, apparition de trouble de la marche et perte de l'équilibre, pendant un traitement de 9 semaines par MEDIATOR, les symptômes sont apparus au bout de 8 semaines
ATCD et terrain : DNID, cirrhose hépatique alcoolique, HTA, exérèse basocellulaire, neuropathie diabétique
Traitement associé : AVLOCARDYL, DAFLON, DAONIL, LASILIX, GLUCOR, TRANXENE, IMOVANE
Evolution favorable à l'arrêt de MEDIATOR

- BX 9700381 : chez un homme de 63 ans, apparition de trouble de la marche et perte de l'équilibre, pendant un traitement de 4 semaines par MEDIATOR,
ATCD et terrain : DNID, cirrhose, HTA, neuropathie périphérique avec paresthésie des extrémités
Traitement associé : DAONIL
Evolution favorable à l'arrêt de MEDIATOR

- BX9700301 : chez un homme de 71 ans, apparition de trouble de la marche et perte de l'équilibre, pendant un traitement de 6 semaines par MEDIATOR,
ATCD et terrain : DNID, infarctus du myocarde, pontage coronarien,artérite des membres inférieurs, OAP,
Traitement associé :LOPRIL, CORDARONE, VASTAREL, PRAXILENE, EUGLUCAN
Franche amélioration à l'arrêt de MEDIATOR

- BX9701022 : chez une femme de 74 ans, apparition de trouble de la marche pendant un traitement de 7 mois par MEDIATOR, les symptômes sont apparus au bout de 4 semaines
Traitement associé : DIAMICRON, MOPRAL, TILDIEM, ALDACTAZINE, LYSANXIA
ATCD et terrain : DNID, angor
Evolution favorable à l'arrêt de MEDIATOR

Cet effet indésirable est mentionné dans les RCP

Annexe 3-2

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
VERTIGE, TROUBLE DE L'EQUILIBRE						
BX8500092 =060141	M,34	3 mois	C3,S2		A	
MA8800356	F,60	1 j	C2,S2		A	
MA8800929	F,47	1 cp	C2,S2	DAFLON, C1,S1	A	
NC9000297	F,58	15 j	C3,S2		A	
LL9200133	F,63	2 j	C1,S1		U	
NY9306790	F,77	2 j	C1,S2		A	
LM9500091	F,84		C2,S1	SOTALEX, C1,S1 LOXEN, C1,S1 ALDACTONE, C1,S1 CORDIPATCH, C1,S1 PREVISCAN, C1,S1	U	
TS9600227	**F,64**	**4 sem.**	**C3,S1**	**RENITEC, C1,S1** **LIPANTHYL, C1,S1**	**A**	
BX9701040	**M,74**	**4 sem.**	**C2,S1**	**PREVISCAN, C1,S1** **DAONIL, C1,S1** **CAPTOLANE, C1,S1** **GLUCOPHAGE, C1,S1**	**A**	
BX9701041	**M,78**	**10 j**	**C2,S1**	**DAONIL** **CORDARONE** **ASPEGIC** **GLUCOR**	**A**	
NC8900097	F,60	1 cp	C2,S2		A	
MA8700143	F,66	?	C1,S1	FLUVERMAL, C1,S1	F	
BX9701023	**F,63**	**9 sem.**	**C2,S1**	**AVLOCARDYL** **DAFLON** **DAONIL** **LASILIX** **GLUCOR** **TRANXENE** **IMOVANE**	**A**	
BX9700381	**M,63**	**4 sem.**	**C2,S1**	**DAONIL**	**A**	
BX9700301	**M,71**	**6 sem.**	**C2,S1**	**LOPRIL** **CORDARONE** **VASTAREL** **PRAXILENE** **EUGLUCAN**	**A**	
BX971022	**F,74**	**7 mois**	**C2,S1**	**DIAMICRON** **MOPRAL** **TILDIEM** **ALDACTAZINE** **LYSANXIA**	**A**	
10060F71	F,47	?	C2,S1	TAGAMET, C1,S1 JONCTUM, C1,S1 LEXOMIL, C1,S1	A	+ prurit + érythème
10060499	F,40	1 semaine	C3,S1	LEVOTHYROX, C1,S1	A	
10060J48	F,74	2 j	C2,S1	MODURETIC, C1,S1 LOXEN, C1,S1 DETENSIEL, C1,S1	A	
123T12	**F,74**	**?**	**C1,S1**	**GLUCOPHAGE** **DIAMICRON** **TILDIEM** **KERLONE** **RISORDAN** **ALDACTAZINE** **MOPRAL**	**A**	***trouble de la démarche***
BX9800963	***M, 80***	***1 j***	***C2,S1***	***hypoglycémiant***	***A***	

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BX9900071	M, 65	3 j	C2,S1	DAONIL GLUCOR VASTAREL PRAXILENE ANAFRANIL	A	
BX9900134	F, 72	4 j	C2,S1	DAONIL GLUCOR ALDACTAZINE MOPRAL TEMESTA	A	
NY9910594	F, 63	2j	C2,S1	ALDACTONE PRACTAZIN	A	+ malaise

Annexe 3-2

Résumé des paramètres métaboliques de benfluorex

In vivo

Chez l'animal comme chez l'homme, benfluorex est hydrolysé très rapidement au niveau plasmatique et hépatique par des estérases. Benfluorex n'a été retrouvé dans aucun fluide corporel sauf chez le rat où il est présent à des taux faibles (Cmax 2.6 ng/ml à1heure) au niveau plasmatique après administration orale (40 mg/kg). Neuf métabolites majeurs ont été identifiés. Il n'existe pas de différence qualitative entre les espèces animales étudiées et l'homme, les métabolites étant produits en proportion différente.

Après administration orale de benfluorex, S 422 (dérivé alcool) est formé très rapidement puis transformé par oxydation (S 1475, dérivé acide) ou déalkylation (S 585, norfenfluramine) (figure1).

Chez l'homme, les composés présents sont identiques. L'administration orale d'une dose de benfluorex pendant 14 jours (steady state) chez 6 volontaires sains révèle que le métabolite majoritaire est le dérivé carboxylique S 1475 (1361±233 ng/ml). Le métabolite primaire S 422 et la norfenfluramine sont retrouvés à des taux très inférieurs (22 ± 7 et 59 ± 15 ng/ml, respectivement).

Après administration de benfluorex radioactif, l'élimination complète de la radioactivité dans les urines (87 à 99 % de la radioactivité après 72 heures) couplée à l'absence de quantité significative dans les fèces montre que le produit est bien absorbée et qu'aucun phénomène d'accumulation n'est observé.

In vitro

Les 3 principaux métabolites de benfluorex, S 422, S 1475 et norfenfluramine, sont retrouvés dans des proportions équivalentes après incubation d'hépatocytes frais humains (figure2).

Cependant, aucun métabolite de benfluorex ou de S 422 n'est produit à partir de cellules hôtes exprimant de manière spécifique l'un des principaux cytochromes P450 (1A2, 2C9, 2C19, 2D6, 2E1 et 3A4). A partir de microsomes humains, S 1475 et S 585 n'exercent aucun effet inhibiteur sur les cytochrome P450 1A1, 2C19, 2C9, 2D6, 2E1, 3A4 à des concentrations correspondant à 10 et 100 fois le C_{max}. Seul, S 422 à 100 fois le C_{max} réduit d'environ 50 % l'activité de CYP2D6. Les faibles taux circulants de ce métabolite par rapport à S 1475 sont néanmoins en faveur d'une vitesse de métabolisation rapide de S 422 par des enzymes de type alcool déshydrogénase ou aldéhyde oxydase.

Sur des préparations d'hépatocytes humains les inhibiteurs sélectifs ou non sélectifs des principaux cytochromes sont sans effet sur le métabolisme de benfluorex.

Ces résultats suggèrent qu'in vitro les principaux cytochromes P 450 jouent un rôle très minoritaire dans le métabolisme de benfluorex.

Enfin, l'inhibition du clivage de benfluorex en S 422 et acide benzoïque par le paroxon confirme que cette réaction est sous la dépendance de carboxylestérase.

Résumé

Benfluorex chez l'animal comme chez l'homme est rapidement métabolisé par des estérases en S 422 puis en au moins 8 autres composés dont S 1475 (majoritaire chez l'homme) et la norfenfluramine. Ces trois métabolites sont produits in vitro à partir de préparations d'hépatocytes frais humains. Les travaux menés sur microsomes et les études d'inhibition révèlent que S 422 emprunte une voie métabolique indépendante des principaux cytochromes P450 (voir Schéma).

Figure 2 :VOIE METABOLIQUE PROPOSEE SUR LA BASE DES TRAVAUX IN VITRO

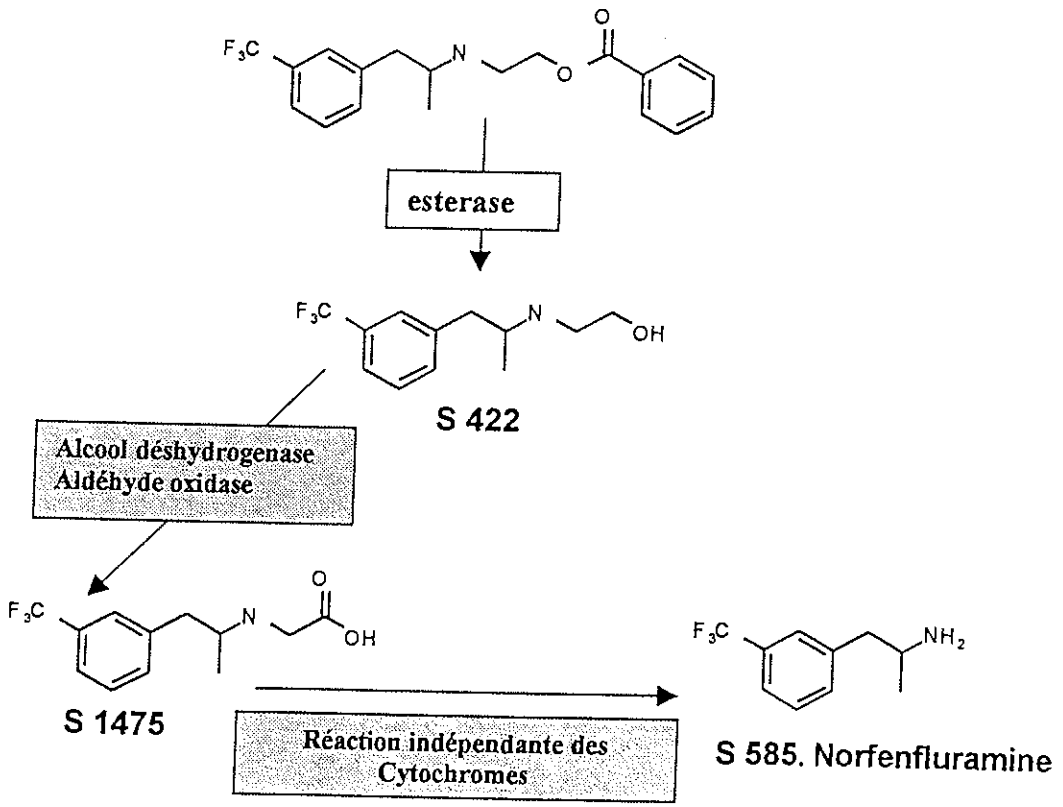
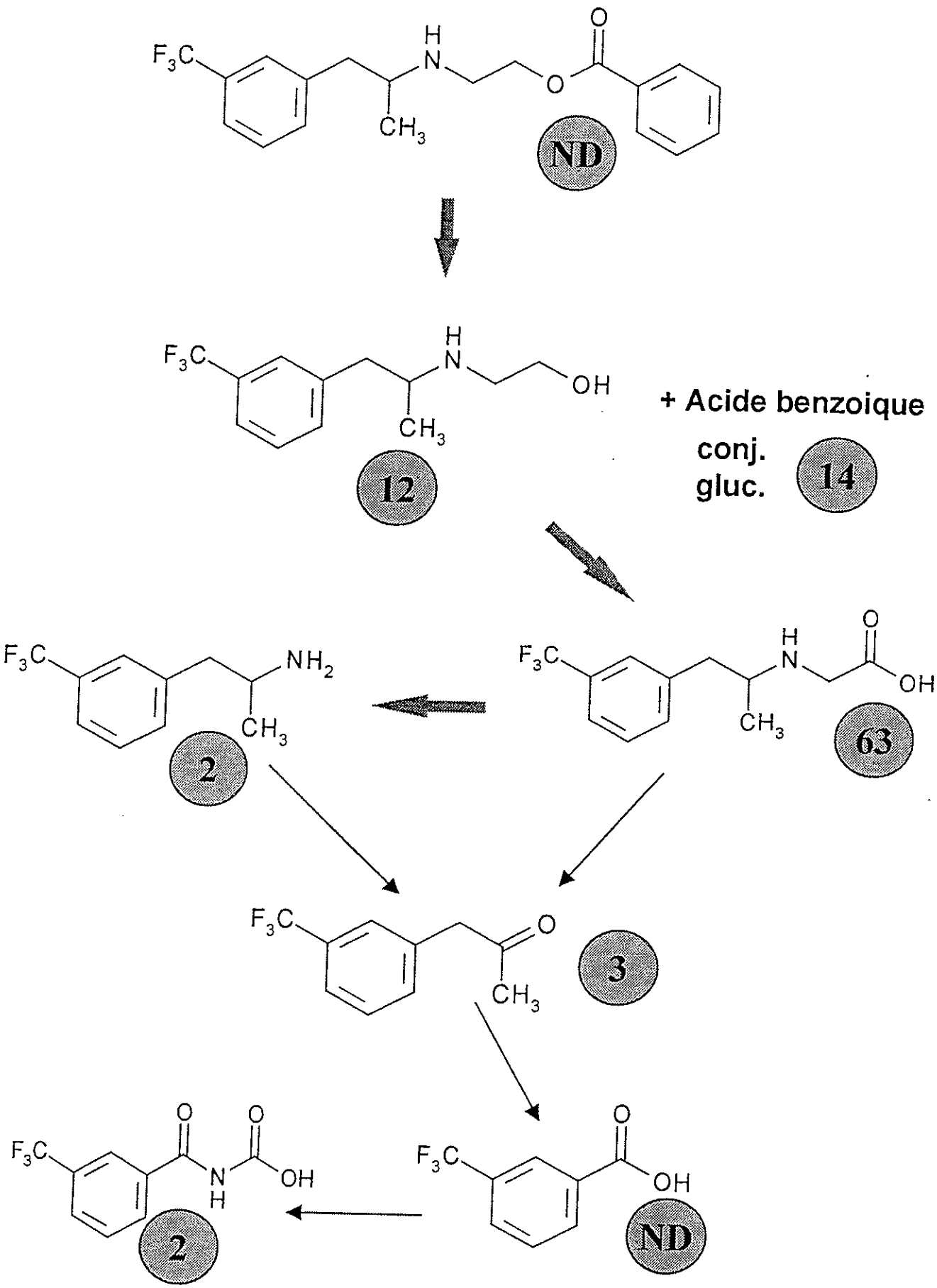


Figure 1 :
Excretion urinaire (% de la dose administrée) sur 24 heures chez l'homme



Annexe 3-3

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis le,

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Jeudi 18 Mai 1995)

Etaient présents

M. IMBS : Président,
Mme ALBENGRES, Mme BENETON (suppléante de M. ALLAIN H.), M. ALLAIN P., M. ANDREJAK, Mme DAVID (suppléante de M. BECHTEL), M. BEGAUD, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), Mme BOURGEON, M. CARON, M. BIOUR (suppléant de M. CHEYMOL), Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme CHIFFOLEAU, M. TRENQUE (suppléant de M. CHOISY), Mme PIERRON (suppléante de Mme EFTHYMIOU), Mme SGRO (suppléante de M. ESCOUSSE), M. VIAL (suppléant de M. EVREUX), M. RODOR (suppléant de Mme JOUGLARD), Mme KREFT-JAIS, M. LAROUSSE, Mme LAVARENNE, M. MERLE, M. MONTASTRUC, Mme NOBLET (suppléante de M. MOORE), Mme MOSQUET (suppléante de M. MOULIN), Mme BAVOUX (suppléante de M. OLIVE), Mme GUY (suppléante de M. OLLAGNIER), Mme PIERFITTE, M. RICHE, M. ROYER, Mme SOUBRIE, M. VANDEL, Mme CASTOT (représentant M. le Directeur Général de l'Agence du Médicament), Mme GOUJARD (représentant M. le Directeur Général de l'INSERM).

Conseiller scientifique

M. LAGIER

Unité de pharmacovigilance

Mme BIDAULT
Mle LE BELLER
M. LE LOUET
Mme LEREBOURS
Mme MORIN

Assistaient à la réunion

Mme BREEMEERSCH

Etaient excusés

Mme AUTRET, M. HUGUES, M. MALLARET, M. le Directeur des Hôpitaux ou son représentant, M. le Directeur Général de la Santé ou son représentant.

Annexe 3-3

I - ADOPTION DES PROCES-VERBAUX DES COMITES TECHNIQUES DU 20 AVRIL ET DU 26 AVRIL 1995

Les procès-verbaux des Comités Techniques du 20/04/95 et du 26/04/95 ont été adoptés sous réserve des modifications suivantes :

Page 25 : POLARAMINE® : remplacer "demande d'exonération" par "demande d'automédication".

Page 32 : Remplacer à l'avant dernier paragraphe "800 mg/m^2" par "700 mg/m^2" et "700 mg/m^2" par "800 mg/m^2".

Page 33 : Remplacer demande d'exonération de liste II en liste II par demande d'exonération de liste I en liste II.
Remplacer "Arylcarboxyliques" par "Aryl-carboxyliques".

Page 36 : Remplacer le troisième paragraphe par "un groupe de travail est mis en place afin d'instaurer une réflexion sur les éventuels échanges d'information concernant les effets indésirables graves et inattendus venant des CRPV vers les Industriels".

II - APROTININE ET THROMBOSE

Une actualisation du bilan de 1993 sur les thromboses survenant lors de traitement par l'aprotinine a été présentée par le C.R.P.V. de Créteil. L'aprotinine, inhibiteur de la plasmine et de la kallicréine, est commercialisée sous forme de trois spécialités : ANTAGOSAN®, INIPROL®, TRASYLOL®.

• Fin 1993, 9 dossiers d'imputabilité faible (C2S1) avaient été retenus. Les résultats des essais cliniques et des études *in vitro* étaient attendus pour clarifier les données de la littérature.

• Depuis :

- Le système national n'a recueilli qu'une seule observation de thrombose, d'évolution fatale, survenue chez une femme de 42 ans lors d'une greffe de foie pour cirrhose hépatique. Etant donné des antécédents notables d'hémorragie importante en post-partum, la greffe avait eu lieu sans héparine, ce qui représente un facteur favorisant la formation de thrombose.

- Les trois essais cliniques menés sur de petits effectifs avec l'INIPROL®, n'ont pas mis le risque de thrombose en évidence.

- Les quelques cas rapportés dans la littérature ont été observés lors d'association de protamine et d'aprotinine.

- Les données épidémiologiques ne montrent pas de différence entre placebo et traitement du point de vue de la sécurité sur des critères de mortalité ou de complications.

Des facteurs favorisant la formation d'une thrombose semblent donc apparaître : un hématocrite élevé, une réintervention chirurgicale (tissus remaniés, thromboses anciennes), une héparinisation incorrecte du patient ou de cathéter, ou une mise en place traumatique de cathéter. La recherche de protocoles d'emplois de l'aprotinine adaptés aux facteurs de risque des patients apparaît nécessaire.

Annexe 3-3

III - AMLOR® (amlodipine) ET EFFETS INDESIRABLES

Le CRPV de Dijon a fait le point des effets indésirables de l'amlodipine en dehors des effets indésirables cardiaques qui ont été examinés par le CRPV de Lille.
A cette enquête officielle s'est ajoutée l'analyse d'une demande de modification de l'ensemble du RCP déposée par la firme et concernant en particulier les effets indésirables. Il est important de mentionner dans ce cadre la demande d'extension d'indication à l'angor spontané.

L' AMLOR® (amlodipine) a obtenu son AMM en 1990 et est commercialisé depuis 1992 par les laboratoires Pfizer.
309 observations d'effets indésirables ont été retenues.
Parmi ceux-ci, **les effets cardiaques** sont en plus grand nombre :

Sur les 137 dossiers examinés, 69 restent exploitables (les autres dossiers sont soit inexploitables soit relèvent d'une inefficacité thérapeutique).

Il s'agit de 16 cas d'insuffisance coronarienne :

	Ins. coronarienne connue et/ou coronarographie anormale	I1	I2	I3
douleur angineuse	12/16	13	2	1 (rech+ mais arrêt β^- aussi : syndrome de sevrage aux β^- possible)
angor instable	2/2	2	0	0
infarctus du myocarde	4/5	5	0	0
précordialgies atypiques	4/10	7	1	2

Il faut remarquer une observation de douleurs angineuses précoces, avec infarctus du myocarde au 3ème jour après introduction du traitement, posant le problème d'une déstabilisation d'une angine de poitrine entraînant un IDM.

2) de décompensation cardiaque : 4 cas contemporains :

- d'un passage en fibrillation auriculaire,

- d'une insuffisance ventriculaire gauche sur cardiopathie hypertensive,

- d'un oedème aigu du poumon compliquant un choc cardiogénique d'un infarctus du myocarde aigu,

- d'un oedème aigu du poumon sur cardiopathie ischémique.

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3) de mort subite chez 4 patients

- aux antécédents d'hypertension artérielle et d'insuffisance coronarienne dans 2 cas,
- ayant fait un effort physique la veille dans 2 cas,

4) d'hypotension et d'hypertension : 11 cas

Parmi ces observations, 5 sont d'imputabilité plausible (I2) mais en association à un facteur favorisant dans 3 cas (hémodialyse, IDM semi-récent, interaction avec un autre médicament) ; il faut préciser pour l'observation d'hypertension qu'elle est survenue immédiatement au moment du relais nifédipine/amlodipine.

5) de tachycardie : 6 cas d'imputabilité douteuse

6) de 3 cas douteux de bradycardie,

7) et de 3 observations diverses (syncope post prandiale, troubles de la repolarisation atypiques, allongement du QT).

De plus le rapport interne de la firme fait état de 14 cas de fibrillation auriculaire et de 10 cas de troubles du rythme ventriculaire sur la période allant du 24.04.92 au 31.12.93.

Dans son ensemble, ce dossier ne paraît pas alarmant.

* La demande de modification de la firme d'introduire la notion d'infarctus du myocarde selon le libellé proposé (qui précise que la relation de cause à effet n'est pas prouvé) est recevable. Il faut noter que cette mention est déjà incluse dans le Vidal®1995.

Il s'agit de la modification suivante (phrase soulignée) :

" chez les coronariens, comme avec les autres inhibiteurs calciques, ont été rarement observés des douleurs thoraciques, éventuellement des douleurs angineuses, voire un infarctus du myocarde, sans que ces événements puissent être distingués de l'histoire naturelle de la maladie. Ces manifestations demeurent extrêmement rares mais imposent l'arrêt du traitement."

* il n'y a pas lieu d'apporter d'autres modifications (les autres mentions existantes sont :"..tachycardie, palpitations..."

* il est souhaitable de compléter la liste des médicaments pouvant donner lieu à une interaction médicamenteuse (baclofène, AINS, anti dépresseurs imipraminiques, corticoïdes et neuroleptiques) ; ces modifications figurent déjà au Vidal®1995.

Annexe 3-3

En ce qui concerne la revue des autres effets (dont l'analyse plus précise fera l'objet d'une présentation à un prochain comité technique à l'automne prochain), il s'agit pour la plupart d'effets déjà bien connus tels que :

- des troubles vaso moteurs périphériques,

- des manifestations dermatologiques (le libellé actuel est succinct : "on observe plus rarement...des réactions cutanées (prurit)..." ; la firme propose actuellement de rajouter "rash",

- des troubles neurologiques et neuro psychiatriques (une attention particulière sera portée sur la possibilité de syndrome parkinsonien) ; le libellé actuel comporte la notion d'étourdissements et la firme souhaite ajouter la notion de somnolence,

- des troubles digestifs à type de nausées, vomissements, douleurs abdominales, dyspepsie ; la notion de nausées existe déjà et la firme souhaite rajouter douleurs abdominales, dyspepsie,

- 10 cas d'effets bronchopulmonaires dont 5 avec toux, d'un cas d'aggravation d'un asthme, de 2 observations de dyspnée d'effort (non cardiogénique) et de 2 pneumopathies interstitielles :**ces manifestations respiratoires nécessitent une analyse plus précise** avant de pouvoir se prononcer sur la proposition de la firme d'un ajout isolé de la mention :"dyspnée".

- des atteintes hépatiques : 10 cas dont 5 d'imputabilité plausible et 3 avec médicaments associés,

- des troubles à type d'élargissement et d'hypertrophie gingivale (effet non nouveau),

- 7 cas de polyurie et pollakiurie (effet décrit avec la nifédipine : à inclure aussi pour l'amlodipine ?),

- des atteintes hématologiques (3 sur la lignée blanche et 3 concernant la lignée plaquettaire),

- des troubles de la coagulation avec hypocoagulabilité sans interaction retrouvée : un effet antiagrégant plaquettaire a déjà été évoqué dans la littérature ;

- et enfin 5 modifications du taux de prothrombine lors d'association avec un anticoagulant oral ; une étude préAMM a conclu l'absence de modification de la liaison protéique de la warfarine en présence de l'amlodipine ; cependant un autre mécanisme d'interaction pourrait être évoqué du fait du métabolisme hépatique oxydatif de cette molécule : **ce point sera donc à revoir ultérieurement**.

Dans un premier temps une réunion de concertation avec la firme est à prévoir en ce qui concerne les effets indésirables cardiaques et la rédaction actuelle du Vidal® 1995.

Annexe 3-3

IV - SPECIALITES CONTENANT DU NAFTIDROFURYL UTILISEES PAR VOIE ORALE ET EFFETS INDESIRABLES HEPATIQUES.

Commercialisées par trois laboratoires, les spécialités de naftidrofuryl sous forme orale sont : PRAXILENE® 200 (comprimés), PRAXILENE® 100 (gélules), GEVATRAN® 200 (gélules LP), DI-ACTANE® 200 (gélules LP) et NAFTILUX® 200 (gélules LP).

Le C.R.P.V. de Lyon a réalisé l'enquête sur les effets indésirables hépatiques lors de l'administration par voie orale de ce principe actif.

De 1985 à fin 1994, 79 cas d'atteinte hépatique ont été collectés par le système national de pharmacovigilance (73 cas) et par les industriels (10 cas, dont 4 doublons).

Après exclusion de 35 observations (autre diagnostic étiologique possible, médicament associé d'imputabilité supérieure, critère chronologique incompatible), les 44 observations retenues impliquent en majorité le PRAXILENE® 200. Le sexe ratio est proche de 1. La moyenne d'âge est d'environ 70 ans et correspond aux données DOREMA de prescription. L'indication est précisée seulement dans 41% des observations (essentiellement traitement de l'artérite).

A l'exception de 3 cas de surdosage, la posologie utilisée est conforme aux recommandations dans 92% des cas. Le délai moyen de survenue est de 11 mois après le début de traitement pour l'ensemble des observations et de 5,1 mois pour les observations plausibles. Les atteintes hépatiques observées sont le plus souvent de type cytolytique. Des signes de gravité sont présents dans 8 cas plausibles (un cas d'hépatite fulminant avec décès, un décès brutal, trois cas avec ictère et/ou baisse du TP<50% et trois cas avec ictère seul) mais aussi dans 9 cas douteux. Un médicament associé de même imputabilité et potentiellement hépatotoxique est retrouvé dans 13 de ces 17 cas présentant un critère de gravité.

A l'exception de 4 décès, l'évolution a été favorable dans les autres cas. Un cas avec réintroduction positive est noté chez une patiente souffrant de la maladie de Gilbert. Les cas douteux comportent toujours un traitement associé.
L'incidence des observations plausibles est très faible : 1 cas pour 1 180 000 mois de traitement.

Au niveau international, 9 cas ont été signalés dont 6 en faveur de la responsabilité du PRAXILENE®.

Les arguments suggérant une hépatotoxicité du naftidrofuryl sont représentés par un cas avec réintroduction positive, et l'homogénéité des types d'atteinte (cytolytique aiguë dans 70% des cas). Cependant, l'incidence demeure très faible et la majorité des observations comporte un traitement concomitant potentiellement hépatotoxique.

Le dossier sera présenté lors d'une prochaine Commission nationale de Pharmacovigilance.

Annexe 3-3

V - ZAGAM® (sparfloxacine) ET PHOTOSENSIBILISATION

Le Comité technique de pharmacovigilance, réuni le 18 mai 1995, a pris connaissance des données de pharmacovigilance concernant la spécialité ZAGAM® et plus particulièrement des **accidents cutanés de phototoxicité.**

Cette étude porte sur les **7 premiers mois de commercialisation** (jusqu'au 24 avril 1995) et regroupe 208 observations en provenance de la firme et des centres régionaux de pharmacovigilance.

Ces réactions de photosensibilisation représentent 30% de l'ensemble des effets et 80% des effets indésirables cutanés signalés avec cette spécialité.

Il s'agit de manifestations cliniques de type phototoxique (érythème de type solaire des parties découvertes) survenant après 3 à 4 jours de traitement en moyenne mais avec des signes de gravité clinique dans **15,6% des observations** : il s'agit alors de **brûlures du 2° degré.**
Ces signes peuvent également survenir après l'arrêt du traitement (jusqu'à 4 jours après l'arrêt).

La gravité de la réaction semble dose dépendante mais pour 26 cas (graves ou non), les lésions sont apparues **sans exposition évidence au soleil.** Ainsi dans les cas graves, l'exposition solaire a été franche pour la moitié des cas, mais inapparente ou modérée dans 27% des cas.
Dans l'ensemble, l'évolution est favorable (65,8%) mais il faut noter que le **délai de guérison** peut dépasser 1 mois.

Il est difficile de préciser si le produit a été pris dans le cadre strict des indications de l'AMM :

- les pneumopathies communautaires présumées bactériennes, pneumococciques et non pneumococciques,

- les exacerbations des bronchopneumopathies chroniques obstructives,

- et les sinusites aiguës purulentes.

Les observations de pharmacovigilance rapportées lors de cette enquête concernaient le traitement de pneumopathies, de bronchites et de sinusites, mais sans plus de précision.

Pendant cette période, 1.034.073 boites de 6 comprimés ont été vendues. Les ventes mensuelles vont de 202.277 boites en octobre 1995 (maximum) à 77.205 boites en avril 1995 (minimum).

La fréquence de notification de ces accidents de photosensibilité est de :

- **1 cas pour 29755 jours de traitement, soit 1 cas pour 4020 patients traités.**

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Par comparaison, il s'agit d'une effet de classe bien connu avec les autres fluoroquinolones étudiées jusqu'à maintenant en France (prévu dans l'AMM : mention dans la mise en garde et effet cité dans la rubrique effet indésirable), mais sa fréquence de notification est 4,5 fois plus élevée par rapport à celle de la pefloxacine, 96 fois pour la ciprofloxacine, 100 fois pour la norfloxacine et 410 fois pour l'ofloxacine.

De plus, les premiers résultats de l'enquête concernant les 21 notifications d' **effets indésirables cardiaques** ont été analysés. Il existait déjà une mise en garde prévenant du risque d'une légère augmentation de l'intervalle QT (allongement inférieur à 3% en moyenne) et une précaution d'emploi lors de l'association aux médicaments connus pour allonger le QT.

Cette analyse rapporte **6 cas d'allongement du QT** de découverte fortuite dans un cas mais symptomatiques dans les 5 autres cas dont 3 cas de **torsades de pointe** avec **2 arrêts cardiaques** initiaux récupérés et une syncope dans le dernier cas.

Dans les 3 observations avec torsades de pointe, on retrouve dans 2 cas un traitement associé par cordarone et un QT long congénital dans le 3°cas (associé à des taux plasmatiques de sparfloxacine élevés de façon inexpliquée).

D'autres observations peuvent évoquer un trouble du rythme aigu mais ne sont pas documentées sur le plan électrocardiographique : il s'agit de 2 cas de mort subite, 2 pertes de connaissance avec hypotension dans un cas et bradycardie dans l'autre.

Ainsi l'estimation de la fréquence est de 1 cas d'effet indésirable cardiaque pour 294.717 jours de traitement, soit 1 notification pour 39.800 patients traités.
Malgré cette fréquence faible, il est inquiétant de voir dès les premiers mois de commercialisation apparaître des observations de torsade de pointes alors que les données pré AMM ne laissaient supposer qu'une augmentation faible et asymptomatique du QT.

En conclusion, le Comité technique est alerté par ces données, concernant en particulier la photosensibilité de ce médicament, et estime qu'elles posent un problème de santé publique urgent (à l'approche de l'été) du fait de la **gravité**, de la **fréquence**, de la difficulté **d'appliquer des mesures préventives.**

Le Comité technique souhaite que des mesures soient prises d'urgence. L'administration propose de convoquer rapidement une Commission nationale extraordinaire.

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VI - EXAMEN DE LA DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE DU TRIATEC® (ramipril)

Le ramipril est un inhibiteur de l'enzyme de conversion indiqué dans le traitement de l'hypertension artérielle.

Une demande de modification du résumé des caractéristiques du produit pour les trois formes commercialisées TRIATEC® FAIBLE 1,25 mg, TRIATEC® 2,5mg et TRIATEC® 5mg a été déposée par le laboratoire Hoechst en mars 1994, transmise à l'unité de pharmacovigilance en mars 1995 et confiée au centre régional de pharmacovigilance de **Paris-Broussais.**

Au vu des notifications de la banque nationale de pharmacovigilance, des déclarations obligatoires de la firme et de la littérature, le Comité Technique s'est montré favorable pour rajouter :

- à la rubrique "Mise en Garde" : à la fin du paragraphe hémodialyse concernant les réactions anaphylactoïdes : "des réactions similaires ont été observées au cours de LDL aphérèses sur sulfate de dextran".

- à la rubrique "Effets Indésirables" :

  - au paragraphe "effets digestifs , "une augmentation des enzymes hépatiques a été notée dans des cas isolés, associée exceptionnellement à une hépatite cholestatique ou mixte nécessitant l'arrêt du traitement".

  - un paragraphe "effets respiratoires" : " Toux, et plus rarement rhinite ou bronchospasme"

  - un paragraphe "effets allergiques et cutanés" : "Prurit , éruption cutanée maculopapuleuse ou urticarienne, flush, et exceptionnellement : dermatose lichénoïde ou psoriasiforme. Fièvre, myalgies arthralgies ont aussi été observées".

En revanche, il n'a pas été jugé nécessaire de signaler la notion d'érythème polymorphe et de purpura vasculaire , les notifications de ces effets étant très rares.

Le dossier sera présenté à une prochaine Commission Nationale de Pharmacovigilance.

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VII - EXAMEN DE LA DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE DU PRESTOLE® (triamtérène et hydrochlorothiazide)

L'analyse de la demande de modification de l'information médicale des laboratoires SmithKline Beecham, concernant leur spécialité PRESTOLE® (association de triamtérène et d'hydrochlorothiazide indiquée dans le traitement de l'hypertension artérielle) a été présentée par le C.R.P.V. d'Amiens.

1/ Interactions médicamenteuses :

La proposition du laboratoire d'introduire à propos des "associations nécessitant une précaution d'emploi" les inhibiteurs de l'enzyme de conversion en raison d'un risque d'hyperkaliémie parait justifiée. Cependant, afin de respecter le schéma commun de rédaction des RCP des diurétiques thiazidiques, cette mention sera libellée en élargissant au risque d'insuffisance rénale aiguë.

En revanche l'interaction médicamenteuse avec le chlorpropamide et son risque de majoration d'une hyponatrémie, mentionnée dans la 29ème édition du Martindale, n'a pas été confirmée lors d'une étude cas/témoin, et semble avoir peu d'intérêt pratique pour le prescripteur.

2/ Effets indésirables :

D'après les données de la littérature, il n'est pas établi qu'une association type PRESTOLE® présente un risque de troubles du rythme. L'hypokaliémie peut favoriser la survenue de troubles du rythme induits par un médicament antiarythmique ou proarythmique (digitaliques, anti-arythmiques et substances non anti-arythmiques susceptibles de donner des torsades de pointe). Cette notion ne sera pas insérée dans la rubrique "Effets indésirables" mais devrait apparaître dans les "Précautions d'emploi" ou les associations déconseillées.

La possibilité d'un pouvoir lithogène du triamtérène est avancée depuis 1979. Si sa responsabilité est discutée et non réellement prouvée, l'analyse des sédiments a montré la présence de triamtérène. Cette proposition parait donc justifiée.

La survenue d'effets indésirables à type de modification de la formule sanguine et thrombopénie est rapportée dans la littérature, pancytopénie, thrombopénies périphériques immunes, anémie hémolytique immuno-allergique. Le libellé proposé par le laboratoire sera reformulé ("exceptionnellement accidents hématologiques avec pancytopénie par déficit en folates").
Des élévations modérées des taux plasmatiques de créatinine, urée, acide urique et glucose, peuvent être observées, et seront donc mentionnées dans le RCP, comme le souhaite le laboratoire.

3/ Précautions d'emploi :

Aucune étude n'étant disponible chez l'enfant, la sécurité d'emploi n'a donc pas été établie. Cette notion peut donc apparaître dans ce chapitre.
Le relevé d'avis du Comité technique relatif à ce dossier sera présenté lors d'une prochaine Commission nationale de pharmacovigilance.

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VIII - EXAMEN DE LA DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE DU SPORANOX® (itraconazole)

Le Centre de pharmacovigilance de Lille a examiné la demande de modification de l'information médicale de SPORANOX®(itraconazole), antifongique azolé commercialisé par les laboratoires Janssen-Cilag.
L'intérêt de cette spécialité réside dans son efficacité dans les mycoses systémiques, notamment l'aspergillose, et sa possibilité d'administration par la voie orale.

Données de pharmacovigilance :

Entre avril 1993, lors de la commercialisation, et fin 1994, 25 observations ont été enregistrées par les CRPV, dont 3 cas d'interactions médicamenteuses imputées I_2 ou I_3 impliquant l'itraconazole.
Il s'agit d' un cas d'augmentation des concentrations plasmatiques de la terbinafine ayant entraîné un allongement de QT avec arrêt cardiaque (imputé I_3), d'un cas d'hémorragie digestive et baisse du taux de prothrombine, lors d'une association à l'acénocoumarol (imputé I_2) et d'un cas de diminution des concentrations plasmatiques d'itraconazole lors d'une association avec le phénobarbital et la carbamazépine (I_3).
Parmi les observations imputées I_1, on note 3 anomalies ou atteintes hépatiques et 3 atteintes nerveuses périphériques.

Les effets indésirables recensés sont :

- des oedèmes de localisation variée (des chevilles, des jambes, des extrêmités ou périphériques, généralisés ou sans précision : 40 cas internationaux, 2 angio-oedèmes dans la déclaration obligatoire française) correspondant pour certains à des interactions médicamenteuses avec les dihydropyridines ou des réactions de type allergiques.

- des neuropathies périphériques (6 neuropathies ou névrites et 6 paresthésies au niveau international, 1 cas publié de potentialisation de la neurotoxicité de la vincristine, 9 dossiers de la banque nationale et 2 cas du laboratoire). Ces deux derniers se caractérisent par une réintroduction positive (certaine dans un cas).

- des anomalies du bilan hépatique ou atteintes hépatiques (37 observations succinctes au niveau international, 31 cas possibles ou probables notifiés en 1992 au niveau international sur une période de 10 mois, pour lesquels on observe que l'incidence augmente lorsque le traitement dure plus d'un mois, 40 cas dans la banque française, 4 cas rapportés dans la littérature et 2 cas d'hépatites fulminantes rapportés par le laboratoire).

- des effets indésirables cutanés, dont 2 cas de syndrome de Stevens-Johnson dans le bilan international, qui méritent d'être inclus dans le RCP.

- des effets auditifs à type d'acouphènes ou diminution de l'acuité auditive (16 observations internationales ou publiées, dont 9 lors d'association avec des quinidiniques, évoquant des manifestations de cinchonisme).

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Pour la grande majorité, les demandes de modification du laboratoire paraissent justifiées :

1/ Contre-indications :

Il s'agit notamment des contre-indications avec l'astémizole ou le cisapride. Des études expérimentales sur microsomes hépatiques humains ont mis en évidence une inhibition de leur métabolisme par l'itraconazole.
L'association avec le triazolam sera aussi mentionnée, en raison d'une étude pharmacocinétique chez des volontaires sains montrant une élévation significative de l'aire sous la courbe, du Cmax et de la demi-vie d'élimination de ce médicament, en présence d'itraconazole. De plus, au niveau international, 5 cas de somnolence ont été notifiés lors d'un traitement concomitant.

2 /Mises en garde :

Les données de pharmacovigilance sur les atteintes hépatiques plaident en faveur de l'introduction d'une surveillance du bilan hépatique lors de traitement de plus d'un mois.

3/ Interactions médicamenteuses :

Avec :

- les dihydropyridines : 16 cas d'oedèmes des membres recensés au niveau international lors d'une prise concomitante d'antagonistes du calcium, le plus souvent des dihydropyridines. Une interaction de type pharmacocinétique semble être possible , certaines dihydropyridines étant métabolisées par le cytochrome P 450 3A4.
- la didanosine : l'anti-ancide présent dans les comprimés de didanosine est susceptible d'interagir dans la solubilisation de l'itraconazole et donc de diminuer son absorption. Un intervalle de 2 heures entre les prises de ces deux médicaments est donc conseillé. Il apparait nécessaire d'étendre cette interaction aux antiacides. En revanche, en l'absence d'arguments, les inhibiteurs de la pompe à protons et les antihistaminiques H2 ne paraissent pas devoir être mentionnés.
- les quinidiniques : 9 notifications de manifestations auditives sont recensées lors d'une association avec un quinidinique (concentrations plasmatiques non déterminées), qui peuvent évoquer un cinchonisme. D'autre part un dossier de la firme fait état d'une surdité avec réintroduction positive. Il apparait prudent, compte tenu de ces constations d'introduire une précaution d'emploi dans le RCP.
- les antivitamines K : les cas observés avec l'acénocoumarol et la warfarine rendent nécessaires un contrôle du taux de prothrombine et une adaptation posologique.
- le tacrolimus : une étude expérimentale sur microsomes hépatiques de rat montre un caractère inhibiteur de l'itraconazole sur le métabolisme de ce produit, non encore commercialisé en France (s'il obtient l'autorisation de mise sur le marché, l'association devra être déconseillée).

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4/ Effets indésirables :

Au vu des données de pharmacovigilance, il apparait nécessaire d'inclure les effets indésirables de type oedème de Quincke, syndrome de Stevens-Johnson et d'élévation des enzymes hépatiques lors de traitements de courte durée, ainsi que la possibilité de survenue d'oedème, hépatites et neuropathies périphériques lors de traitements de longue durée.

L'association avec le midazolam, disponible uniquement par voie IV en France, pourrait être déconseillée. De plus, le Comité technique suggère un réexamen des cas de neuropathies avec une analyse du rapport de toxicologie animale.

Le relevé d'avis relatif à cette demande de modification d'information sera présenté lors de la prochaine Commission nationale de pharmacovigilance.

Annexe 3-3

IX - POINT SUR LES EFFETS INDESIRABLES DES INTERFERONS ALFA 2 RECOMBINANT (INTRONA® ET ROFERON®)

Le C.R.P.V. de Paris-Créteil a fait le point des effets indésirables survenant lors de traitement par interféron.
Pour l'INTRONA® (laboratoires Schering-Plough), 226 dossiers ont été collectés par la firme et le système national de pharmacovigilance entre 1992 et 1995. Il s'agit essentiellement de réactions indésirables cutanées, neuropsychiatriques, cardiovasculaires, mais aussi de dysthyroïdies.
148 dossiers ont été dénombrés pour le ROFERON® (laboratoires Roche).

Au vu de ces premiers résultats, le comité technique souhaite ouvrir une enquête officielle de pharmacovigilance sur les effets indésirables de l'interféron alfa-2 recombinant et la pondération du risque en fonction des indications en hépatologie et en oncologie.

Après validation de l'ensemble des observations par le centre régional de Paris-Créteil :

- l'examen des effets neurologiques et psychiatriques sera confié, respectivement, aux C.R.P.V. de Toulouse et Montpellier.

- l'analyse des effets indésirables de type dysimmunitaires et dysthyroïdiens sera réalisée par le C.R.P.V. de Lyon.

- et les effets indésirables touchant les organes génitaux seront évalués par le C.R.P.V. de Paris-Pitié Salpétrière.

Le C.R.P.V. de Paris-Créteil, coordonnateur de l'enquête, est chargé de l'évaluation le rapport bénéfice/risque en fonction des indications.

Annexe 3-3

X - EXAMEN DE LA DEMANDE D'EXONERATION A L'INSCRIPTION SUR LA LISTE II DES SUBSTANCES VENENEUSES DU DOMPERIDONE

La demande d'exonération déposée par les laboratoires JANSSEN concerne :

- une présentation de 20 sachets de dompéridone granulés effervescents par voie orale dosée à 10 mg ;
- une quantité maximale de 200mg par conditionnement
- dans l'indication : "manifestations dyspeptiques de l'adulte et de l'enfant de plus de 15 ans ",
- pour une posologie recommandée de 3 sachets par jour pour une durée d'utilisation limitée à 7 jours.

L'examen de cette demande a été présenté par le CRPV de Toulouse.

La dompéridone est un antagoniste dopaminergique bloquant préférentiellement les récepteurs D2. Son action est donc essentiellement antidopaminergique périphérique.

L'analyse des données de pharmacovigilance a reposé sur deux types d'enquête :

- d'une part, sur une enquête officieuse de pharmacovigilance concernant les syndromes extrapyramidaux réalisée par le CRPV de Tours.

- d'autre part, sur l'analyse des effets indésirables recueillis sur SOS V6 de janvier 1990 à 1994.

L'analyse du dossier ne concerne que les patients âgés de plus de quinze ans.

Deux types de problèmes ont été soulevés :

- le premier concerne la vigilance des conducteurs de véhicules et des utilisateurs de machine (les CRPV ont recensés 8 observations de somnolence sous dompéridone). Le laboratoire ne dispose pas d'études de pharmacologie clinique. Ce principe actif semble, cependant, franchir difficilement la barrière hémato-encéphalique)
- le deuxième a trait à l'utilisation du médicament durant la grossesse (aucune étude clinique permette d'évaluer le risque; cependant un effet tératogène a été observé à forte dose chez l'animal).

Le Comité technique a émis un avis défavorable à cette demande d'exonération, en raison de l'absence de données de vigilance et de données concernant la femme enceinte. Cet avis sera présenté lors d'une prochaine Commission Nationale de Pharmacovigilance.

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XI - CEREDASE®

Dans le cadre d'une procédure européenne concernant la spécialité CEREDASE®, l'Agence Française devait donner un avis sur le rapport hollandais (pays rapporteur) concernant les dernières données disponibles sur l'efficacité et la tolérance de ce traitement de la maladie de Gaucher (déficit en glucocérébrosidase) de type I par une enzyme extraite du placenta en attendant la production d'une enzyme recombinante.
Hormis cette enzymothérapie, les thérapeutiques ne peuvent être que palliatives (splénectomie, prothèses articulaires, greffe de moelle osseuse...).

Les point soulevés en ce qui concerne la tolérance sont :

- 2 cas de diminution de l'efficacité thérapeutique à la suite d'apparition d'anticorps ; ces deux cas restent isolés : d'après les données du registre ICGG (International Collaborative Gaucher Group), 360 malades n'ont pas développé d'anticorps alors que 106 ont eu une séroconversion mais sans effet cliniquement mesurable.
La proposition d'inclure le texte suivant est donc acceptable :"une baisse d'activité a été notée chez moins de 0,5% des patients traités à cause de la présence d'anticorps IgG anti-alglucérase. Il n'y a pas d'autres mesures envisagées pour l'instant."

- l'observation d'une puberté précoce avec accélération de l'âge osseux chez un enfant de 11 ans ayant reçu de fortes doses de CEREDASE®, repose le problème du risque de la contamination par de l'hCG liée à l'origine placentaire du produit. Ainsi, l'information devient :" L'hCG, une hormone se trouvant naturellement dans le placenta humain a été détectée dans la CEREDASE®. Il est probable que cette hCG soit partiellement déglycosylée. Les études initiales suggèrent que cette hCG déglycosylée est éliminée rapidement, à une vitesse environ 40 fois plus importante que l'hCG initiale . Chez les hommes, l'administration de CEREDASE® résulte en une augmentation de production de testostérone, *mais il n'a pas été mis en évidence d'effets cliniques à des doses en dessous de 120U/kg/4semaines. Cependant il faut surveiller la survenue de signes de virilisation précoce chez les jeunes garçons, particulièrement quand la posologie dépasse 120/U/kg/ 4 semaines."*

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XII - CAS MARQUANTS ET NOUVELLES ENQUETES

• Le CRPV de Lyon signale un cas marquant avec **DEROXAT®** : il s'agit d'une hépatite fulminante grave, avec diminution du TP, chez un homme traité par neuroleptique depuis plusieurs années et par paroxétine depuis un mois.

• **AULIN®** (nimésulide) : spécialité italienne anti-inflammatoire non stéroïdien : une hépatite chronique active chez un homme de 66 ans est signalée par le CRPV de Paris-Saint Vincent de Paul.

• **MEDIATOR®** (benfluorex) : à la suite d'interrogation sur les potentialités anorexigènes du MEDIATOR® et de la possibilité de l'utiliser dans des préparations magistrales à la place des anorexigènes interdits, une enquête officielle sur l'ensemble des effets indésirables est confiée au CRPV de Besançon.

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XIII - QUESTIONS DIVERSES

A - Dossier de toxicologie animale de l'itraconazole pour le CRPV de Lille.

B - Suivi National des Hémophiles

Le CRPV de Saint-Antoine a souligné que le Suivi national des Hémophiles, pendant 5 ans, avait débuté depuis 2 ans et que les premiers patients avaient été inclus récemment. Le promoteur est l'Agence du Médicament. Deux types d'effets indésirables sont plus particulièrement étudiés : l'apparition d'anticorps anti facteur VIII ou anti facteur IX, ainsi que le risque de contamination virale.
(Liste des Centres de Traitement de l'Hémophilie en annexe)

C - Fichier des établissements de santé

L'Unité de Pharmacovigilance a pris contact avec les services compétents de la Direction des Hôpitaux (SESI) et transmettra dès leur réception les informations requises.

D - Procédure d'agrément des CRPV

1°) Le décret n°95-278 relatif à l'organisation générale de la pharmacovigilance ayant été promulgué le 13 Mars 1995, les établissements de santé hébergeant un centre régional de pharmacovigilance ont jusqu'au 13 Septembre 1995 seulement pour déposer une demande d'agrément et conformément à la note remise en Avril.
L'attention des centres est attirée sur le fait que seulement 4 dossiers ont été reçus à ce jour.

2°) Concernant la nature de l'unité fonctionnelle, il est rappelé que l'esprit du texte veut que cette unité fonctionnelle soit une unité médicale plutôt qu'une unité de gestion. La nécessité de voir un médecin à sa tête le confirme.
Il apparaît donc indispensable aux centres qui n'auraient pas encore entamé la procédure nécessaire auprès de leur CME de le faire rapidement.

3°) Il est rappelé que cette procédure a pour objectif une meilleure intégration hospitalière des centres et un fléchage facilité des postes (internes, vacations hospitalières, praticiens hospitaliers).
Les centres attirent l'attention de l'Administration sur la vigilance qui doit s'exercer en terme budgétaire, car la création de postes de praticiens hospitaliers pourrait entraîner la disparition d'un nombre de vacations supérieur à celui entraîné par la création du poste, ce qui est préjudiciable à l'activité du centre.
En ce qui concerne les hôpitaux parisiens, les centres rappellent également que les vacations allouées au titre de la subvention doivent être absolument prises en considération lors des modifications statutaires, ce qui n'est pas le cas actuellement.

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4°) Dans cette optique, les centres doivent faire parvenir à l'Agence leur besoin précis et les candidats possibles à de tels postes.

5°) Un arrêté définissant les territoires géographiques d'intervention doit être pris prochainement.
En accord avec les centres de Nantes et de Poitiers, le département des Deux-Sèvres fera partie du territoire d'intervention de Poitiers.
En ce qui concerne les centres d'Ile de France, il leur est demandé que, lors d'une réunion, ils définissent ensemble d'éventuelles modifications devant notamment tenir compte de leur activité, mais aussi de la superposition de la répartition géographique par arrondissement et par C.H.U., leur proposition devant parvenir courant Juin à l'Agence, pour pouvoir être pris en compte dans l'arrêté.
Les éventuelles propositions des autres centres sont également attendues.

E - Autorisation Temporaire d'Utilisation (A.T.U.)

1°) La liste des médicaments bénéficiant d'une A.T.U. ainsi que leurs indications vont parvenir prochainement aux centres.

2°) Il est précisé que ces médicaments dont la pharmacovigilance a la charge ne peuvent être saisis sur le système national de pharmacovigilance.

F - Fiche de déclaration des effets indésirables

Les centres ont tous reçu la version faisant la synthèse de tous les commentaires sur la version de travail précédent.
Cette fiche ayant reçu l'accord des ordres professionnels, la procédure d'agrément au CERFA va débuter, le modèle de formulaire étant dorénavant considéré comme définitif.

G - Médicaments dérivés du sang

- Le décret relatif aux règles particulières applicables à la pharmacovigilance des médicaments dérivés du sang a été promulgué le 7 Mai 1995. Il est applicable à compter du 1er Décembre 1995.

- Le Laboratoire du Fractionnement et des Biotechnologies a édité une documentation sur l'ensemble de ses produits qui doit être prochainement adressée à tous les centres.

H - Le PALFIUM® injectable ne serait plus utilisable par les anesthésistes, car il serait contre-indiqué par voie intra-veineuse. Ce point a été soulevé par le C.R.PV de Lille et est à vérifier auprès de la Commission des Stupéfiants.

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LISTE DES CENTRES DE TRAITEMENT DE L'HEMOPHILIE (C.T.H.)

VILLE	CODE POSTAL	ADRESSE	TELEPHONE
AMIENS	80054 CX	1 Pl. Victor Pauchet	22.66.84.55
ANNEMASSE	74100	Rte de Taninges	50.37.20.22
ANGERS	49022 CX	16 Bd Mirault	41.72.44.44
ANNECY	74000	1 Av. du Tresum	50.45.49.12
BESANÇON	25020 CX	1 Bd Flemming BP 1937	81.66.82.32
BOIS GUILLAUME	76230	609 Chemin de la Bretèque	35.60.50.50
BORDEAUX	33076 CX	Place Amélie Raba Léon	56.79.59.78
BORDEAUX	33065 CX	Place Amélie Raba Léon	56.96.85.96
BOUEXIERE (LA)	35340	Ctre Médical Rey Leroux	99.62.62.66
BREST	29609 CX	5 Avenue Foch	98.22.33.33 p 2235
BULLION	78380	CPR de Bullion	34.85.43.11
CAEN	14033	Av. de la Côte de Nacre	31.06.48.49
CHAMBERY	73011 CX	8 square Massalaz BP 1125	79.96.50.50
CHESNAY (LE)	78153 CX	2 rue J.L. Forain BP 122	39.63.91.33
CLERMONT-FERRAND	63003 CX	30 Place Henri Dunant	73.62.56.60
DIJON	21034 CX	2 Bd de Lattre de Tassigny	80.29.33.14
GRENOBLE	38043 CX	BP 217	76.76.54.87
KREMLIN-BICETRE (LE)	94275 CX	78 rue du Général Leclerc	45.21.21.67
LILLE	59012 CX	21 rue Camille Guérin	20.49.43.43
LILLE	59037 CX	Place de Verdun	20.44.48.45
LIMOGES	87042	Bd Martin Luther King	55.05.68.07
LYON	69437	Ed. Herriot, 3 Pl. d'Arsonval	72.11.73.38
LYON	69322	CH Debrousse	72.38.57.57
MANS (LE)	72000	194 Av. Rubillard	43.43.44.45
MARSEILLE	13385 CX	264 rue St Pierre	91.38.67.76
MONTMORENCY	95160	1 rue Jean Moulin	34.17.81.81
MONTPELLIER	34295 CX 05	CH St Eloi Av. Bertin Sans	67.33.70.31
MONTPELLIER	34265 CX	Av. Doyen G. Giraud	67.33.83.55
MULHOUSE	68051 CX	87 Av. d'Alkrich	89.64.74.10
NANTES	44011 CX 01	376 Bd Jean Monnet BP 349	40.12.33.37

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VILLE	CODE POSTAL	ADRESSE	TELEPHONE
NEVERS	58020 CX	1 Avenue Colbert	86.61.09.47
NICE	06004 CX	1 Avenue Victoria	92.03.41.00
OSSEJA	66344 CX	Le Joyau Cerdan	68.30.72.00
PARIS-COCHIN	75014	27 Fg Saint-Jacques	42.34.15.89
PARIS-NECKER	75015	149 rue de Sèvres	44.49.52.73
POITIERS	86021 CX	350 av. J. Coeur BP 577	49.44.38.59
REIMS	51092 CX	Rue Alexis Carrel	26.78.77.89
RENNES	35000	1 rue H. Le Guilloux	99.28.43.21
ROUEN	76031	1 rue Germon	35.08.81.91
ST ALBAN LEYSSE	73230	Domaine St-Alban BP 13	79.33.81.20
ST ETIENNE	42055 CX 2	Hôpital Nord	77.82.83.19
STRASBOURG	67085 CX	10 rue Spielman	88.21.25.06
TOULOUSE	31059 CX	CH Purpan	61.77.25.05
TOURS	37044 CX	CH Trousseau	47.47.46.72
VANDOEUVRE LES NANCY	54500	Avenue Bourgogne	83.44.62.62

AGENCE DU MEDICAMENT

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 11 Juillet 1995)

Etaient présents

M. IMBS : Président, M. HUGUES : Vice-Président,
Mme ALBENGRES, Mme BENETON (suppléante de M. ALLAIN H.), M. ALLAIN P., M. CHETAILLE (suppléant de M. ANDREJAK), Mme AUTRET, Mme DAVID (suppléante de M. BECHTEL), Mme HARAMBURU (suppléante de M. BEGAUD), Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), M. CARON, M. BIOUR (suppléant de M. CHEYMOL), Mme CHICHMANIAN, M. CHOISY, Mme PIERRON et Mme JULLIAN (suppléantes de Mme EFTHYMIOU), M. ESCOUSSE, M. VIAL (suppléant de M. EVREUX), Mme JOUGLARD, Mme KREFT-JAIS, M. LAROUSSE, Mme LAVARENNE, M. MALLARET, M. MERLE, Mme BAGHERI (suppléante de M. MONTASTRUC), M. MOORE, M. MOULIN, Mme BAVOUX (suppléante de M. OLIVE), M. OLLAGNIER, M. RICHE, Mme PIERFITTE (suppléante de M. ROYER), Mme SOUBRIE, M. VANDEL, Mme GOUJARD (représentant M. le Directeur Général de l'INSERM), Mme BARON (représentant M. le Directeur Général de la Santé), M. LAMOUREUX (représentant de M. le Directeur Général de l'Agence du Médicament).

Conseiller scientifique

M. LAGIER

Unité de pharmacovigilance

Mme BIDAULT
Mlle LEBELLER
Mme LEREBOURS

Experts

Mme BAUMELOU
M. LAMBERT

Assistait à la réunion

Mme DEWILDE
Mme MANCEL

Annexe 3-4

I INTRODUCTION de M. P. LAMOUREUX (sous-directeur de l'Agence du Médicament)

M. LAMOUREUX annonce que le conseil d'administration, après avis du conseil scientifique, a approuvé le projet de subvention. Pour l'année 1995, son montant sera de 10 M francs (pour 5,9 M de francs en 1994).
Cette subvention sera versée en deux fois. Les procédures de versement de la première partie seront mises en place au mois de juillet. La somme versée à chaque centre sera du même montant que celle de la subvention de l'année précédente. Le complément de la subvention 1995 ne sera versé que lorsque toutes les demandes d'agrément seront transmises au directeur de l'Agence du Médicament, au cours du dernier trimestre de l'année civile.

M. LAMOUREUX rappelle aux centres la nécessité de transmettre à l'Agence du Médicament la demande d'agrément prévue par le décret n°95-278 du 13 mars 1995 qui, n'étant qu'une démarche de régularisation, ne remet pas en cause l'existence des 31 centres. Cette demande doit être adressée obligatoirement au directeur de l'Agence du Médicament avant le 13 septembre. Il est préférable qu'elle soit signée par le directeur du centre hospitalier.

Tous les centres ayant transmis leur demande d'agrément à leur directeur d'hôpital et n'ayant pas eu de réponses doivent le signaler à l'unité de pharmacovigilance.

II ADOPTION DU PROCES-VERBAL DES COMITES TECHNIQUES DU 26/04/95 et du 18/05/95

Les procès-verbaux ont été adoptés avec les modifications suivantes :

Proçès-verbal du 26/04/95 :
- M. OLLAGNIER, M. MONTASTRUC et M. RICHE étaient bien présents et non excusés .
- ajouter, p 2 : l'enquête sur les vaccins PENTACOQ® et PENTHIBEST® reste ouverte.

Proçès-verbal de la réunion du 18/05/95 :
- M. OLLAGNIER était remplacé par Mme le Docteur BEYENS
- p 4 remplacer "Il s'agit de 16 cas d'insuffisance coronarienne" par
" Il s'agit :
1) de 16 cas d'insuffisance coronarienne".

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III TOUR DE TABLE DES CAS MARQUANTS RELEVES PAR LES CENTRES

La répartition des effets tient compte des définitions européennes en matière de gravité et de nouveauté.

A - LES EFFETS GRAVES

1) Les effets graves et nouveaux

- **ACUITEL®** (quinapril) : Pancréatite aiguë oedémateuse chez une femme de 68 ans, (ROUEN)

- **AGRAM®** (amoxicilline) + ORACILLINE® (phénoxyméthylpénicilline) + COQUELUSEDAL® (niaouli, grindélia, gelsémium, phénobarbital) + PANOTILE® (polymyrine, néomycine, fludrocortisone, lidocaïne) + MUCICLAR® (carbocistéine) : Syndrome de Lyell chez un enfant de 30 mois, (NANTES)

- **AMLOR®** (amlodipine) + **BACTRIM®** (sulfaméthoxazole, triméthoprime) : Vascularite aiguë nécrosante chez une femme de 73 ans, (MONTPELLIER)

- **ANSATIPINE®** (rifabutine) : Uvéite chez 3 hommes de 34, 37 et 49 ans, (PARIS-SAINT ANTOINE)

- **ART 50®** (diacerhéine) : Ulcère gastrique hémorragique avec présence d'helicobacter pylori chez une femme de 87 ans, (LIMOGES)

- **ASPEGIC®** (acétylsalicylate de lysine) : Hépatite, obnubilation chez un enfant de 3 ans et demi, (NANTES)

- ATRIUM®
(fébarbamate, difébarbamate, phénobarbital)
+
LEXOMIL®
(bromazépam) : Syndrome de Stevens-Johnson chez une femme de 34 ans, (RENNES)

- AUGMENTIN®
(amoxicilline, acide clavulanique)
+
AMIKLIN®
(amikacine)
+
PEFLACINE®
(pefloxacine) : Eruption cutanée, purpura non thrombopénique chez une femme de 22 ans,
(RENNES)

- COGNEX®
(tacrine) : Décompensation circulatoire cérébrale, décès chez une femme de 73 ans,
Décompensation cardio-respiratoire sur bronchopneumopathie chez un homme de 88 ans,
(LIMOGES)
Troubles du rythme chez une femme de 80 ans,
Infarctus du myocarde chez une femme de 73 ans,
(BESANCON)

- CYTOTEC®
(misoprostol) : Hyperthermie, oedème cérébral, ischémie myocardique, insuffisance hépatique, (tentative d'autolyse) chez un homme de 34 ans,
(AMIENS)

- DEPAKINE®
(acide valproïque sel de sodium) :

- Malaise, cyanose chez un nouveau-né de 24 heures, après prise par la mère.

- Petite dysmorphie faciale, hyperthrophie clitoridienne, CIA haute, reflux gastro-oesophagien à la naissance, allongement TCK, baisse fibrinogène, facteur II à 24 heures, mort subite, chez un nourrisson de 3 mois après prise de la mère pendant toute la grossesse,

- Allongement TCK, baisse fibrinogène, facteur II à la naissance, puis mort subite chez un nourrisson de 4 mois, après prise de la mère pendant toute la grossesse,
(PARIS-SAINT VINCENT DE PAUL)

- **DEPAMIDE®** (valpromide) + **PEPDINE®** (famotidine) :	Syndrome de Lyell chez une femme d'age non précisé (PARIS-CRETEIL)
- **DEROXAT®** (paroxétine) :	Eruption cutanée, hépatite chez une femme de 67 ans, (RENNES)
- **DEROXAT®** (paroxétine) + MODITEN® (fluphénazine) + DROLEPTAN® (dropéridol) + SOLIAN® (amisulpride)	Hépatite fulminante chez un homme de 35 ans, (LYON)
- **FELDENE®** (piroxicam) : + **COLTRAMYL®** (thiocolchicoside) + **CLAMOXYL®** (amoxicilline) + **MOPRAL®** (oméprazole) + **TOPLEXIL®** (oxomémazine, guaïfénésine, paracétamol) :	Erythème annulaire centrifuge chez un homme de 51 ans, (MONTPELLIER)
- **FLOXYFRAL®** (fluvoxamine):	Fibrose rétropéritonéale chez une femme de 40 ans (BREST)

- FONZYLANE®
(buflomédil)
+
DI-ANTALVIC®
(dextropropoxyphène,
paracétamol) : Choc anaphylactique chez une femme de 45 ans,
(ST ETIENNE)

- FLUVERMAL®
(flubendazole) : Malformation foetale, résidus branchiaux sous une oreille chez un nouveau né,
(CAEN)

- FRAZOLINE SPRAY®
(framycétine, naphazoline,
amyléine) : Bradycardie, hypertension artérielle, coma chez un nouveau-né 1 mois (sexe féminin),
(TOULOUSE)

- HYDROSOL POLYVITAMINE BON®
(vitamines A, D2, D3, E, B1, B2,
B6, C, nicotinamide,
dexpanthénol) : Irritabilité, urticaire géante, poussée hypertensive chez un nourrisson de 7 jours,
(DIJON)

- IMIGRANE®
(sumatriptan): Choc chez une femme de 33 ans,
(MARSEILLE)

- IMODIUM®
(lopéramide): Occlusion chez un nouveau-né après prise du médicament par la mère en fin de grossesse,
(ST VINCENT DE PAUL)

- Interferon alfa
+
HYDREA®
(hydroxycarbamide): Ostéonécrose multifocale chez un homme de 49 ans,
(ST ETIENNE)

- IVADAL®
(zopidem) : Diplopie transitoire chez une femme de 39 ans,
(ST ETIENNE)

-LAMISIL®
(terbinafine) : Gynécomastie unilatérale chez une homme 45 ans,
(FERNAND WIDAL)

- LOPRIL®
(captopril) — Pancréatite aiguë oedemateuse chez un homme de 52 ans,
(ROUEN)

- MEDIATOR®
(benfluorex)
+
LIPANTHYL®
(fénofibrate)
+
Amfépramone
+
CANOL®
(cynara, lawsonia, chimaphylla, aphloïa)
+
PILOSURYL®
(piloselle, phyllantus)
+
OLIVIASE®
(olivier)
+
STRESAM®
(étifoxine)
+
CRAETEGUS®
(aubépine)
+
RELVENE®
(hydroxyéthylrutosides) : Bouffée délirante, épisode confusionnel chez une femme de 59 ans,
(ROUEN)

- Méthotrexate
+
ZOPHREN®
(ondansétron)
+
LEDERFOLINE®
(folinate de calcium)
+
NUBAIN®
(nalbuphine) : Erythème anal chez une adolescente de 13 ans,
(MONTPELLIER)

- MIGWELL®
(ergotamine, caféine, cyclizine)
+
Sumatriptan : Délire aigu, agitation, confusion chez une femme de 40 ans,
(ST ETIENNE)

- **NEURIPLEGE®**
(chlorproéthazine)
+
SURGAM®
(acide tiaprofénique) : Syndrome extra-pyramidal chez un enfant de 10 ans,
(ST VINCENT DE PAUL)

- **NIFLURIL®**
(acide niflumique)
+
CLAMOXYL®
(amoxicilline)
+
DOLIPRANE®
(paracétamol) : Syndrome de Stevens-Johnson chez une fillette de 22 mois,
(MONTPELLIER)

- **OXEOL®**
(bambutérol) : Décès chez un homme de 71 ans,
(MARSEILLE)

- **PARA-PLUS®**
(perméthrine, malathion,
butoxyde de pipéronyle) : Brûlure au visage, suite à une explosion dans les cheveux chez une fillette de 4 ans,
(ST ETIENNE)

- **PEFLACINE®**
(péfloxacine)
+
DI-ANTALVIC®
(dextropropoxyphène,
paracétamol) : Aggravation d'une myasthénie chez une femme de 82 ans,
(LYON)

- **PENTASA®**
(mésalazine) : Lupus érythémateux disséminé chez une femme de 32 ans,
(CAEN)

- **PLACENTAFIL®**
(extrait placentaire
humain): Hépatite C chez une femme 37 ans,
(LYON)

- **PRAGMAREL®**
(trazodone)
+
MODIODAL®
(modiodal) : Psychose aiguë chez une femme de 66 ans
(LYON)

- PROFENID® gel (kétoprofène) :	Choc anaphylactique chez une femme de 74 ans, (RENNES)
- PYOSTACINE® (pristinamycine) :	Erythrodermie, ischémie des extrêmités des membres chez une femme de 58 ans, (BESANCON)
-PYOSTACINE® (pristinamycine) + FLAGYL® (métronidazole) :	Erythème morbilliforme, oedème de la face chez un homme de 35 ans, (BESANCON)
- ROACCUTANE® (isotrétinoïne) :	Névrite optique chez une femme de 36 ans, (RENNES)
- ROFERON® (interféron alfa-2a recombinant) :	Décès brutal probablement par arrêt cardio-respiratoire d'un homme de 32 ans, (TOULOUSE)
- RULID® (roxithromycine) + INDOCID® (indométacine) + XANAX® (alprazolam) :	Hépatite fulminante chez une femme de 81 ans, (PARIS-SAINT ANTOINE)
- SERC® (bétahistine) + **LEXOMIL®** (bromazépam) :	Eruption discoïde fixe non pigmentée chez une femme de 61 ans, (MONTPELLIER)
- SOLUMEDROL® (méthylprednisolone) :	Mort subite (infarctus septal) chez un homme 48 ans, (ST ETIENNE)

- **SPASFON®**
(phloroglucinol)
+
DIPRIVAN®
(propofol)
+
PRODAFALGAN®
(propacétamol)
+
SOPROL®
(bisoprolol) : Choc anaphylactique chez une femme de 57 ans, (BORDEAUX)

- **TENORMINE® IV**
(aténolol)
+
-ACTILYSE®
(altéplase) Choc anaphylactique chez un homme 65 ans, (NICE)

- **UTROGESTAN®**
(progestérone) : Cytolyse hépatique chez une femme de 30 ans, (POITIERS)

- **VASTEN®**
(pravastatine)
+
- TENORMINE®
(aténolol) : Myasthénie chez une femme de 82 ans, (LYON)

- **XENETIC®**
(iobitridol) : Ischémie myocardique chez un homme de 67 ans, (TOURS)

- **ZECLAR®**
(clarithromycine)
+
ICAZ®
(isradipine) : Hépatite aiguë mixte chez un homme de 78 ans, (CAEN)

INTERACTION MEDICAMENTEUSE

- **DI-HYDAN®**
(phénytoïne)
+
FLOXYFRAL®
(fluvoxamine) : Troubles de l'équilibre, nygstamus, taux de phénytoïne 4xN chez un homme de 73 ans, (PARIS-FERNAND WIDAL)

- **NIZORAL®**
(Kétoconazole)
+
TINSET®
(oxatomide)
+
ADALATE®
(nifédipine)
+
PIPRAM®
(acide pipémidique)
+
DAONIL®
(glibenclamide) : Allongement QT, pas d'hypokaliémie chez une femme de 69 ans,
(FERNAND WIDAL)

- **ZECLAR®**
(clarithromycine)
+
GYNERGENE® CAFEINE
(ergotamine, caféine) : Paresthésies, froideur des extrêmités chez une femme de 36 ans,
(ANGERS)

2) Les effets graves "connus"

- **ALINAM®**
(chlormézanone)
+
MINALFENE®
(alminoprofène) : Syndrome de Lyell chez une femme de 47 ans,
(LILLE)

- **APRANAX®**
(naproxène) : Oedème de Quincke chez une femme de 50 ans,
(BESANCON)

- **AROLAC®**
(lisuride) : Chute de la pression artérielle chez trois patientes âgées de 25 ans, de 34 ans et de 36 ans,
(ST ETIENNE)

- **AUGMENTIN®**
(amoxicilline, acide clavulanique)
+
CLAVENTIN®
(ticarcilline,
acide clavulanique) : Ictère cholestatique, syndrome de Stevens-Johnson grave chez un homme de 69 ans,
(NICE)

- **AZANTAC®**
(ranitidine) : Dyskinésie, confusion, puis encéphalopathie myoclonique chez un homme de 78 ans,
(NANTES)

- **CALCIPARINE®**
(héparine calcique) : Thrombopénie, thromboses multiples chez une femme de 67 ans,
(NANTES)

- **CIBLOR®**
(amoxicilline) : Hépatite aiguë mixte chez un homme de 60 ans,
(CAEN)

- **CLAMOXYL®**
(amoxicilline)
+
OROKEN®
(céfixime)
+
ROCEPHINE®
(ceftriaxone) : Colite pseudomembraneuse chez une femme de 45 ans,
(CLERMONT-FERRAND)

- **COLCHICINE®**
(colchicine)
+
SANDIMMUM®
(ciclosporine) : Rhabdomyolyse chez un homme de 42 ans,
(CLERMONT-FERRAND)

- **DEPAKINE® 500**
(acide valproïque, sel de sodium)
+
XATRAL®
(alfuzosine) : Agranulocytose chez un homme de 82 ans,
(CLERMONT-FERRAND)

- **DEROXAT®** (paroxétine) + **PROTHIADEN®** (dosulépine) :	Hyponatrémie chez une femme de 72 ans, (ST ETIENNE)
- **DIANE®** (cyprotérone acétate, éthinylestradiol) :	Thrombose veineuse fémoro-iliaque gauche chez une jeune femme de 19 ans, (DIJON)
- **DISTILBENE®** (diéthylstilbestrol) :	Adénose cervico-vaginale chez la fille découverte à l'âge de 18 ans, après prise par la mère âgée de 28 ans, (STRASBOURG)
- **EFFERALGAN VIT C®** (paracétamol, acide ascorbique) :	Choc anaphylactique chez une femme de 30 ans, (REIMS)
- **FELDENE®** (piroxicam) + **TAGAMET ®** (cimétidine) + **EFFERALGAN®** (paracétamol) + **PRIMALAN®** (méquitazine) :	Syndrome de Stevens-Johnson sévère chez une femme de 49 ans, (RENNES)
- **FLAGYL®** (métronidazole) :	Encéphalo-neuropathie chez un homme de 34 ans, (ANGERS)
- **Fludarabine :**	Encéphalopathie chez un homme de 64 ans, (TOULOUSE)
- **FLUORESCEINE®** (fluorescéine sodique) :	Choc anaphylactoïde chez un homme de 59 ans, (STRASBOURG)

- FLUOTHANE®
(halothane)
+
Rifampicine : Hépatite avec insuffisance hépato-cellulaire chez un enfant de 9 mois,
(TOURS)

-GLIFANAN®
(glafénine)
+
VOLTARENE® 100 LP
(diclofénac)
+
TEMESTA®
(lorazépam) : Insuffisance rénale aiguë (tentative d'autolyse ?) chez un homme de 44 ans,
(AMIENS)

- GYNERGENE® CAFEINE
(ergotamine, caféine): Ischémie iléale chez un homme de 51 ans,
(STRASBOURG)

- Hormone de croissance extractive®
+
LEVOTHYROX®
(lévothyroxine sodique)
+
TRINORDIOL®
(lévonorgestrel,
éthinylestradiol) : Maladie de Creutzfeldt-Jakob chez une femme de 24 ans (traitement entre Janvier 1981 et Décembre 1987),
(PARIS PITIE SALPETRIERE)

- ISOMERIDE®
(dexfenfluramine) : Hypertension pulmonaire chez une femme de 49 ans,
(POITIERS)

- LAMISIL®
(terbinafine) : Erythème polymorphe buccal chez un homme de 52 ans,
(FERNAND WIDAL)

- LEPONEX®
(clozapine) : Agranulocytose chez un homme de 39 ans,
(TOURS)

- **LEPONEX®**
(clozapine)
+
NOZINAN®
(lévomépromazine)
+
SURMONTIL®
(trimipramine) : Agranulocytose fatale chez un homme de 53 ans, (LIMOGES)

- **LIPANOR®**
(ciprofibrate)
+
PRACTAZIN®
(spironolactone, altizide)
+
PIPRAM®
(acide pipénridique)
+
CERVOXAN®
(vinburnine) : Rhabdomyolyse chez une femme de 66 ans, (CAEN)

- **LYMPHOGLOBULINE®**
(immunoglobulines de cheval antilymphocytes humains) : Réaction allergique chez une femme de 45 ans, (REIMS)

- **MOPRAL®**
(oméprazole)
+
PREPULSID®
(cisapride) : Cholestase chez une femme de 49 ans, (RENNES)

- **NALGESIC®**
(fénoprofène) : Néphrite interstitielle chez un homme de 66 ans, (DIJON)

- **NOCERTONE®**
(oxétorone)
+
PARLODEL®
(bromocriptine)
+
LAROXYL®
(amitriphyline) : Diarrhée chez une femme de 57 ans, (MONTPELLIER)

- **NOROXINE®**
(nofloxacine) : Syndrome de Lyell chez une femme de 36 ans,
(NICE)

- **PEDIAZOLE®**
(érythromycine
sulfafurazole) : Agranulocytose chez une enfant de 4 ans,
(TOURS)

- **PEDIAZOLE®**
(érythromycine sulfafurazole)
+
ORELOX®
(cefpodoxine)
+
EXOMUC®
(acétylcystéine)
+
CELESTENE®
(bétaméthasone)
+
FLUIMUCIL®
(acétylcystéine)
+
IRS 19®
(lysats d'antigènes
bactériens)
+
BECOTIDE SPRAY®
(béclométasone) : Syndrome de Lyell chez un enfant de 3 ans,
(TOURS)

- **PEFLACINE®**
(péfloxacine) : Hydarthrose, impotence fonctionnelle chez un adolescent de 16 ans,
(ST ETIENNE)

- **PREPULSID®**
(cisapride) : Convulsions chez un nourrisson de 3 semaines,
(LIMOGES)

- **PREVISCAN®**
(fluindione) : Néphropathie interstitielle, hépatite cholestatique chez une femme de 54 ans,,
(RENNES)

- **PROTHIADEN®**
(dosulépine) : Allongement du QT chez une femme de 81 ans,
(NANTES)

- **PROZAC®**
(fluoxétine)
+
MODURETIC®
(amiloride,
hydrochlorothiazide) : Hyponatrémie avec chute, confusion et obnubilation chez un homme de 66 ans,
(SAINT-ETIENNE)

- **RETROVIR®**
(zidovudine)
+
CYMEVAN®
(ganciclovir)
+
GAVISCON®
(alginate de sodium) : Pancytopénie chez un homme de 39 ans,
(CLERMONT-FERRAND)

- **ROFERON®**
(interféron alfa-2a
recombinant)
+
PROLEUKIN®
(aldesleukine) : Cardiomyopathie dilatée chez un homme de 71 ans,
(ANGERS)

- **SINEMET®**
(levodopa, carbidopa) : Mélanome malin chez un homme,
(MARSEILLE)

- **TEGRETOL®**
(carbamazépine): Toxidermie chez un homme de 34 ans,
(DIJON)

- **TEGRETOL®**
(carbamazépine)
+
FLUANXOL®
(flupentixol décanoate) : Aplasie médullaire chez un homme de 34 ans,
(LYON)

- **TEGRETOL®**
(carbamazépine)
+
ORTENAL®
(phénobarbital,
amphétamine) : Syndrome de Lyell chez une femme de 20 ans,
(DIJON)

- **TELDANE®** (terfénadine) + **PREPULSID®** (cisapride) + **PRACTAZIN®** (spironolactone, altizide) :	Torsades de pointe chez un homme de 86 ans, (CLERMONT-FERRAND)
- **TELEBRIX 38®** (ioxitalamate de sodium et de méglumine) :	Oedème de Quincke chez une femme de 30 ans, (REIMS)
- **TICLID®** (ticlopidine) :	Aplasie médullaire grave chez un homme de 82 ans, (SAINT-ETIENNE)
- **TICLID®** (ticlopidine) + **CIFLOX®** (ciprofloxacine) :	Agranulocytose chez un homme de 51 ans, (REIMS)
- **TRANCOPAL®** (chlormézanone) :	Erythème pigmenté fixe chez chez un homme de 48 ans, (DIJON)
- **VACCIN ROR®** (vaccin à virus vivants atténués rougeole, oreillons, rubéole) :	Purpura thrombopénique chez une enfant de 17 mois, (BREST)
- **VANCOCINE®** (vancomycine) + **BACTRIM®** (sulfaméthoxazole, triméthoprime) + **MOPRAL®** (oméprazole) + **ZOVIRAX®** (aciclovir) :	Syndrome de Stevens-Johnson chez un homme de 54 ans, (RENNES)

- **VANCOCINE®** (vancomycine) + **TARGOCID®** (téicoplanine) :	Récidive d'un syndrome de Stevens-Johnson chez un homme de 54 ans, (RENNES)
- **VASTEN®** (pravastatine) + FLUDEX® (indapamide) + DIAMOX® (acétazolamide) + DIAMICRON® (glicazide) :	Rhabdomyolyse chez une femme de 85 ans, (ROUEN)
- **VENTOLINE®** (salbutamol) : solution pour aérosol	Bronchospasme avec détresse respiratoire chez un homme de 62 ans, (TOURS)
- **ZAGAM®** (sparfloxacine) :	Phototoxicité chez un homme de 79 ans, Photo-allergie chez une femme de 46 ans, (BESANCON) Photosensibilisation majeure et prolongée au niveau de la face et des mains chez un homme de 40 ans, (BREST) Erythème, oedème, prurit chez une jeune femme de 19 ans, (LILLE) Photosensibilité chez un homme de 41 ans et une femme de 25 ans, (RENNES) Phototoxicité chez une femme de 25 ans, (AMIENS)

Annexe 3-4

INTERACTION MEDICAMENTEUSE

- SERECOR® (hydroquinidine) + CORDARONE® (amiodarone) + DIGOXINE® (digoxine) :	Tachycardie ventriculaire, fibrillation ventriculaire chez une femme de 38 ans, décès, (LILLE)
- TICLID® (ticlopidine) + FRAGMINE® (daltéparine sodique) :	Rectorragies abondantes chez un homme de 75 ans, (CLERMONT-FERRAND)

B - LES EFFETS NON GRAVES

1) Les effets nouveaux

- COGNEX® (tacrine) :	Pancréatite biologique chez une femme, (PARIS-CRETEIL)
- DEBRIDAT® (trimébutine) + NEO-CODION® (camphosulfonate de codéine, sulfogaïacol, grindélia) :	Pharmacodépendance, toxicomanie chez un homme de 30 ans, (ROUEN)
- DEDROGYL® (calciférol) + OSTRAM® (phosphate tricalcique) + DIDRONEL® (acide étidronique) :	Crise de "pseudo-goutte" chez une femme de 68 ans, (CAEN)

Annexe 3-4

- **DI-ANTALVIC®** (dextropropoxyphène, paracétamol) :	Surdité de perception unilatérale chez une adolescente de 15 ans, (LIMOGES)
- **KARAYAL®** (oxyde de magnésium, sulfate de magnésium, kaolin, gomme de sterculia) :	Ulcère de l'oesophage chez une femme de 60 ans, (ROUEN)
- **LAMISIL®** (terbinafine) :	Hallucinations auditives et troubles de l'humeur chez un homme de 24 ans, (PARIS-FERNAND WIDAL
- **LOVENOX®** (énoxaparine) :	Hyperplaquettose chez un homme de 50 ans, (BREST)
- **MOCLAMINE®** (moclobémide) :	Urticaire chez une femme de 40 ans, (RENNES)
- **MOCLAMINE®** (moclobémide) + STILNOX® (zolpidem) + XANAX® (alprazolam) :	Convulsion chez un homme de 73 ans, (MARSEILLE)
- **MOPRAL®** (oméprazole) + **DOGMATIL®** (sulpiride) :	Gynécomastie, impuissance chez un homme de 37 ans, (SAINT-ETIENNE)
- **ODRIK®** (trandolapril) :	Erythème pigmenté fixe muqueux invalidant chez un homme, (MARSEILLE)

- **ORELOX®** (cefpodoxime) + **SPIRAMYCINE COQUELUSEDAL®** (spiramycine) :	Maladie pseudo-sérique chez un homme de 24 ans, (REIMS)
- **ROACCUTANE®** (isotrétinoïne) :	Sensations vertigineuses, irritabilité, nervosité, idées suicidaires chez une femme de 30 ans, (ROUEN)
- **TEMGESIC®** (buprénorphine) :	Chute brutale du taux de prothrombine à 56 % chez un homme de 82 ans, (CLERMONT-FERRAND)
- **UTROGESTAN®** (progestérone) :	Cytolyse hépatique chez trois femmes de 28, 30 et 33 ans, (POITIERS)
- **UTROGESTAN®** (progestérone) + **ERYTHROTON®** (cyanocobalamine) + SPECIAFOLDINE® (acide folique) :	Cytolyse hépatique chez une femme de 33 ans, (POITIERS)
- **UTROGESTAN®** (progestérone) + **SPASFON®** (phloroglucinol) :	Cytolyse hépatique chez une femme de 32 ans, (POITIERS)
- **ZOLTUM®** (oméprazole) :	Gynécomastie chez un homme de 24 ans, (SAINT-ETIENNE)

Annexe 3-4

2) Les effets non graves et connus

- ANAFRANIL® (clomipramine) :	Diarrhée, veinite au point d'injection chez un homme de 74 ans, Diarrhée chez un homme de 43 ans, Prurit au niveau du point de ponction chez une femme de 68 ans, Oedème au niveau du point de ponction chez un homme de 61 ans, (NANCY)
- AROLAC® (lisuride) :	Nausées, vomissements (dose-dépendant) chez une femme de 28 ans, (NANTES)
- CORTANCYL® (prednisone) :	Ulcère gastrique chez un homme de 62 ans, (CAEN)
- CYCLADOL® (piroxicam, bêta-cyclodextrine) + EFFERALGAN CODEINE® (paracétamol, codéine) :	Epidermolyse toxique nécrotique (extrêmités des membres) chez un homme de 32 ans, (CLERMONT-FERRAND)
- ENURETINE® (isopropamide, thiamine, phénobarbital, vitamine E, éphédrine) + NEO-CODION® (camphosulfonate de codéine, sulfagaïacol, grindélia) :	Usage abusif chez un homme de 34 ans, (CAEN)
- FACTEUR IX Hp LFB :	Toux, fièvre, bronchospasme, chez un enfant de 10 mois, (NANTES)
- IMIJECT® (sumatriptan) :	Malaise, asthénie, oppression thoracique et de la gorge, vertige et fourmillements cutanés chez un homme de 41 ans, (CLERMONT-FERRAND)

- **IMMUNOGLOBULINES HUMAINES DE L'HEPATITE B I.V.** : (immunoglobulines spécifiques)	Urticaire chez un homme de 54 ans (MARSEILLE)
- **IMMUNOGLOBULINES HUMAINES NORMALE LFB I.V.** : (immunoglobulines polyvalentes)	Frissons, fièvre chez une femme de 80 ans, (MARSEILLE)
- **KETUM®** (kétoprofène) :	Réaction cutanée (bulles + vésicules) chez un homme de 68 ans, Eczéma de contact chez un homme de 28 ans, (MONTPELLIER)
- **KETUM®** (kétoprofène) + TRIACANA® (tiratricol) :	Eczéma de contact chez un homme de 43 ans, (MONTPELLIER)
- **LYMPHOGLOBULINE®** (immunoglobuline de cheval antilymphocytes humains) :	Maladie sérique chez une femme de 29 ans, (REIMS)
- **NORCURON®** (vécuronium) :	Syndrome myogène chez une femme de 24 ans, (CLERMONT-FERRAND)
- **PLAQUENIL®** (hydroxychloroquine) :	Oedème de la face, des genoux, des chevilles chez une femme de 43 ans, (RENNES)
- **PRANTAL®** (diphémanil) :	Excitation, anorexie, troubles du sommeil chez une femme, (PARIS-SAINT VINCENT DE PAUL)
- **PREVISCAN®** (fluindione) :	Augmentation isolée ALAT chez une femme de 58 ans, (RENNES)

- **RYTHMOL®** (propafénone) :	Dysgueusie chez un homme de 71 ans, (TOULOUSE)
- **UMATROPE 16®** (somatropine) :	Céphalées violentes avec oedèmes palpébraux et picotement de la face chez un garçon de 9 ans, (STRASBOURG)
- **VIBRAMYCINE®** (doxycycline monohydrate) :	Photosensibilisation (dos des mains) chez un homme de 73 ans, (CLERMONT-FERRAND)
- **ZAGAM®** (sparfloxacine) :	Réaction de phototoxicité chez une femme de 64 ans, (MONTPELLIER) Photosensibilité chez un homme de 30 ans, (RENNES) Réaction de photosensibilité, uvéite antérieure bilatérale chez une femme de 66 ans, (BREST) Eruption des zones exposées chez un homme de 43 ans, Erythème des zones exposées chez une femme de 53 ans, (DIJON) Phototoxicité chez un homme de 38 ans, (BESANCON)
- **ZAGAM®** (sparfloxacine) + **AUGMENTIN®** (amoxicilline, acide clavulanique) :	Eruption bulleuse et purpurique chez un homme de 62 ans, (CAEN)
- **ZAGAM®** (sparfloxacine) + CELESTAMINE® (bétaméthasone, dexchlorphéniramine) + NETUX® (codéine, phényltoloxamine) :	Réaction de phototoxicité chez une femme de 32 ans, (MONTPELLIER)

- ZAGAM® (sparfloxacine) + SOLUPRED® (prednisolone) :	Réaction de phototoxicité chez une femme de 41 ans, (MONTPELLIER)
- **ZAGAM®** (sparfloxacine) + SOLUPRED® (prednisolone) + ZYRTEC® (cétirizine) :	Photosensibilisation chez une femme de 53 ans, (MONTPELLIER)
- **ZAGAM®** (sparfloxacine) + TENORMINE® (aténolol) :	Réaction de phototoxicité chez un homme de 65 ans, (MONTPELLIER)
- **ZAGAM®** (sparfloxacine) + **ZYRTEC®** (cétirizine) :	Tendinopathie bilatérale (tendon d'Achille) chez une femme de 70 ans, (CLERMONT-FERRAND)

INTERACTIONS MEDICAMENTEUSES

- **ZOCOR®** (simvastatine) + **BEFIZAL®** (bézafibrate) :	Elévation des CPK chez un homme de 37 ans, (CLERMONT-FERRAND)

Annexe 3-4

C - NOUVELLES ENQUETES ET NOUVEAUX DOSSIERS

Enquêtes officieuses :

- SINEMET® : Les C.R.P.V. de Nice et de Marseille sont chargés de faire le point sur la possibilité de survenue de mélanome malin lors de traitement avec ce médicament.

- UTROGESTAN® : Le C.R.P.V. de Poitiers est chargé d'effectuer un bilan des mésusages, risques et bénéfices de l'utilisation de la progestérone sous forme micronisée.

- EUPHYTOSE® : Un point sur l'hépatotoxicité de cette spécialité de phytothérapie est confiée au C.R.P.V. de Toulouse.

- ROACCUTANE® : Les C.R.P.V. de Tours et de Paris Saint-Vincent de Paul sont chargés de rassembler des informations sur les cas d'initialisation du traitement alors qu'une grossesse est en cours.

Enquêtes officielles :

- PRANTAL® : Une enquête officielle a été confiée au C.R.P.V. de Paris Saint-Vincent de Paul, à la suite de la présentation du point sur les effets indésirables du diphémanil méthylsulfate chez l'enfant.

- Une enquête officielle de pharmacovigilance sur la sécurité d'emploi des LYMPHOGLOBULINE® Merieux est confiée aux C.R.P.V. de Dijon et Lyon.

Nouveaux dossiers :

- L'analyse des Déclarations obligatoires 1994 des effets indésirables des spécialités PENTASA® et ALTIM® a été confiée au C.R.P.V. de Marseille.

- La demande de modification de l'information médicale de la spécialité INDOCID® a été confiée au C.R.P.V. de Nancy.

- ELOHES® et HESTERIL® : La demande de modification de l'information médicale concernant l'utilisation des dihydroxyéthylamidons chez la femme enceinte a été confiée au C.R.P.V. de Paris Saint-Vincent de Paul.

- La demande de modification de l'information médicale de la spécialité DOBUTREX® a été confiée au C.R.P.V. de Saint-Etienne.

Annexe 3-4

IV -CANTOR® (minaprine) ET SURDOSAGE

Les résultats d'une enquête des centres anti-poison français concernant les intoxications aiguës par la minaprine ont été présentés aux membres du comité technique par Mr le Pr Lambert du Centre Anti-poison de Nancy.

Il s'agit d'un psychotrope indiqué dans "les états d'inhibition pouvant s'exprimer par : ralentissement psychomoteur, baisse de la libido, baisse d'activité ou manque d'initiative, difficultés mnésiques et de concentration".

La minaprine présente une affinité pour les récepteurs à la glycine, neuromédiateur inhibiteur, prouvée par la potentialisation des convulsions à la strychnine, antagoniste glycinergique.
Le pic plasmatique est atteint en 1 heure et la demi-vie du produit inchangé est de 2,5 heures. La parahydroxylation hépatique, variable selon les individus, est la voie prépondérante de métabolisation de la minaprine.

Cette molécule a obtenu une AMM en 1979 avec un conditionnement de 30 comprimés à 50mg, soit 1,5 g par boîte.
En 1990, l'AMM a été modifiée avec un conditionnement de 20 comprimés dosés à 100mg, soit 2g par boîte.

En 1993, la Commission Nationale de Pharmacovigilance a souhaité que le conditionnement soit de nouveau restreint à 1,4 g par boîte (2 blisters de 7 cps de 100mg). Il était prévu d'apprécier le retentissement de ces mesures au bout d'un an, mais elles n'ont été effectives qu'en 1995. Ceci reviendrait à réévaluer le dossier début 1996.

Toxicité aiguë expérimentale : la mort survient rapidement après des signes d'hyperexcitabilité et des convulsions de type clonique antagonisées dans toutes les espèces par les barbituriques et non antagonisées par les benzodiazépines ; la minaprine potentialise les effets de la strychnine. La DL 50 représente deux fois la dose pharmacologiquement active.

Intoxications aiguës chez l'homme :
L'analyse des données issues de la banque nationale des Centres anti-poisons depuis 1978 permet de dénombrer 1346 dossiers d'intoxication aiguë par la minaprine. Sur les 1093 cas notifiés de 1978 à 1990, 6% des patients ont présenté des convulsions et 1,5% ont une évolution fatale.
253 autres cas ont été collectés de 1990 à 1995, dont 14,6% avec des convulsions et 3,6% d'évolution mortelle.

Plus particulièrement à partir des 322 cas recensés par la dernière étude multicentrique 1990-1994, on peut conclure que :

* la symptomatologie est constituée de troubles neurologiques précoces (convulsions, état de mal convulsif, coma) qui font la gravité de l'intoxication (évolution rapide vers un décès et coma végétatif), de symptômes cardio-vasculaires (hypotension, tachycardie, arrêt cardio-circulatoire, troubles du rythme, de la conduction) et de troubles digestifs.

* des signes cliniques sont observés pour une dose annoncée (DA) supérieure ou égale à 200 mg,

* il existe dans 26% des cas des convulsions pour une DA de 200 à 10.000 mg,

* l'évolution dans 9,8% des cas s'est faite vers un décès ou un état végétatif.

Ainsi, il existe une très grande variabilité clinique en fonction des doses supposées ingérées qui peuvent aller de 1/2 cp à 100 cps. Il apparaît que le décès survient en général à partir de 1 gramme ingéré. Il existe cependant 2 décès pour des doses allant de 500 mg à 1 g. La gravité provient aussi de la rapidité de survenue des troubles, avant même l'arrivée des secours.
L'attention est attirée par les cas d'intoxications survenant chez des patients jeunes (20,6 ans en moyenne).
La preuve de l'intoxication n'est pas toujours apportée dans ces observations (7 cas documentés).
La réduction du conditionnement n'apparait pas comme une solution suffisante.

Les membres du Comité Technique souhaitent :

1) disposer d'informations complémentaires sur la nouvelle présentation orale (gouttes) qui a obtenu une AMM mais qui n'est pas encore commercialisée. Le Comité est alarmé par le risque d'intoxication accidentelle grave chez l'enfant et la possibilité d'une survenue encore plus précoce des convulsions en cas d'intoxication aiguë, favorisée par la biodisponibilité de cette forme galénique,

2) une réévaluation de l'efficacité de la molécule, afin de pouvoir en apprécier le rapport bénéfice/risque,

3) la mise à disposition par la firme des données de toxicologie précliniques sur le système nerveux central aux centres de pharmacovigilance de Marseille et de Lyon qui ont en charge l'enquête officielle,

4) la réévaluation par la Commission Nationale de Pharmacovigilance du risque de ces intoxications, avant un délai de 1 an, du fait de leur gravité potentielle.

Annexe 3-4

V - ANTHRACYCLINES ET SURVENUE DE LEUCEMIES

Le laboratoire PHARMACIA a fait une demande de modifications de l'information médicale de la rubrique "effets indésirables" des monographies des produits ADRIAMYCINE®, ADRIBLASTINE® et FARMORUBICINE®.

Cette demande a été examinée par Mme le Docteur E. BAUMELOU, du C.M.C. FOCH de Suresnes.

L'analyse des diverses publications (1990 à 1995) a permis de montrer qu'il existe des arguments cliniques, pharmacologiques et moléculaires pour considérer qu'il existe un risque particulier de leucémies secondaires aux inhibiteurs de Topo-Isomérase II et/ou agents intercalants.

Plusieurs questions restent cependant sans réponse :

- tous les agents de la classe ont-ils le même effet leucémogène ?
- se potentialisent-ils les uns les autres ?
- y-a-t-il des cofacteurs ?
- le risque est-il augmenté avec les doses ?

Le comité technique a donc considéré :

- qu'il n'était pas possible d'accepter les propositions de modifications de l'information médicale du laboratoire. Le risque de leucémies induites par les anthracyclines semble confirmé mais il est difficile d'en apprécier le niveau qui pourrait être différent entre les anthracyclines. Les patients atteints de leucémie secondaire ayant très généralement reçu de multiples agents cancéreux, il est très difficile de faire la part du rôle de l'un par rapport à l'autre.
En conséquence, la modification des monographies, si elle est décidée, devrait concerner tous les agents anticancéreux interagissant directement avec l'ADN.

- qu'il est nécessaire d'organiser un groupe de travail en EUROPE comparable à celui des USA, pour établir un registre des leucémies et myélodysplasies secondaires à ces traitements en association avec des oncologues et des hématologues. En France une enquête type cohorte pourrait être menée par une équipe constituée de : Mme le Dr RM. CHICHMANIAN, Mme le Dr GOUJARD, M. le Pr G. LAGIER, Mme le Dr C. SOUBRIE et d'experts.

Annexe 3-4

VI -IDARAC® (floctafénine) ET EFFETS INDESIRABLES

Le Centre Régional de Pharmacovigilance de Paris Saint-Antoine a présenté les résultats de l'enquête nationale de pharmacovigilance sur les effets indésirables de la floctafénine, suivi d'un premier bilan entre 1983 et 1988.

Cette étude a porté sur tous les effets indésirables notifiés entre le 1er janvier 1988 et 31 décembre 1994 et plus particulièrement, sur les effets graves à type de choc ou de malaise.

Parmi les 249 notifications colligées (dont 83,1% proviennent du système national de pharmacovigilance), 165 ont été analysées après exclusion des doublons et des dossiers inexploitables. Les observations de choc (22), malaise grave (16), malaise modéré (12) et malaise léger (14) sont en augmentation par rapport à la période 1982-1987. Aucun décès imputable à la floctafénine et secondaire à un état de choc n'a été recensé. Les chocs sont survenus essentiellement lors d'utilisation de la floctafénine en automédication. Un préchallenge positif à la glafénine ou la floctafénine pourrait constituer un facteur de risque dans la survenue des effets indésirables allergiques.

D'autre part, l'imputabilité de la floctafénine est douteuse pour les 7 observations d'atteintes hématologiques et les 13 atteintes hépatiques recueillies.

Au total, cette enquête montre que les incidences relatives de décès et d' hospitalisations sont en nette progression. L'augmentation des notifications (x 3,3) apparaît paradoxale face à la chute des chiffres de vente (-50%).

Le Comité technique propose de compléter l'enquête par l'analyse des données internationales et la comparaison des taux de notification au cours des deux périodes couvertes par les enquêtes successives de 1983 à 1988 puis de 1988 à 1994. Un groupe de travail constitué des C.R.P.V. de Tours, Nice, Paris Saint-Antoine, Bordeaux, ainsi que Mme le Dr J. Goujard et M. le Pr G. Lagier est chargé d'évaluer la faisabilité de cette étude de sous-notification.

Annexe 3-4

VII - BUFEXAMAC ET EFFETS INDESIRABLES CUTANES

Un point sur l'enquête officielle relative aux spécialités contenant du bufexamac a été réalisé par le Centre Régional de Pharmacovigilance de Rennes. Trois spécialités sont concernées : le PARFENAC®, le CALMADERM® et le BUFAL® qui sont des produits conseils vendus dans les pharmacies.

Cette enquête est menée en association avec le centre de Saint-Etienne et en collaboration avec le service de dermatologie du Pr J. CHEVANT-BRETON. Les centres GERDA ont été contactés.

Deux enquêtes ont été réalisées :

- de 1974 à 1990, 69 cas ont été notifiés dont 46 hospitalisations.
- de 1990 à 1995, 127 cas ont été notifiés (91 par les CRPV, 9 par les laboratoires et 27 par les GERDA) dont 53 hospitalisations.

L'analyse des notifications de la deuxième enquête montre que 42 % des cas sont graves. Il s'agit de 29 eczéma, de 6 aggravations d'eczéma ; parmi les 18 autres cas, on trouve 1 érythrodermie, 1 éruption généralisée, 1 pustulose exanthématique et 3 éruptions à type d'érythème polymorphe. L'évolution est favorable dans 88,6% des cas. La durée moyenne d'hospitalisation est de 8,6 j. Dans 37 cas, une hospitalisation a été nécessaire. Dans 75,5 % des cas, l'imputabilité est I2 et dans 68% I3.

L'incidence totale des notifications est de 6 cas pour 1 million de tubes vendus. Une seule de ces spécialités est remboursée par la sécurité sociale.

Le coût en journées d'hospitalisation d'une dermatose liée au bufexamac est de 26 178,40 F.

En conclusion :

L'incidence est faible mais il existe une forte sous notification.

42% des effets sont graves entraînant un coût élevé des effets indésirables. Il a été évoqué la possibilité d'inscription de ces spécialités sur la liste I des substances vénéneuses, en contre-indiquant l'emploi en cas d'eczéma, de peau lésée, d'antécédents allergiques.

Le Comité Technique a souhaité que cette enquête soit prolongée sur un plan prospectif avec la collaboration des GERDA, en ciblant sur une incidence plus précise et en évaluant la possibilité d'une sensibilité croisée.
Il a été également suggéré qu'une enquête auprès des pharmaciens soient menée quant à l'utilisation dans l'érythème fessier du nourrisson.

Annexe 3-4

VIII - GAMMAGARD®

A la suite du rappel mondial des lots de GAMMAGARD® par la firme Baxter motivé par la survenue de cas de séroconversion HVC en Suède et en Espagne, une enquête de pharmacovigilance a été initiée en France afin de dépister d'éventuels cas. Le C.R.P.V. de Paris Fernand Widal a présenté les résultats de cette enquête.

Ces immunoglobulines sont importées et utilisées comme traitement substitutif d'un déficit humoral ou comme traitement immunomodulateur.

Une fois la traçabilité effectuée, les patients susceptibles d'avoir reçu certains lots à partir du 01.01.1993 ont été convoqués pour dépistage, selon un protocole défini par une lettre circulaire émanant de la DGS, de l'Agence Française du Sang et de l'Agence du Médicament.

Au total, le dernier bilan mondial recensait 223 cas ; en France, 19 cas ont été identifiés dont 10 patients qui avaient reçu ce traitement dans le cadre d'une allogreffe de moelle, 4 pour un déficit immunitaire et 5 pour d'autres pathologies diverses.
Plus particulièrement pour les patients qui avaient subi une greffe de moelle dans le même service, il y a eu aussi transfusion de produits sanguins labiles.

Toutes les PCR sont positives pour le virus C ; 13 patients avaient une PCR négatives, avant d'avoir reçu des GAMMAGARD® ou avant le 01.01.93 ; pour les 6 autres cas, les sérologies étaient négatives.
Le génotype viral est le 2b pour 11 patients, le 1a pour 6 et le 3 pour 1 patient. Ce génotype 2b est exceptionnel pour la population générale.

Les hypothèses formulées initialement étaient basées sur :

- le changement de test de dépistage du virus HCV sur les pools de plasma : les tests de deuxième génération éliminant une plus grande quantité d'anticorps VHC empêchant la formation de complexes VHC-Ac, la neutralisation du virus ou son exclusion de la fraction d'immunoglobulines,

- l'absence d'étape d'inactivation virale par un procédé solvant-détergent : cette dernière étape existe pour le GAMMAGARD® S/D disponible actuellement avec une ATU.

Actuellement, l'enquête continue au niveau international. Le suivi des patients se poursuit ; certains d'entre eux demandent des informations sur la relation causale et sur les conclusions pratiques de cette enquête pour laquelle leur participation a été vivement sollicitée.

Annexe 3-4

IX - POINT SUR LES EFFETS INDESIRABLES DU PRANTAL EN PEDIATRIE (Diphémanil méthylsulfate)

Suite à des accidents cardiaques chez les prématurés rapportés au système national de pharmacovigilance en 1993 et 1994, un point sur les effets indésirables du diphémanil méthylsulfate a été réalisé par les Centres Régionaux de Pharmacovigilance de Paris Saint-Vincent de Paul et de Rennes.

Commercialisé jusqu'en 1991 par les laboratoires Schering Plough, le diphémanil méthylsulfate est distribué par la Pharmacie Centrale des Hôpitaux depuis 1992, sous forme de comprimés sécables dosés à 2 et 10 mg et disponible sous forme de matière première pour les pharmacies hospitalières et officinales, au niveau de la Coopération Pharmaceutique Française. Le diphémanil méthylsulfate est utilisé dans la prévention de la mort subite du nourrisson.

Vingt-cinq observations, émanant de la banque nationale de pharmacovigilance et concernant 12 prématurés et 13 nourrissons, ont été retenues.
Dans 13 cas (10 prématurés et 3 nourrissons), il s'agit d'effets indésirables de nature cardiaque. Les dossiers des prématurés sont les plus préoccupants. De plus, 7 cas récents dont 6 chez le prématuré ont été recensés dans la littérature.

Les indications sont la bradycardie, l'apnée, l'hypertonie vagale chez des grands prématurés de 27 SA à 32 SA. Un décès a été constaté par arrêt cardiaque chez un prématuré né à 29 SA avec des taux thérapeutiques d'environ 30 fois supérieurs à ceux signalés dans la littérature. Trois erreurs d'usage sont à noter : 2 intoxications aiguës et une erreur d'administration. Les autres effets rapportés sont essentiellement des effets digestifs, dont un sévère et atropinique.

Au vu de ces premiers résultats, le Comité technique a décidé l'ouverture d'une enquête officielle.

Annexe 3-4

X -SPASFON® INJECTABLE (phloroglucinol) ET TROUBLES ATROPINIQUES

Le phloroglucinol est un antispasmodique musculotrope présenté comme non atropinique.
Un point effectué par le Centre Régional de Pharmacovigilance de Limoges sur ses éventuels effets atropiniques avait révélé l'existence d'accidents sévères, notamment allergiques, avec la forme injectable et a conduit à la mise en place d'une enquête officielle de pharmacovigilance.

Soixante quatre observations d'effets indésirables ont été retenues et analysées. Elles concernent en majorité des femmes, dans le cadre d'indications urinaires, digestives, hépato-biliaires et obstétricales. L'âge moyen est de 40 ans. Les effets indésirables recueillis sont essentiellement de nature allergique : cutanés, respiratoires, malaises généraux à traduction cardio-vasculaire et/ou neurologique. L'évolution est en général favorable. Quatre décès sont survenus : par choc septique, SIDA, embolie amniotique et arrêt cardio-respiratoire.

Au total, la fréquence des effets indésirables apparaît faible mais un tiers d'entre eux sont sévères et essentiellement de type allergique. Le résumé des caractéristiques du produit mérite donc d'être modifié par la mention dans la rubrique "Effets indésirables" de la possibilité de survenue de "réactions allergiques rares mais parfois graves", et la contre-indication en cas d'allergie connue au phloroglucinol. Il semble excessif de maintenir à la rubrique pharmacodynamie que ce produit ne présente pas d'inconvénients atropiniques. La compatibilité physico-chimique du phloroglucinol avec certains AINS et certains antiémétique doit être évaluée, car il s'agit d'associations fréquemment employées.

Au vu de l'ensemble de ces données, le SPASFON® sous sa forme injectable mériterait de figurer sur la liste II.

Le Comité technique est favorable aux modifications du RCP proposées par le rapporteur et à l'étude des incompatibilités physico-chimiques. Cependant si l'inscription en liste II est proposée, elle s'appliquera au principe actif quelque soit sa voie d'administration.

Annexe 3-4

XI - POINT SUR LES MICROANGIOPATHIES THROMBOTIQUES ET LE FLUCONAZOLE (TRIFLUCAN®)

Un point sur la possibilité de survenue de microangiopathie thrombotique (M.A.T.) en relation avec la prise de TRIFLUCAN® (fluconazole) a été présenté par le Centre Régional de Pharmacovigilance de Paris Saint-Antoine.

La M.A.T. est une pathologie grave d'évolution spontanée fatale en quelques semaines à quelques mois, regroupant les purpuras thrombotiques et thrombocytopéniques, associés à des syndromes hémolytiques et urémiques.
De nombreux facteurs étiologiques ont été avancés : viraux, bactériens ou médicamenteux, mais aussi la grossesse et la greffe de moelle ou de rein. Le diagnostic est porté avec certitude, après histologie du cerveau ou du rein montrant des microthromboses vasculaires.

Entre 1993 et fin 1994, 16 observations colligées par l'équipe du Pr. W. Rosenbaum (Hôpital Rothschild AP-HP, Paris) ont permis la réalisation d'une étude cas-témoins par le réseau national de santé publique.
Dans 7 cas l'histologie n'a pas permis de confirmer le diagnostic (3 cas) ou n'a pas été réalisée (4 cas). Parmi les 9 cas dont l'histologie confirmait le diagnostic, 8 patients recevaient du fluconazole.
Il s'agit de patients atteints de SIDA (CD4<30/mm3). Le délai d'apparition est compris entre 10 jours et 1 an et demi. Le traitement par fluconazole est utilisé à la posologie recommandée et l'apparition d'une M.A.T. n'a pas conduit à l'arrêt du traitement. L'évolution a été fatale dans 6 cas en 2 semaines à 8 mois et 2 fois stabilisée par des échanges plasmatiques répétés. Tous ces patients présentaient des facteurs de risque associés : infection à CMV (7), candidose (7), ainsi que des comédications : cotrimoxazole (7), ganciclovir (6) et zidovudine (4). L'imputabilité du fluconazole reste douteuse pour ces 8 observations.
L'analyse de l'étude cas-témoins montre une association significative entre l'apparition de M.A.T. et l'infection à CMV, la prise de fluconazole, ainsi que les deux associés.
Cependant, la méthodologie de cette étude paraît discutable notamment dans la sélection des cas, le diagnostic n'étant confirmé que dans 9 des 16 cas.

Les résultats ne permettent donc pas de confirmer ou d'infirmer le rôle du fluconazole dans la survenue de M.A.T. Les nouveaux cas de M.A.T. continuent d'être inclus dans l'étude. L'enquête officieuse reste donc ouverte.

Annexe 3-4

XII - Suivi de l'enquête ZAGAM® (sparfloxacine)

Le premier bilan présenté au dernier Comité Technique faisait état de 208 cas de phototoxicité avec 83 cas cliniquement graves (15,6%).

Au 31.05.1995, 371 observations ont été recueillies dont 22,3% présentent des lésions de brulûres graves (phlyctènes).

Certains paramètres sont précisés :

- le délai de survenue ainsi que la durée du traitement sont plus courts : 1,5 jours au lieu de 3, 3 jours au lieu de 5. L'influence de l'exposition solaire sur la gravité clinique se confirme mais il reste un certain nombre de cas où les lésions apparaissent sans exposition directe au soleil.

- la fréquence de survenue du mois de mai diffère peu du mois d'avril : 1 cas pour 683 patient et 1 pour 790 en avril.

Des mesures ont été prises à partir du 1er juin à la suite de la Commission Nationale de Pharmacovigilance du 24 mai 1995 : restrictions d'indications, renforcement de l'information sur la phototoxicité (nouveau RCP, lettre aux médecins et pharmaciens).

Les cas analysés survenant en juin sont actuellement au nombre de 12 avec 3 cas graves cliniquement (1/569). La fréquence reste élevée mais il est difficile de comparer cette fréquence aux chiffres précédents. La surveillance intensive doit se poursuivre pendant les mois ensoleillés avec une prochaine présentation au Comité Technique de septembre.

Un avis est demandé aux membres du Comité Technique sur le projet de feuille de recueil des cas de phototoxicité sous ZAGAM®. Il est souhaité de mieux présenter le paragraphe "Indications", et d' identifier le patient par ses initiales au lieu des trois première lettres.
Cette fiche sera à adresser au centre de Nancy qui effectuera la centralisation.

Il apparaît que certains médecins hospitaliers n'ont pas reçu le courrier d'information du laboratoire.

Les autres effets secondaires comprennent :

- 111 effets musculo-squelettiques dont 83 tendinites et 5 ruptures tendineuses,
- 100 effets neuro-psychiatriques (vertiges, ébriété, céphalées, insomnie, cauchemars, hallucinations, dysesthésies),
- 94 effets cutanés en dehors des cas de phototoxicité (essentiellement des réactions allergiques),
- 53 effets digestifs (nausées, vomissements, diarrhée, constipation, gastralgies),
- 39 réactions anaphylactiques,
- 11 observations d'élévation des transaminases,
- 7 atteintes hématologiques.

Les effets cardiologiques ont déjà fait l'objet d'une présentation au Comité Technique du mois de mai.

Annexe 3-4

XIII - DEMANDE DE MODIFICATION DE L'INFORMATION MEDICALE DE LA SPECIALITE SORIATANE® (acitrétine)

Le C.R.P.V. de Reims a examiné la demande de modification d'information des laboratoires Roche concernant l'interaction entre l'alcool et l'acitrétine.

En 1990, une étude multicentrique cinétique menée dans les pays nordiques et en Angleterre a mis en évidence dans le plasma de patients traités par acitrétine (demi-vie = 50h) de l'étrétinate de demi-vie beaucoup plus longue (80 à 100j). Il apparait nécessaire de prendre en compte cette donnée afin de proposer une période de contraception adaptée à l'arrêt du traitement par l'acitrétine.

De plus, des études in vitro ont montré que l'éthanol pouvait favoriser dans la transformation de l'acitrétine en étrétinate. En 1992, une étude cinétique comparant la formation d'étrétinate à partir d'acitrétine en présence ou en l'absence d'alcool, montre qu'après absorption concomitante d'alcool, l'étrétinate a été retrouvé chez tous les sujets. En revanche, les taux d'étrétinate restaient inférieurs à la limite de quantification de la méthode de dosage lorsque l'acitrétine était administrée seule.

La mention dans les RCP d'une interaction avec l'alcool, d'une précaution d'emploi déconseillant la prise de boissons alcoolisées pendant le traitement et la conservation des mesures de contraception inchangées et identiques à celles initialement arrêtées pour l'étrétinate semblent donc justifiées. Le dossier sera présenté lors d'une prochaine Commission Nationale de Pharmacovigilance, après la recherche d'information complémentaire sur le seuil plasmatique d'action tératogène de l'étrétinate.

Annexe 3-4

XIV - ENQUETE OFFICIELLE SUR LES EFFETS INDESIRABLES DU MEDIATOR®

Le C.R.P.V. de Besançon a présenté les premières données issues de l'enquête officielle de pharmacovigilance sur les effets indésirables du benfluorex (MEDIATOR®), commercialisé par les laboratoires Servier.

Le benfluorex, indiqué comme adjuvant du régime adapté des hypertriglycéridémies et dans le diabète asymptomatique avec surcharge pondérale, possède une structure voisine de celle des anorexigènes.

Un total de 210 dossiers d'effets indésirables ont été recueillis. Ils sont majoritairement observés dans le cadre de polythérapies associant le MEDIATOR®. Il s'agit notamment d'atteintes hépatiques (hépatites mixtes, cytolytiques, cholestatiques et élévations de transaminases), d'atteintes hématologiques (leucopénie, hyperlymphocytose, thrombopénies isolées ou associées à une leucopénie, lymphopénie ou anémie), des effets cardio-vasculaires et des effets cutanés et allergiques (notamment 3 chocs anaphylactiques avec réadministration positive).

Dix notifications spontanées concernent des hypertensions pulmonaires d'allure primitive : 9 font partie de l'enquête sur les anorexigènes présentée en avril 1995, seul un cas est survenu postérieurement. Six d'entre elles ont été validées par l'expert et atteignent 4 femmes et 2 hommes âgés de 42 à 57 ans. Dans 3 cas, la chronologie d'apparition de la dyspnée est compatible avec la prise d'anorexigènes et de MEDIATOR®. Aucun cas n'a été observé lors d'une monothérapie par le benfluorex.

Depuis la commercialisation en 1976, les chiffres de vente sont en augmentation régulière, les prescriptions étant destinées à des femmes dans 2 cas sur 3.

Le Comité Technique prend note qu'il n'existe aucun cas d'hypertension pulmonaire d'allure primitive résultant d'une monothérapie au MEDIATOR® et souhaite que l'enquête reste ouverte.

Annexe 3-4

XV - SURVEILLANCE DE LA LITTERATURE : PUBLICATIONS IMPORTANTES EN MATIERE DE SANTE PUBLIQUE

"Seminars in Medicine of the Beth Israel Hospital, Boston : The Hypothalamic Pituitary-Adrenal Axis and Immune-Mediated Inflammation"
G.P. GHROUSOS,
N. Eng. J. Med., 1995, vol. 332, 20 : 1351-1362
(NANTES)

α 1 bloquants - inhibiteurs de la 5 α reductase - hypertrophie bégnine de la prostate
"Alpha 1 blockers vs 5 alpha-reductase inhibitors in benign prostatic hyperplasia"
J. T. ANDERSEN
Drugs and Aging, 1995, 6, 388-396
(LIMOGES)

Acide folique - et malformation des membres
"Limb-reduction defects and folic acid supplementation"
A.E. CZEIZEL,
Lancet, 1995, vol. 345, 8954 : 932
(REIMS)

AINS - gastropathie - ulcères gastriques
"From peptic ulcer disease to NSAID gastropathy"
S. H. ROTH
Drugs and Aging, 1995, 6, 358-367
(LIMOGES)

Amiodarone - grossesse
"Pregnancy outcome after gestational exposure to amiodarone in Canada"
MAGEE L.A., DOWNAR E., SERMER M., BOULTON B.C., ALLEN L.C., KOREN G.
Am. J. Obstet. Gynecol. 1995, 172, 4 : 1307-11
(PARIS-SAINT VINCENT DE PAUL)

Anti-ulcéreux - troubles oculaires
"Ocular safety of antiulcer drugs"
L.A.G. RODRIGUES , et al.,
Lancet, 1995, vol. 345, 8956 : 1059
(REIMS)

Bêta-agonistes oraux - accouchements prématurés
"Efficacy of oral beta-agonist maintenance therapy in preterm labor : a meta-analysis"
MACONES G.A., BERLIN M., BERLIN J.A.
Obstet. Gynecol., 1995, 85, 2 : 313-17
(PARIS-SAINT VINCENT DE PAUL)

Bronzage - cancer de la peau
"Non melanic skin cancer associated with use of a tanning bed"
N. Eng. J. Med., 1995, vol. 332, 21 : 1450
(ANGERS)

Annexe 3-4

Carmustine - polymères - chimiothérapie - tumeur du cerveau
"Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas"
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S.R. AHMAD , et al.
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"Clozapine therapeutic plunge in patient with Parkinson's disease"
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(REIMS)

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"Clozapine in Parkinson's disease"
P. GONSKI,
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"Net effect or oral contraceptive use on the risk of cancer in women in the United States"
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"Corticosteroid Osteonecrosis"
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Cyclosporine - Colite ulcérante sévère
"Cyclosporine in Severe Ulcerative Colitis"
F. VINCENT, T.A. BENSOUSAN
N. Eng. J. Med, 1995, vol. 332, 2 : 127
(NANTES)

Décret de Pharmacovigilance en France
"Exhortation pharmacovigilance in france"
A. HERXHEIMER,
Lancet, 1995, vol. 345, 8956 : 1037-1038
(REIMS)

Desmopressine - décès
"Fatal complication of desmopressin"
S. HARTMANN, W. REINHART,
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(REIMS)

Diéthylstilbestrol - fertilité
"Fertility in men exposed prenatally to diethylstilbestrol"
N. Eng. J. Med., 1995, vol. 332, 21 : 1411-1416
(ANGERS)

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"The Use of Estrogens and Progestins and the Risk of Breast Cancer in Postmenopausal Women"
G.A. GOLDITZ and Others,
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"Clotting factor VIII and risk of deep-vein thrombosis"
P.K. Mc CALLUM , et al.,
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S.L. BLOMGREN, G.D. TOLLEFSON,
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"Systemic effects of glucocorticoids - a response"
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"Heparin-induced Thrombocytopenia in Patients treated with Low-Molecular-Weight Heparin or Unfractionated Heparin"
T.E. WARKENTIN and Others,
N. Eng. J. Med., 1995, vol. 332, 20 : 1330-1335
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"Acute Pancreatitis Associated with Growth Hormone Therapy for Short Stature"
S. MALOZOWSKI, W. HUNG, D.C. SCOTT, B.V. STADEL,
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Huile de primevère - eczéma atopique
"Evening primrose oil and atopic eczema"
J. BERTH-JONES , et al.,
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"Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia"
S. CHARACHE and Others,
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"Transient hypoxaemia during neutrophil recovery in febrile patients"
K. WHITE , et al.,
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G.B. ZULIAN, E. TULLEN, B. MATON,
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(NANTES)

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"Hepatitis C and Immune Globulin"
S.D. DOUGLAS, H.B. SLADE,
N. Eng. J. Med, 1995, vol. 332, 18 : 1235
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"Breast implants and breast cancer, reanalysis of a linkage study"
N. Eng. J. Med, 1995, vol. 332, 23 : 1535-1539
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"More on breast implants and connective-tissue diseases"
N. Eng. J. Med., 1995, vol. 332, 19 : 1306-1307
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Interferon Alfa-2b - Hépatite non-A et non-B
"A Comparison of Three Interferon Alfa-2b Regimens for the Long-Term Treatment of Chronic Non-A, Non-B Hepatitis"
T. POYNARD and Others,
N. Eng. J. Med., 1995, vol. 332, 22 : 1457-1462
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"Sever necrotizing cutaneous lesions complicating treatment with interferon Bêta 1b"
N. Eng. J. Med, 1995, vol. 332, 23 : 1584
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"Levonorgestrel implants and intracranial hypertension"
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Mammoplastie - tissus cellulaires
"Silicone breast implants and the risk of connective tissue diseases and symptoms"
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"A 70-Year-Old Woman with Atrial Fibrillation and the Rapid Onset of Hemorrhagic Manifestations"
D.B. CINES, M. LAPOSATA,
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"Severe Adverse Cutaneous Reactions to Drugs"
F.J. FERNANDEZ-FERNANDEZ,
N. Eng. J. Med, 1995, vol. 332, 14 : 959
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"OKT3 treatment for allograft rejection is a risk factor for cytomegalovirus disease in liver transplantation"
PORTELA D., PATEL R., LARSON KELLER J.J., ILSTRUP D.M., WIESNER R.H., STEERS J.L., KROM R.A.F., PAYA C.V.
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(PARIS-SAINT ANTOINE)

Polysorbate 80 - hypersensibilité
"Polysorbate 80 hypersensitivity"
W.B. SHELLEY , et al.
Lancet, 1995, vol. 345, 8960 : 1312-1313
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Remoxipride - libération de la prolactine
"Influence of the dosing interval on prolactin release after remoxipride"
G. MOVIN-OSSWALD, M. HAMMARLUND-UDENAES, C. VON BAHR, P. ENEROTH, K. WALTON-BOWEN,
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R. FOX, C. BARRY,
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K.L. DAVIS, P. POWCHIK,
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P. ATKISON , et al.,
Lancet 1995, vol. 345, 8954 : 894-895
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"Screening for prostate cancer"
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Drugs and Aging, 1995, 6, 345-350
(LIMOGES)

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"Drug Therapy : Prevention and Treatment of the Complications of Diabetes Mellitus"
C.M. CLARK Jr, D.A. LEE,
N. Eng. J. Med, 1995, vol. 332, 18 : 1210-1217
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Traitement - cholestérol - Maladie de l'artère coronaire
"Beneficial Effects of Cholesterol-Lowering Therapy on Coronary Endothelium in Patients with Coronary Artery disease"
C.B. TREASURE and Others
N. Eng. J. Med., 1995, vol. 332, 8 : 481-487
(NANTES)

Traitement anti-tuberculeux - insuffisance rénale sévère
"Antituberculous therapy and acute liver failure"
F. DURAND , et al.,
Lancet, 1995, vol. 345, 8958 : 1170-1172
(REIMS)

Traitement contre la stérilité - Cancer de l'ovaire
"Risk of ovarian cancer after treatment for infertility"
N. Eng. J. Med, 1995, vol. 332, 19 : 1300-1302
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Traitement antihypertensif - reins
"Renal function during antihypertensive treatment"
S. MADHAVAN , , et al.,
Lancet, 1995, vol. 345, 8952 : 749-751
(REIMS)

Traitement d'estrogènes - lupus érythémateux systémique
"Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus"
J. SANCHEZ-GUERRERO, M.H. LIANG, E.W. KARLSON, D.J. HUNTER, G.A. GOLDITZ
Ann. Intern. Med., 1995, 122, 6 : 430-33
(PARIS-SAINT ANTOINE)

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"Hormone replacement therapy and endometrial cancer risk : a meta-analysis"
GRADY D., GEBRETSADIK T., KERLIKOWSKE K., ERNSTER V., PETITTI D.
Obstet. Gynecol., 1995, 85, 2 : 304-13
(PARIS-SAINT VINCENT DE PAUL)

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"Clinical Outcomes after Transfusion-Associated Hepatitis C"
M.J. TONG, N.S. ET-FARRA, A.R. REIKES, R.L. CO,
N. Eng. J. Med, 1995, vol. 332, 22 : 1463-1466
(NANTES)

Vaccin R.O.R. - allergie aux oeufs
"Safe administration of the measles vaccine to children allergy to eggs"
N. Eng. J. Med, 1995, vol. 332, 19 : 1262-1266
(ANGERS)

Zidovudine - Enfants
"Something better than zidovudine for children"
P.M. ROWE,
Lancet, 1995, vol. 345, 8948 : 511
(REIMS)

Zofénopril - ACE - mortalité - morbidité
"The effect of the Angiotensin-Converting-Enzyme Inhibitor Zofenopril on Mortality and Morbidity after Anterior Myocardial Infarction"
E. AMBROSIONI, C. BORGHI, B. MAGNANI
N. Eng. J. Med, 1995, vol. 332, 2 : 80-85
(NANTES)

Annexe 3-4

XVI - QUESTIONS DIVERSES

- Le Comité technique de pharmacovigilance demande qu'une réflexion approfondie soit menée sur le rapport bénéfice/ risque de l'utilisation des gammaglogulines antitétaniques par rapport à la vaccination.

- Des irritations locales des mains ont été signalées lors de l'utilisation d'un savon contenant un antiseptique (Pousse-mousse Antibactérien®). Un courrier sera envoyé à l'unité de Pharmacovigilance qui transmettra au service compétent.

- Suite à une observation rapportant un mésusage d'IMIGRANE® échantillon médical, le Comité technique souhaiterait savoir s'il était prévu que les laboratoires Glaxo délivrent des échantillons gratuits de cette spécialité aux médecins.

- CELESTENE® injectable : Cette spécialité ne comporterait plus de sulfites dans sa composition. Le Comité technique souhaiterait avoir confirmation de cette information et s'interroge sur le moyen de distinguer les anciens lots avec sulfites de la nouvelle formulation.

- Le Comité technique est préoccupé par la circulation de produits présentés comme traitant le SIDA. L'analyse du traitement de Mr Beljanski a mis en évidence une quantité non négligeable de plomb. Un autre produit en provenance de la Suisse est composé de dérivés du safrol, connus pour leur pouvoir mutagène.

Annexe 3-4

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Annexe 3-5

Saint-Denis, le

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 30 avril 1998)

Etaient présents

M. LAROUSSE : Président
M. LE LOUET (suppléant de Mme ALBENGRES), Mme PENFORNIS (suppléante de M. ALLAIN H.), Mme LAINE CESSAC (suppléante de M. ALLAIN P), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme. ASSOULY, Mme AUTRET, Mme BAVOUX, Mme DAVID (suppléante de M. BECHTEL), M. BIOUR, M. BLAYAC, M. CARLHANT, M. CARON, Mme. CHAMBOST, Mme CHICHMANIAN, Mme GINISTY (suppléante de M. DALLY), Mme ZENUT (suppléante de M. ESCHALIER), Mme C. SGRO (suppléante de M. ESCOUSSE), M. VIAL (suppléant de M. EVREUX), M. GILLET, Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR (suppléante de Mme JOUGLARD), Mme KREFT-JAIS, M. MALLARET, M. MERLE, M. MONTASTRUC, M. LE DOZE (suppléant de M. MOULIN), M. NETTER, M. NORDMAN, M. OLLAGNIER, Mme RICHARD, M. RICHE, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. MOREL (suppléant de M. VANDEL),
Mme TUBERT-BITTER (représentant Monsieur le Directeur Général de l'INSERM),
Mme BARON (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur de l'Agence du Médicament).

Conseiller scientifique

M. LAGIER

Unité de pharmacovigilance

Melle AUGUSTE
Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme JOUSSELIN-PAUTROT
Melle JULLIAN
M. MAIGNEN
Mme PARIENTE-KHAYAT
Melle PIERRON
M. ROPERS
Mme VERROUST

Assistaient à la réunion (D.E.V.)

M. BRASSARD
Mme CALLENS-LAVELOT
Mme DUMARCET
Mme DURANTEAU
Mme DURETTE
Mme SAINT-RAYMOND

Expert

M. Le Pr NORDMAN

I - POINT VIGABATRIN (SABRIL®)

Le CRPV de Paris Pitié (C. SOUBRIE) a présenté les données récentes concernant les troubles du champ visuel retrouvés chez des patients traités par SABRIL®. En effet, après la notification et la publication de cas symptomatiques de constriction persistante du champ visuel, des études ont montré récemment que chez des patients asymptomatiques, un pourcentage élevé de patients (14 %) présentait des anomalies à l'examen périmétrique. La signification clinique et l'évolution de ces troubles ne sont pas connues.

Le Pr NORDMAN, qui a expertisé les données ophtalmologiques pour le compte de la firme Hoechst Marion Roussel, a détaillé les cas rapportés :
- Les caractéristiques des examens périmétriques des cas évoquent une anomalie d'origine rétinienne (régularité concentrique de l'atteinte portant principalement sur le champ nasal en épargnant relativement le champ temporal) ;
- Ce type de problème est peu fréquent en médecine générale ;
- La fréquence des cas symptomatiques est de l'ordre de 0,1 %. Elle contraste avec la fréquence de 10-15 % de cas asymptomatiques. On ne connait pas de formes de passage entre les 2 états, ni les éventuels facteurs déclenchants. Il n'y a pas eu d'aggravation observée à l'arrêt du traitement, des améliorations ont été rarement observées. C'est l'intensité de la constriction qui détermine vraisemblablement l'état symptomatique ou non, et lorsque la constriction préserve les 20° centraux, le patient est le plus souvent asymptomatique.

Le Pr NORDMAN a évoqué les étiologies possibles des constrictions périmétriques : un artefact lié au bord supérieur des lunettes chez les porteurs, le glaucome, la rétinopathie pigmentaire, l'hystérie.

Le Pr NORDMAN a souligné que l'examen par confrontation ne permettait de détecter que les formes majeures de réduction du champ visuel. En conséquence, l'examen qui devrait être utilisé pour dépister et suivre ces troubles est l'examen périmétrique automatisé, à cause du caractère subjectif de la méthode avec un opérateur. Une surveillance adéquate devrait comporter un examen avant la mise sous traitement, et des examens régulièrement tous les 6 mois. Il demeure qu'il n'existe pas de méthode permettant de suivre le champ visuel des enfants de moins de 6-8 ans.

Le Pr NORDMAN a jugé que les anomalies de l'électrorétinogramme observées chez le volontaire sain étaient vraisemblablement une conséquence de l'effet pharmacologique du traitement, sans rapport avec les constrictions du champ visuel observées.

De plus, le Pr NORDMAN a décrit un cas de constriction du champ visuel observé lors d'un traitement par progabide. La constriction observée chez ce patient était analogue aux cas trouvés avec le vigabatrin. Cela pourrait être en faveur d'une possible toxicité liée au mécanisme d'action impliquant le GABA.

Le Comité Technique a estimé que les nouvelles données ne justifiaient pas de modifier à nouveau le RCP en urgence et a souhaité que le sujet fasse l'objet d'une présentation à la Commission Nationale du 9 juin 1998.

Annexe 3-5

II - ADOPTION DU PROCÈS-VERBAL DU COMITÉ TECHNIQUE DU 26/02/98

Le procès-verbal du Comité Technique du 26 février a été adopté après les corrections suivantes :

Page 3	Dernier paragraphe : rajouter "l'efficacité de l'allopurinol dans le traitement de la goutte est indiscutable". Remplacer "souhaitable" par "décidée" et "permettrait" par "permet".
Page 4	Dans l'analyse de la littérature : L'énurésie et les oedèmes généralisés ne sont pas des effets antiadrénergiques.
Page 6	3ème ligne : remplacer "aigüe" par "aiguë". 9ème ligne : supprimer "puissant et sélectif".
Page 7	16ème ligne : rajouter "confusion mentale".
Page 14	Concernant les laboratoires RHONE POULENC RORER, remplacer "proarythmogène" par "arythmogène".
Page 16	Dernier paragraphe : "la France a rappelé aux Etats Membres sa préoccupation concernant les effets indésirables neurologiques, les pathologies auto-immunes au décours d'une vaccination contre l'hépatite B et l'intense couverture médiatique".
Page 19	12ème ligne : rajouter "hypotension artérielle". 14ème ligne : rajouter "anesthésiques généraux".
Page 21	Rajouter dans le titre "ALFATIL® LP". 6ème ligne : remplacer "obtenue" par "observée". Avant-dernière ligne : supprimer "puissants".
Page 23	3ème ligne : rajouter "...agoniste dopaminergique prescrit comme antiparkinsonien" 29ème ligne : remplacer "dossiers" par "notifications".
Page 24	Dans la conclusion : - supprimer "forte" - remplacer "intéraction" par "interaction" et rajouter "anticoagulants oraux"
Page 25	3ème ligne : Remplacer "1996." par "1995." Rajouter "... ces effets indésirables sont déjà inclus dans le RCP".
Page 26	Remplacer "la qualité médiocre des données" par "le texte bien que très correctement présenté".
Page 35	40ème ligne : Rajouter "*Eur J Clin Pharmac*"

Suivant les recommandations de Vancouver, le comité Technique a souhaité que la bibliographie soit référencée de manière homogène,.

III - TOUR DE TABLE DE LA LITTERATURE

Annexe 3-5

AINS / élévation de la pression artérielle.
"NSAIDs and blood pressure"
A.G. JOHNSON
Drugs & Aging 1998 ; 12 (1) : 17-27
(CRPV de LIMOGES)

AINS / insuffisance rénale chez le sujet âgé
"Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subject. Results of a case-control study"
D. HENRY et al
British Journal of Clinical Pharmacology 1997 ; 44 : 85-96 (signalé dans Adverse Drug Reactions and Toxicological Review 1997 ; 16 : 207)
(CRPV de RENNES)

Alendronate / glucocortoicoïdes / ostéoporose.
"Alendronate increases low mineral density in patients on glucocorticoid therapy : result of multinational study"
P.E. POUBELLE et al
Arthritis and Rheumatism 1997 ; 40 : 327.
(CRPV de SAINT-ETIENNE)

Alendronate / glucocortoicoïdes / ostéoporose.
"Alendronate for the management of glucocorticoïd - induced osteoporosis : result of a multicarter US study"
K. SAAG et al
Arthritis and Rheumatism 1997 ; 40 : 136.
(CRPV de SAINT-ETIENNE)

Anémies auto-immunes du nouveau-né.
"Inhibition of erythroid progenitor cells by anti-kell antibodies in fetal alloimmune anemia"
JANET I. VAUGHAN and others
New England Journal of Medicine 1998 ; 338 (12) : 798-803.
(CRPV de NANTES)

Antidépresseurs / syndrome de sevrage.
"Antidepressants discontinuation reactions are preventable and simple to treat"
P. HADDAD, M. LEJOYEUX, A. YOUNG
Br. Med. J. 1998 ; 316 : 1105-1106.
(CRPV de TOULOUSE)

Bosentan / vasoconstricteur / effets indésirables.
"The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension"
HENRY KRUM et al
New England Journal of Medicine 1998 ; 338 (12) : 783-790. (CRPV de NANTES)
Chutes liées à une prise médicamenteuse chez les personnes agées de plus de 65 ans.
"Epidemiology of medication-related falls and fractures in the elderly"
R.G. CUMMING
Drugs & Aging 1998 ; 12 (1) : 43-53
(CRPV de LIMOGES)

Dexamethazone / nouveaux-nés / ventilation assistée.

"A multicenter trial of two dexamethasone regimes in ventilator-dependent premature infants"
LU-ANN PAPILE and others
New England Journal of Medicine 1998 ; 338 (14) : 1112-1118
(CRPV de NANTES)

Dexfenfluramine / anomalies valvulaires.
"Dexfenfluramine : no increase significant valvular abnormalities".
Reactions 1998 ; 697 : 3-4.
(CRPV de BREST)

Diététique.
"Is obesity worth treating in the elderly ?"
R.M. ORTEGAN
Drugs & Aging 1998 ; 12 (2) : 97-101
(CRPV de LIMOGES)

Effets indésirables dans les études de phase I.
"Adverse events in phase I studies : a report in 1015 healthy volunteers"
M. SIBILLE et al
European Journal of Clinical Pharmacology 1998 ; 54 : 13-20
(CRPV de LIMOGES)

Effets indésirables médicamenteux.
"Adverse drug reactions remain a major cause of death"
D. BONN
Lancet 1998 ; 351 : 1183
(CRPV de REIMS)

Hypovitaminose D / facteurs de risque.
"Hypovitaminosis D in medical inpatients"
MELISSA K. THOMAS et al
New England Journal of Medicine 1998 ; 338 (12) : 777-783.
(CRPV de NANTES)

Iatrogénie.
"Iatrogénie évitable : un gisement considérable"
Les Nouvelles Pharmaceutiques 1998 ; 153 : 3-6.
(CRPV de GRENOBL

Imagerie médicale.
"Medical Progress : Imaging the Brain (First of two parts)"
S. GILMAN
New England Journal of Medicine 1998 ; 338 (12) : 812-820.
(CRPV de NANTES)

Interaction médicamenteuse / macrolides et statines / rhabdomyolyse.
"Lovostatin - induced rhabdomyolysis possibly associated with clarithromycin and azithromycin"
J.W. GRUNDEN, K.A. FISHER
Annals of pharmacotherapy 1997 ; 31 : 859-863 (signalé dans Adverse Drug Reactions and Toxicological Review 1997 ; 16 : 210-211)
(CRPV de RENNES)

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Interaction médicamenteuse / paracétamol et warfarine
"Acetaminophen and other risk factors for excessive warfarine anti-coagulation"
E.M. HYLEK et al
J.A.M.A. 1998 ; 279 : 702-703
(CRPV de SAINT-ETIENNE)

Losartan / pancréatite.
"Pancreatitis after losartan"
Lancet 1998 ; 351 : 1178
(CRPV de REIMS)

Médicaments / grossesse.
"Drugs and Pregnancy"
GIDEON KOREN et al
New England Journal of Medicine 1998 ; 338 (14) : 1128-1137
(CRPV de NANTES)

Médicaments / grossesse / inhibiteurs de l'enzyme de conversion
" Pregnances outcome with ACE - inhibitor use in early frequency"
F.H. STEFFENSEN et al
Lancet 1998 ; 351 : 596.
(CRPV de SAINT-ETIENNE)

Mésalamine / diarrhée.
"Diarrhea associated with mesalamine in patient with chronic non granulomatous enterocolitis"
K.D. FIVE, H.E. SARLES
New England Journal of Medicine 1998 ; 338 (13) : 923-924
(CRPV d'ANGERS)

Midodrine dans l'hypotension orthostatique.
"Midodrine. A review of its therapeutic use in the management of orthostatic hypotension"
K.J. MC CLELLAN et al
Drugs & Aging 1998 ; 12 (1) : 75-86
(CRPV de LIMOGES)

Névirapine / syndrome de Stevens-Johnson.
"Nevirapine - associated Stevens-Johnson syndrome"
K.J. WARREN et al
Lancet 1998 ; 351 : 567
(CRPV de SAINT-ETIENNE)

Oméprazole et misoprostol / étude comparative dans le traitement des ulcères liés aux AINS.
"Omeprazole compared with misoprostol for ulcers associated with non-steroidal anti-inflammatory drugs"
C.J. HAWKEY et al
New England Journal of Medicine 1998 ; 338 (11) : 727-734
(CRPV d'ANGERS)

Oméprazole et ranitidine / étude comparative dans le traitement des ulcères liés aux AINS.
"A comparaison of omeprazole with ranitidine for ulcers associated with non-steroidal anti-inflammatory drugs"
N.D. YEOMANS et al

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New England Journal of Medicine 1998 ; 338 (11) : 719-726
(CRPV d'ANGERS)

Particules de caoutchouc provenant de bouchons de flacons de perfusion / embolie.
"Rubber emboli"
W.H. SETA et al
European Journal of Clinical Pharmacology 1998 ; 53 : 313-315
(CRPV de LIMOGES)

Propionyl-1 carnitine dans l'artérite des membres inférieurs.
"Propionyl-1-carnitine"
L.R. WISEMAN et al
Drugs & Aging 1998 ; 12 (3) : 243-250
(CRPV de LIMOGES)

Ranitidine et sucralfate / étude comparative dans la prévention de l'ulcère de stress.
"A comparaison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation"
DEBORAH COOK et al
New England Journal of Medicine 1998 ; 338 (12) : 791-797.
(CRPV de NANTES)

Schémas d'administration des médicaments.
"Enhancing patient compliance in the elderly"
J.A. CRAMER
Drugs & Aging 1998 ; 12 (1) : 43-53
(CRPV de LIMOGES)

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Sélégiline / lévodopa / mortalité/ maladie de Parkinson / Royaume Uni
"Investigation by Parkinson's disease reseach group of United Kingdown into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease : further results of randomised trial and confidential inquiry"
Y. BEN-SHLOMO, A. CHURCHYARD, J. HEAD, B. HURWITZ, P. OVERSTALL, J. OCKELFORD, A.J. LEES.
Br. Med. J. 1998 ; 316 : 1191-1196.
(CRPV de TOULOUSE)

Tamoxifène / troubles hépatiques.
"Tamoxifen - induced fatty liver in patients with breast cancer"
Y. OGAWA, Y. MURATA, A. NISHIOKA, T. INOMATA, S. YOSHIDA
Lancet 1998 ; 351 : 725
(CRPV de REIMS)

Trisomie 21 / dépistage prénatal précoce.
"Screening of maternal of maternal serum for fetal down's syndrome in the first trimester"
JAMES E. HADDOW et al
New England Journal of Medicine 1998 ; 338 (14) : 955-961.
(CRPV de NANTES)

Troglitazone / hépatotoxicité
"Hepatic dysfunction associated with troglitazone"
P. WATKINS, R.W. WHITCOMB
New England Journal of Medicine 1998 ; 338 (13) : 916-917
(CRPV d'ANGERS)

Troglitazone / metformine / effets indésirables.
"Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus"
S.E. INZUCCHI et al
New England Journal of Medicine 1998 ; 338 (13) : 867-872
(CRPV d'ANGERS)

Troglitazone / utilisation chez les patients insulino-dépendants.
"Effect of troglitazone in Insulin - Treated Patients with type II diabets mellitus"
S. SCHWARTZ et al
New England Journal of Medicine 1998 ; 338 (13) : 861-866
(CRPV d'ANGERS)

Vigabatrin / troubles du champs visuel.
"Vigabatrin - associated retinal cone system dysfunction"
G.L. KRAUSS, M.A. JOHNSON, N.R. MILLER.
Neurology 1998 ; 50 : 614-618.
(CRPV DE GRENOBLE)

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Vitamines A, C et E / équilibre nutritionnel
"Should antioxydant vitamines be routinely recommended for older people ?"
J.A. WARD
Drugs & Aging 1998 ; 12 (3) : 169-175
(CRPV de LIMOGES)

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IV - ENQUÊTE OFFICIELLE SUBUTEX® (buprénorphine) - POINT SUR LES DÉCÈS

Rappel :

Le Subutex® a obtenu une AMM en France le 31 juillet 1995 dans le cadre d'une procédure nationale et est commercialisé depuis février 1996.
Le Subutex® est indiqué dans le traitement substitutif des pharmacodépendances majeures aux opiacés, dans le cadre d'une prise en charge médicale, sociale et psychologique.
Il peut être prescrit par tout médecin, sur un bon extrait du carnet à souche pour une durée ne pouvant excéder 28 jours.
Toutefois, il est recommandé au médecin, notamment en début de traitement, de prescrire pour une durée plus courte afin de limiter le risque d'utilisation détournée par voie intraveineuse.

Une enquête officielle de pharmacovigilance a été initiée (CRPV de Grenoble) en septembre 1996, à la suite de la notification de cas de décès de personnes toxicomanes traitées par Subutex®.
La Commission Nationale de Pharmacovigilance du ***6 février 1997*** a examiné ***onze cas*** de décès alors rapportés : une dépression respiratoire était évoquée dans la majorité des cas, et la notion de prise de benzodiazépines souvent associée a fait évoquer un rôle potentialisateur éventuel.
De plus, la notion de mésusage avec utilisation intraveineuse avait été suspectée pour un certain nombre d'observations.
Le 24 mars 1997, sur proposition de la Commission Nationale, l'AMM a été modifiée afin de mentionner clairement le risque de dépression respiratoire apparaissant principalement lors de mésusage et d'association avec les benzodiazépines.

Le centre de Pharmacovigilance de Grenoble (Dr Mallaret), dans le cadre de l'enquête officielle de Pharmacovigilance, a présenté un point sur les décès rapportés sous buprénorphine.

A ce jour, le système national recense **32 observations de décès**.
Parmi ces cas, 21 patients étaient connus comme "toxicomanes"et 3 "polytoxicomanes".
La notion de mésusage intraveineux est très probable ou probable pour 7 patients (présence de seringue, témoins. ..).
La notion de prise de benzodiazépines est mentionnée pour 23 patients.
Il faut souligner que les dosages biologiques confirment la prise de benzodiazépine associée dans 20 cas (15 clorazepate, 5 flunitrazepam) et ne retrouvent que dans 2 cas une présence de buprénorphine seule.
De plus, 20 patients avaient à l'autopsie des signes évocateurs de syndrome asphyxique (dont 2 avec oedème pulmonaire, 1 avec possible défaillance cardiaque).
Dans 1 cas, l'autopsie retrouve des aliments dans les voies respiratoires.

Les causes de décès pouvant être évoquées chez les 32 patients sont :
- l'oedème pulmonaire,
- l'insuffisance hépatocellulaire,
- la fausse route,
- l'histaminolibération,
- la dépression respiratoire.

Il faut noter que les concentrations sanguines de buprénorphine, lorsque les dosages ont été réalisés, semblent être dans les limites des taux thérapeutiques et surtout moins élevées que les concentrations cérébrales. Ceci confirme les données de la littérature quant à la lipophilie de la buprénorphine et pourrait contribuer à la dépression respiratoire.
L'analyse de la littérature et les cas rapportés sont en faveur d'une cause de décès par dépression respiratoire, le risque dépresseur pouvant être augmenté par l'administration intraveineuse de la buprénorphine et majoré par l'association aux benzodiazépines.
Cependant, si la co-responsabilité des benzodiazépines ne peut être écartée, il existe des cas sans benzodiazépine associée (la recherche de benzodiazépines s'est avérée négative dans 3 cas de décès sur les 23 pour lesquels cette recherche avait pu être effectuée).

En conclusion :

Les données actualisées présentées ne remettent pas en cause le profil de sécurité de la buprénorphine, cependant une meilleure évaluation du risque de décès par dépression respiratoire serait souhaitable (études expérimentales, potentialisation par les benzodiazépines...).
Le Comité Technique souligne que la dispensation fractionnée de la buprénorphine, pour des durées ne pouvant excéder 7 jours, permettrait de limiter le risque d'utilisation détournée par voie intraveineuse.

Le Comité Technique souhaite par ailleurs que le développement de la spécialité associant buprénorphine et naloxone (SUBOXONE) par voie sublinguale se poursuive.
En effet la mise à disposition d'une telle spécialité limiterait le risque de mésusage et donc le risque de décès par dépression respiratoire de même que les risques infectieux liés à la pratique de la voie intraveineuse, et sans doute le "trafic" de la buprénorphine.

Le Dr Riché (CRPV de Brest) fera une présentation à un prochain Comité technique sur le potentiel d'interactions entre buprénorphine - benzodiazépines - méthadone.

V - POINT BENFLUOREX (MEDIATOR®)

Le Centre Régional de Pharmacovigilance de Besançon a effectué une mise au point concernant les

effets indésirables observés avec le benfluorex.

Le MEDIATOR® (chlorydrate de benfluorex) est commercialisé en France (depuis 1976) dans les indications suivantes :
- adjuvant du régime adapté dans les hypertriglycéridémies.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex est inscrit depuis le 10 mai 1995, comme les anorexigènes, sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales.

Sur les 291 notifications rapportées avec le benfluorex, 152 ont été retenues au 30 avril 1998 (lors de la précédente mise au point de juillet 1995, 101 notifications avaient été rapportées).

● Les atteintes hépatiques : 16 cas
Les cas les plus souvent rapportés sont des hépatites et des perturbations de la biologie hépatique : élévation des transaminases. Ces effets ne sont pas mentionnés dans le RCP.

● Les atteintes digestives : 16 cas
Les cas les plus souvent notifiés sont les diarrhées. Cet effet indésirable est mentionné dans le RCP.

● Les atteintes hématologiques : 8 cas
Les effets les plus fréquents sont les thrombopénies. Il n'y a pas eu de nouveaux cas rapportés depuis juillet 1995.

● Les atteintes respiratoires : 8 cas
Les cas rapportés sont principalement des toux et des hypertensions pulmonaires (dans les 2 cas rapportés, il existe un traitement anorexigène associé).

● Les atteintes cardiovasculaires : 11 cas
Des cas d'hypertension artérielle, de tachycardie, d'extrasystoles ventriculaires et de syndrome de Raynaud sont le plus souvent notifiés.

● Les atteintes rénales : 9 cas
Parmi lesquelles on observe le plus souvent des dysuries, des pollakiuries.

● Les atteintes métaboliques : 3 cas
Une hyperlipémie, une hypothyroïdie et une crise de goutte ont été rapportées.

● Les atteintes cutanées : 38 cas
Des urticaires, des chocs anaphylactiques, des eczémas, des vascularires, des érythèmes ainsi que des purpuras sont les effets les plus fréquents. Ces effets indésirables ne sont mentionnés pas dans le RCP.

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● Les atteintes neuro-psychiatriques : 27 cas
Des cas d'asthénie ou de somnolence sont le plus souvent notifiés ; ceux-ci sont mentionnés dans le RCP. Parmi les troubles psychiatriques, on observe principalement des cas d'agressivité, d'agitation, de nervosité, ou de délire. Les paresthésies sont les troubles neurologiques les plus fréquents.

● Les troubles de l'équilibre, vertiges : 16 cas
Dans 16 cas (sur les 152 rapportés), le benfluorex est associé avec un anorexigène.
En 1995, le nombre de boîtes de MEDIATOR® vendues a été estimé à 5 millions/an.

Le nombre d'effets indésirables observés ne semble pas plus important depuis la dernière mise au point de juillet 1995. Cependant on ne peut écarter la possibilité d'une déviation de l'utilisation du benfluorex comme anorexigène étant donné que l'indication "adjuvant de régime..." entretient une certaine ambiguïté. De plus, la métabolisation du benfluorex dans l'organisme entraîne la formation de norfenfluramine, métabolite apparenté à la fenfluramine, elle-même impliquée dans l'apparition d'hypertensions pulmonaires graves.

Compte tenu de la suspicion de détournement d'usage et de la formation lors de la métabolisation de norfenfluramine, le Comité Technique propose la mise en place d'une enquête officielle de Pharmacovigilance qui permettra, entre autres, de récupérer les chiffres de vente, afin d'infirmer ou de confirmer un éventuel mésusage, et les données précliniques.

L'enquête nationale est confiée au CRPV de Besançon et l'Observatoire de la Prescription sera consulté.

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VI - POINT VINORELBINE (NAVELBINE®) ET CARDIOTOXICITÉ

Ce travail a été réalisé par le Centre Régional de Pharmacovigilance de CAEN à la suite de la notification de deux atteintes myocardiques (une nécrose et une ischémie myocardique).

L'analyse des cas de la banque et des cas de la littérature met en évidence une cardiotoxicité potentielle.

Depuis la commercialisation, et jusqu'au 26 janvier 1998 (soit 9 ans de commercialisation), 24 dossiers ont été retenus : il s'agit de 10 accidents ischémiques, 7 troubles du rythme et 7 observations diverses (4 chocs cardiogéniques, 1 défaillance cardiaque congestive, 1 péricardite, 1 cardiopathie).
Il s'agit de 13 hommes et 11 femmes, d'âge moyen 59 ans et pour lesquels la vinorelbine avait été prescrite pour un cancer bronco-pulmonaire (13 cas), du sein (8 cas) et autres (3 cas).
11 personnes sur 21 avaient des antécédents cardio-vasculaires ; l'évolution est fatale dans 7 cas, inconnue dans 2 cas et favorable dans les autres cas.

La réintroduction a réentraîné l'apparition de troubles cardiaques dans 8 cas.

Il faut noter l'association (avec la même imputabilité) avec d'autres molécules connues pour leur éventuelles toxicité cardiaque dans 11 cas.

Pour la littérature, 8 articles rapportent une ischémie cardiovasculaire faisant suite à un traitement par la vinorelbine (pour 13 patients et 17 cures de vinorelbine). 4 cas sont des doublons des dossiers des CRPV.

Il est proposé l'ouverture d'une enquête officielle permettant de consulter les essais pré-cliniques, et les données internationnales.

Au vu de ces données, il faudra déterminer la nécessité de modifier ou non les rubriques "effets indésirables" et "précautions d'emploi" du RCP.

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CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Jean Minjoz 25030 BESANCON Cedex

MEDIATOR (benfluorex)
Effets indésirables

Mise au point

Comité Technique du 30 Avril 1998

Confidentiel

M.DAVID
P.BECHTEL

Annexe 3-5

Le MEDIATOR (chlorhydrate de benfluorex) est commercialisé en France depuis [illegible] sous forme de comprimés, dosés à 150 mg. La posologie recommandée est 3 comprimés par jour.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène.
(Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Une enquête officieuse a été ouverte, suite à la première mise au point des effets indésirables du benfluorex, présentée lors du Comité Technique du 11 juillet 1995.

Pharmacocinétique humaine du chlorhydrate de benfluorex :

L'absorption gastro-intestinale du chlorhydrate de benfluorex est complète et rapide, avec une concentration plasmatique maximale entre 1h et 2 h après l'administration.
Le volume de distribution est faible : 0,37 ± 0,03 l/Kg chez l'homme (1,4 l/Kg chez le rat, 1,6 l/Kg chez le chien,0.36l/Kg chez le singe et 0,31 l/Kg chez le babouin.
Le chlorhydrate de benfluorex est métabolisé rapidement dans le foie. Au niveau tissulaire, il n'y a aucune accumulation ou rétention de métabolites.

Les métabolites principaux retrouvés dans l'urine sont :
- le 1-(3-trifluorométhylphényl)-2-N-(carboxyméthyl)amino propane : 65% de la dose
- le 1-(3-trifluorométhylphényl)-2-N-(2-hydroxyéthyl)amino propane : 22% de la dose

- la 3-trifluorométhylphényl)-1 -hydroxy-propanone-2 sous forme conjuguée (5% de la dose)
- la Nor-fenfluramine : 2% de la dose.

Les métabolites principaux retrouvés dans le plasma sont :
- le 1-(3-trifluorométhylphényl)-2-N-(carboxyméthyl)amino propane
- le 1-(3-trifluorométhylphényl)-2-N-(2-hydroxyéthyl)amino propane

On ne retrouve pas de benfluorex inchangé dans le plasma.,

A. BILAN GLOBAL :

Parmi 291 notifications dans lesquelles le MEDIATOR est présent, et qui sont rapportées aux Centres Régionaux de Pharmacovigilance, 152 notifications ont été retenues.

Elles concernent 54 hommes et 97 femmes (1 sexe non précisé), dont l'age moyen est de :
- 57 ans pour les hommes (N = 54)
- 55,6 ans pour les femmes (N = 92)

Pour les notifications reçues jusqu'à 1995 , l'age moyen est de :
- 55,4 ans pour les hommes (N = 45)
- 56,7 ans pour les femmes (N = 66)

Pour les notifications reçues après 1995 , l'age moyen est de :
- 64,7ans pour les hommes (N = 9)
- 52,8 ans pour les femmes (N = 26)

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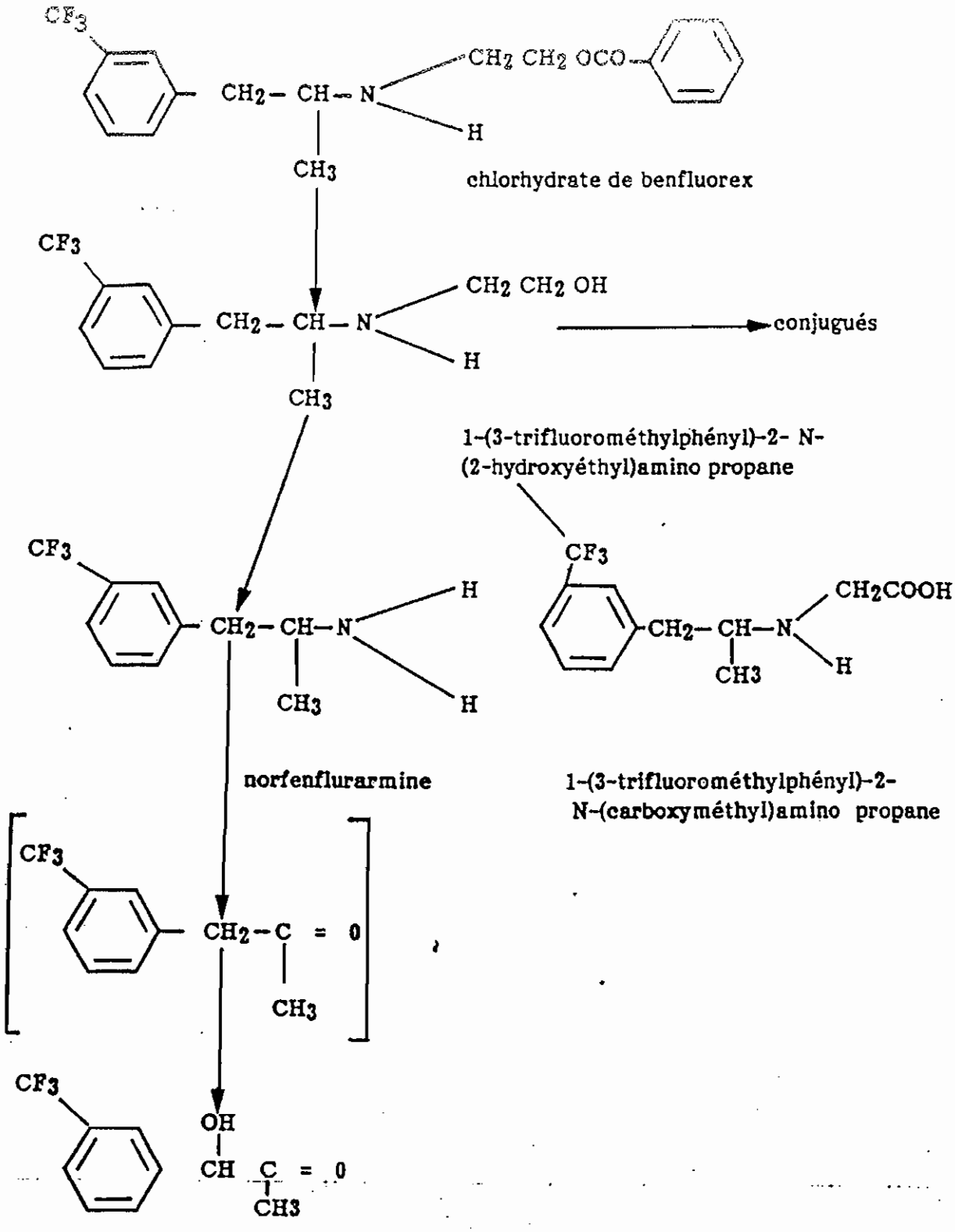

3-trifluorométhylphényl-1-hydroxypropanone-2

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Répartition des notifications par année de déclaration aux CRPV :

- 1985 : 3
- 1986 : 6
- 1987 : 7
- 1988 : 13
- 1989 : 9
- 1990 : 6
- 1991 : 11
- 1992 : 9
- 1993 : 21
- 1994 : 10
- 1995 : 21
- 1996 : 7
- 1997 : 26
- 1998 : 3

Répartition par classe-organe des effets indésirables notifiés au CRPV :

APPAREIL	Nombre de Notifications au 30 juin 1995	Nombre de Notifications au 30 avril 1998	
FOIE	9	16	7
APP. DIGESTIF (sauf foie)	13	16	3
HEMATOLOGIE	8	8	-
APPAREIL RESPIRATOIRE	4	8	4
CARDIO-VASCULAIRE	5	11	6
APPAREIL URINAIRE	7	9	2
PEAU - ALLERGIE	25	38	13
EURO-PSYCHIATRIE	19	27	8
VERTIGES	9	16	7
METABOLISME	2	3	1
TOTAL	101	**152**	51

N.B : les nouvelles notifications par rapport à la mise au point de Juillet 1995, sont imprimées «**en gras** » dans les tableaux suivants.
Dans la colonne, « traitement associé », le médicament est souligné, lorsque l'imputabilité bibliographique est supérieure au MEDIATOR.

Annexe 3-5

ATTEINTES HEPATIQUES

Dans 14 cas sur 26 cas d'hépatites ou perturbations de la biologie hépatique notifiés aux CRPV, le MEDIATOR est le seul suspect ou d'imputabilité égale ou supérieure aux médicaments associés.

Dans la majorité des dossiers, le délai de survenue est de ≅ 3 mois.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
Hépatite mixte						
RE8600098	M,82	1 mois	C2,S1	CORVASAL, DIAMICRON TADENAN	A	
DJ9300271	F,50	8 jours	C2,S2	Amfépramone, C2,S2	A	
Hépatite cytolytique						
NY8804047	M,47	3 mois	C2,S2		A	
DJ9100164	M,61	3 ans	C2,S2	RENITEC, C2,S2 DOGMATIL	A	
Hépatite cholostatique						
NC9200360	F,85	3 mois	C2,S1	TENSTATEN, C2,S1	A	
Biologie hépatique perturbée						
NC9600020	**F,39**	**8 mois**	**C2,S2**		**A**	**ALAT↑**
MA9700402	**F,47**	**12 sem.**	**C2,S1**		**A**	**ALAT↑**
MA9400451	F,57	3 mois	C1,S1	Amfépramone, C1,S1	U	ALAT↑
BX9700611	**F,51**	**6 j**	**C2,S1**	**LUTERAN, C2,S1** **LEVOTHYROX , C2,S1** **TENORMINE, C2,S1**	**F**	**ALAT↑**
PA9803765	**F,66**	**3 mois**	**C1,S1**	**LAROXYL** **GLUCOR** **TEATROIS** **TEALINE...**	**U**	**ALAT↑** **Prep.Magistr.**
PB9300028	M,60	15 j	C1,S1	Prep. magistrale: 15 j Yohimbine Dexfenfluramine Metformine, 2 ans ANAFRANIL, 2 ans	A	ALAT↑
NY9608618	**F,36**	**4 mois**	**C2,S2**		**A**	**ALAT+Bil↑**
PA8851623	M,61	3 ans	C2,S1	(Myocoril,C1,S1)	F	ALAT+P.A↑
BX9700024	**F,59**	**4sem.**	**C2,S2**	**LOXEN,C2,S2** **ACUILIX, C2,S2**	**A**	**ALAT+P.A↑**

• AUTRES ATTEINTES HEPATIQUES

CIRRHOSE						
BX8800309	M,57	13 ans	C1,S1	ZYLORIC,13 ans, C1,S1 VISKEN,13 ans,C1,S1	U	autre étiologie
STEATOSE						
LY9500598	**F,59**			**EQUANIL** **LEVOTHYROX** **LOXAPAC** **ANAFRANIL** **ROHYPNOL**	**U**	**dossier succinct**

Annexe 3-5

II. AUTRES ATTEINTES DIGESTIVES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DIARRHEE						
LY8600250	F,70	6 j	C2,S1		A	
MP8600156	M,60	2 mois	C3,S2	MODUCREN, C1,S1	A	
LY8700109	M,71	21 j	C2,S2	DIGOXINE	A	
BX8800223	M,40	3 j	C3,S2		A	
LY8800383	F,72	10 mois	C1,S1		F	
LY8800202	F,58	18 j	C2,S1		A	
MA9000721	F,29	3 j	C2,S2	DININTEL,C1,S2	A	
NC9200041	F,42	3 ans	C2,S2		A	
BR9300084	F,63	1 j	C2,S1	ZOCOR,C1,S1 ZYLORIC, C1,S1 ARMOPHYLLINE, C1,S1 DIAMICRON, C1,S1 BRICANYL, C1,S1	A	
NC9300212	M,75	47 j	C2,S2	DIACTANE, C1,S1	A	
DJ9400277	F,81	7 mois	C1,S2		U	
NC9500365	**F,70**	**2 sem.**	**C2,S2**	**BEFIZAL, C1,S2**	**A**	
CF9700156	**F,62**	**3 sem.**	**C2,S1**		**A**	
PANCREATITE						
MA9000382	M,40	6m	C2,S1	ISOMERIDE ,C2,S1	A	
MA9700296	**F,54**	**8j**	**C2,S1**		**A**	**autre étiologie!**
EPIGASTRALGIE						
LY8600060	M,72	13j	C2,S1		A	

Dans les 13 cas de diarrhée rapportés, le MEDIATOR est utilisé en monothérapie, ou son imputabilité est supérieure aux médicaments associés.

Cet effet indésirable est mentionné dans les RCP.

III. ATTEINTES HEMATOLOGIQUES

- Dans toutes les observations, il existe un traitement associé, qui peut être responsable de l'effet indésirable.
- Aucun nouveau cas n'a été rapporté depuis la mise au point de Juillet 1995

-Ils concernent 3 hommes (Age moyen = 60,7 ans) et 5 femmes (Age moyen = 55,6 ans)

Annexe 3-5

	Age	Durée TTT	Imput MEDIATOR	Imputabilité		
THROMBOPENIE						
LY8500365	M,51	3 mois	C1,S1	RISORDAN, 4 ans, C1,S1 SECTRAL, 4 ans, C1, S1 TILDIEM, 7 mois, C1S1	U	
SE9100183	F,64	2 mois	C1,S1	TENSTATEN, 2m, C1S1 EFFERALGAN, C1S1	U	
PS9400301	F,61	?	C1,S1	GERIMAX, C1,S1 OROCAL, C1,S1 LEVOTHYROX, C1,S1	A	
NC9400153	F,19	2 mois	C2,S1	DOXYCLINE, 5j, C2,S1 ALDACTONE, 2m, C2,S1	A	
LEUCOPENIE						
MA8801234	F,58	2 mois	C1,S1	LIPUR, 2ans, C2,S1	A	
LYMPHOPENIE						
DJ8800131	F,76	6 j	C1,S1	DIGOXINE, C1,S1 CALCIPARINE, C1,S1 RYHTMPODAN, C1,S1	A	somnolence
MA9100793	M,59	8 j	C1,S1		A	hyperthermie
NEUTROPENIE + THROMBOPENIE						
NC8900022	M,72	2 ans	C1,S1	HEMIDAONIL, 6 ans, C1S1	A	

IV. ATTEINTES RESPIRATOIRES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION PULMONAIRE						
PP8990081	F,42	1 an	C1,S1	DININTEL, 5ans, C1,S1 Tenuate Dospan,5ans,C1,S1 FRINGANOR, 5ans, C1,S1	U	
NC9300007	M,48	4 ans	C1,S1	ISOMERIDE, 3 ans, C1,S1 ZYLORIC, 6 ans, C1,S1	F	
TOUX						
MA9000654	F,60	2 ans	C1,S1	ARTEX, 1 an, C1,S1 GLUCINAN, 2 ans,C1,S1	U	
NC9500265	**F,48**	**10mois**	**C1,S1**	**EUTHYRAL, 2mois, C1,S1**	**A**	
MA9600518	**F,63**	**8 mois**	**C1,S1**	**MONOTILDIEM, 1 an, C1,S1** **KARDEGIC, 1 an, C1,S1** **ADANCOR, 1 an, C1,S1**	**U**	
SYNDROME HEMORRAGIQUE INTRA-ALVEOLAIRE						
MP9500482	**F,45**	**1 mois**	**C1,S1**	**PONDERAL, 1 mois, C1,S1**	**A**	
TUBERCULOME						
SE9400175	F,46	2 mois	C1,S1	ISOMERIDE, 2 mois, C1,S1 DININTEL, 2 mois, C1,S1	A	autre étiologie !
FIBROSE INTERSTITIELLE						
NT9800036	**M,69**	**10 ans**	**C1,S1**	**DETENSIEL, C1,S1** **JOSIR, C1,S1** **LEXOMIL, C1,S1**	**F**	

Dans les 2 cas d'hypertension pulmonaire, il existe un traitement anorexigène associé : ISOMERIDE ou DININTEL, TENUATE DOSPAN et FRINGANOR.

Annexe 3-5

V. ATTEINTES CARDIOVASCULAIRES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION ARTERIELLE						
NC9100093	F,51	1an	C2,S2	RENITEC, C1S1 LOPRESSOR, C1S1	A	
CF9300241	F,73	6j	C2,S1		A	
SYNCOPE						
PP9010597	F,37	1j	C1,S2	Amfepramone, C1,S2 LUMITENS, C1,S2	A	
TACHYCARDIE						
GR9500235	**F,52**	**?**	**C1,S1**	**SOTALEX, C1,S1**	**A**	
NC8900097	F,60	1j	C2,S2	CERVOXAN, C1,S1 DIGOXINE, C1,S1	A	
FIBRILLATION AURICULAIRE						
LY9700643	**F,25**	**9 m**	**C2,S3**	**MODERATAN ,C2,S3** **CANOL, C2,S3** **TEALINE, C2,S3**	**A**	**Terrain dépressif**
EXTRASYSTOLES VENTRICULAIRES						
CN9500150	**F,?**		**C2,S1**		**A**	**dossier succinct**
CN9500151	**F,?**		**C1,S1**		**U**	**dossier succinct**
ACCIDENT VASCULAIRE CEREBRAL						
LL9700372	**F,39**	**3 mois**	**C2,S1**	**SPIRONONE, 3 mois, C2,S1**	**A**	
SYNDROME DE RAYNAUD						
PC9300059	M,63	3 mois	C1,S1	MINIDIAB, 2ans, C1,S1	F	
PC9700170	**F,30**	**2 sem.**	**C2,S2**		**A**	

VI. ATTEINTES RENALES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DYSURIE						
BR9100053	F,42	?	C3,S1	VARNOLINE,C1,S1	A	
NC9300208	M,78	5 mois	C2,S2		A	
SE9700347	**F,?**	**2 j**	**C2,S1**		**A**	
POLYURIE						
BX8700115	F,40	7 mois	C2,S1		A	
POLLAKIURIE						
NC8800144	M,62	4 mois	C3,S1		A	
NC9300297	F,67	16 j	C2,S2		A	
ANURIE						
MA8900044	M,79	2 mois	C1,S1	ARTEX, 2mois, C1,S1 ZYLORIC, 2 mois, C1,S1 HEMIDAONIL, 2 mois, C1,S1 ALDACTAZINE, 2 mois,C1,S1	N	dossier succinct, non informatif

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			GLOMERULONEPHRITE			
LY8700356	M,52	5 mois	C1,S1	ZYLORIC, C1,S1 DIAMICRON, C1 S1	U	
			SYNDROME NEPHROTIQUE			
BX 9700689	**F,71**	**?**	**C1,S1**	**TROLOVOL, C1,S1** **LASILIX,C1,S1** **MONOTILDIEM, C1,S1** **TRINITRINE, C1,S1** **GLUCOPHAGE, C1,S1** **DAONIL, C1,S1** **VOLTARENE, C1,S1** **CYTOTEC, C1,S1** **AZANTAC, C1,S1**	**F**	

VII. ATTEINTES METABOLIQUES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
			HYPERLIPEMIE			
BX8600168	?,55	15j	C1,S1		U	
			HYPOTHYROIDIE			
BS9600267	**F,86**	**?**	**C1,S1**	**DAONIL, C1,S1** **SERMION, C1, S1** **LIPANTHYL,C1,S1** **VASTAREL, C1,S1**	**A**	
			GOUTTE			
LY8500568	M,71	8j	C2,S1	LASILIX, C3,S2	U	

Annexe 3-5

VIII. ATTEINTES CUTANEES et REACTIONS ALLERGIQUES

Elles concernent 13 hommes (Age moyen = 51,2 ans) et 23 femmes (Age moyen = 53,8 ans)

1 . Allergie, eczema :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
URTICAIRE						
CF8500013	M,50		C1,S2	LEXOMIL, C1,S2	A	
LY8700092	F,69	15 j	C3,S1		A	
TO9100366	M,34	7 j	C2,S2		A	
NC9400046	F,38	1 j	C3,S2		A	
MA9500024	M,45	3 mois	C3,S1	MAXEPA, C3,S1	U	
NY9507878	**M,61**	**2 mois**	**C2,S1**		**A**	
MA9700146	**F,50**	**1 j**	**C2,S2**		**A**	
OEDEME DE QUINCKE						
PA9200399	F,41	1 j	C2,S1	GLUCINAN, C2,S1	A	
MA9500231	F,56	1 j	C3,S1		A	
CHOC ANAPHYLACTIQUE						
DJ9200119	F,73	2 j	C3,S2		A	
MA9300967	F,50	8 j	C3,S2		A	
MA9400018	F,?	1 j	C3,S2		A	
MA9700036	**F,60**	**1j**	**C2,S2**		**A**	
ALLERGIE						
LY9300329	F,53	12j	C3,S2		A	
ECZEMA						
NC9300394	F,?	3 ans	C1,S2		F	
MA9500621	**F,68**	**2 ans**	**C2,S2**		**A**	
NY9809751	**M,70**	**10 mois**	**C1,S1**	**MOPRAL, C1,S1** **GLUCOR, C1,S1**	**F**	
SUDATION EXCESSIVE						
PA9240186	F,79		C1,S2	DIAMICRON, C1,S2 MEDIATENSYL, C1,S2 BRUFEN, C1,S2	A	

Parmi les réactions allergiques, on note:

- 7 cas d'urticaire
- 2 oedèmes de Quincke
- 4 chocs anaphylactiques
- 1 allergie cutanée

Le délai de survenue est le plus souvent ytrès rapide (1 jour).

Parmi les 3 cas d'eczéma, l'évolution est favorable dans un seul cas!

Annexe 3-5

5. Eruption, vascularite, purpura

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Ev.	
ERUPTION						
DJ9100155	M,31	10j	C3,S2		A	éruption érythémateuse
MP9300201	F,36	1 mois	C1,S1	DOLIPRANE, 1j,C1,S1 CLARADOL, 1j, C1,S1	A	éruption érythémateuse, prurit
PA9333879	F,54	5 sem.	C1,S1	GLUCOPHAGE,3 sem,C1,S1	U	prurit
MA9500227	**M,38**	**16j**	**C3,S1**		**A**	**éruption prurigineuse**
LY9700381	**F,56**	**11 sem.**	**C2,S1**	**LIPANTHYL, 11 SEM, C2S1**	**A**	**éruption**
MA9300723	F,41	1 cp	C2,S1	HEXALYSE,1cp, C2,S1	A	éruption maculopapul.
LY9400078	F,46	1 mois	C2,S1	TOCO 500, C1,S1 CYCLO 3, C1S1 CONFLICTAN, C1,S1 LEXOMIL, C1,S1	A	éruption maculeuse, prurit
LM9100055	M,56	1 an	C1,S1	DETENSIEL, C1,S2 DIDRONEL, C1,S1	U	prurigo
NC9100505	F,48	1 mois	C2,S2	SOPROL, 1 mois, C2S2	A	éruption pustuleuse
NC9100194	M,60	15 j	C2,S1	EUPRESSYL, C2,S1	A	érythème polymorphe
MA9700614	**F,50**	**3 mois**	**C1,S2**	**TANAKAN, C1,S2** **MEGAMAG, C1,S2**	**U**	**érythème polymorphe**
NY9300951	M,68	6 mois	C2,S1		A	érythème polymorphe
MP9700134	**F,58**	**6 j**	**C1,S1**	**SECTRAL** **BOP** **LEVOTHYROX**	**F**	**vascularite**
RE9420042	M,41	4 j	C1,S1	SORBITOL	A	vascularite
MA9700957	**F,50**	**8 ans**	**C1,S1**	**STAGID, 8 ANS, C1,S1**	**A**	**vascularite**
PP8990384	F,75	3 sem.	C2,S1	DAONIL, C1,S1 STAGID, C1,S1 TILDIEM, C1,S1 NATIROSE, C1,S1	A	purpura
CF9200106	F,67		C2,S2	VASTAREL, C2,S2 DAFALGAN, C2,S2 ELISOR, C2,S2	A	purpura
PO9700410	**M,47**	**2 sem.**	**C1,S1**	**ATHYMIL,C1,S1**	**F**	**purpura rhumatoide**
PA9739366	**M,65**	**8 mois**	**C1,S1**	**COZAAR, 5 j, C1,S1** **DAONIL, 8 mois, C1,S1** **GLUCOPHAGE, 8 m., C1,S1** **ZYLORIC, 33 mois, C1,S1** **LOXEN, 33 mois, C1,S1**	**A**	**lichen plan**
NC9400417	F,20	1 mois	C1,S2		F	acné

Annexe 3-5

- 3 cas d'érythème polymorphe, avec une évolution favorable à l'arrêt du MEDIATOR chez 2 hommes agés de 60 et 68 ans.

- 3 notifications de vascularite aigue leucocytoclasique:
  - dans 1 cas, l'évolution est favorable à l'arrêt du MEDIATOR (RE9420042)
  - dans 1 cas, l'évolution est favorable sans arrêt du MEDIATOR , mais avec un traitement corticoïde (lorsque la corticothérapie est arrêtée, 4 moisplus tard, survient un érythème polymorphe :MA9700957)
  - dans le troisième cas (MP9700134), l'évolution n'est pas complète malgré l'arrêt du MEDIATOR et une corticothérapie.

- 3 cas de purpura:
  - purpura des membres inférieurs avec un oedème apparu une semaine après le début du traitement par MEDIATOR (PP8990384)
  - purpura des membres inférieurs, s'étendant aux membres supérieurs, disparaissant 1 semaine après l'arrêt du traitement (CF9200106)
  - purpura rhumatoïde survenant après 2 semaines de traitement, l' évolution est inconnue (PO9700410)

IX. ATTEINTES NEURO-PSYCHIATRIQUES :

Elles concernent 18 hommes (Age moyen : 54,5 ans) , 25 femmes (Age moyen : 58,7 ans)

1. Asthénie, Somnolence, Impuissance :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
ASTHENIE						
LM8600219	M,56	2 ans	C2,S2		A	
TO8900326	M,49	1 mois	C1,S1		F	
MA9300480	F,45	6 mois	C2,S1	PRAXINOR, 1 mois, C2,S1 PONDERAL, C1,S1	A	
LY9600435	**F,53**	**8 sem.**	**C2,S1**	**GLUCOPHAGE, 8 sem., C2,S1** **PROZAC**	**A**	
SOMNOLENCE						
DJ8800131	F,76	?	C2,S2		A	+ lymphopénie
TO9200397	F,64	6 j	C3,S2		A	
MA9300577	F,42			ISOMERIDE		
RE9510102	**F,69**	**4 j**	**C2,S1**	**LASILIX, C1,S1** **PREVISCAN, C1,S1** **COVERSYL, C1,S1** **INSULATARD, C1,S1**	**A**	
IMPUISSANCE						
NC9500466	**M,55**	**3 j**	**C3,S2**		**A**	

Dans la plupart des observations:
- soit le délai de survenue semble long : 2ans (LM8600219) ou inconnu (DJ8800131)
- soit le traitement associé peut être responsable de tels effets: PROZAC, GLUCOPHAGE...

Cet effet indésirable est mentionné dans les RCP.

Annexe 3-5

2. troubles psychiatriques :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
TROUBLES PSYCHIATRIQUES						
LY9600963	**M,45**	**1 mois**	**C1,S1**	**LEXOMIL, C2,S1**	**A**	**agressivité**
NC9700094	**F,74**	**6 j**	**C2,S2**		**A**	**agressivité**
MA8900523	F,40		C1,S1	ISOMERIDE, 1j, C2,S1	A	agitation
NC9300347	M,39	11 mois	C2,S2		A	irritabilité
NC9500171	F,50	1 cp	C3,S2		A	nervosité
NC9300349	M,50	9 mois	C2,S2	LOPRIL, C1,S1	A	dépression
MA9100069	M,40	1 j	C2,S2		A	angoisse
TS9500338	**F,69**	**8 j**	**C2,S1**	**DAONIL, C1,S1 ALPRESS BITILDIEM DIAMICRON...**	**A**	**stupeur**
LY8900392	M,52	20 j	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1	A	cauchemars
SE9500017	F,41	84 j	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1	A	confusion
CF9000137	F,79		C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2	A	désorientation
RN9500096	**F,59**	**73 j**	**C1,S2**	**LIPANTHYL, C1,S2 PILOSURYL, C1,S2 CANOL, C1,S2 OLIVIASE, C1,S2 Amfépramone, C1,S2**	**A**	**délire**
GR8700216	M,45	16 j	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1	A	délire

Les troubles psychiatriques sont divers : la responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue.

3. Troubles neurologiques :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
CONVULSION						
PA9223988	M,60	?	C2,S1	TENSIONORME, C2;S1 DIFFU K	A	
NEUROPATHIE						
MA8700716	M,73	9 ans	C1,S1	HEMOCLAR TORENTAL	U	autre étiologie!
PARESTHESIE						
BX8800193	M,36	8 j	C1,S1	PRAXINOR, 8j, C1,S1	F	
LM9500090	M,61	4 j	C2,S1		A	
MA9700170	**F,42**	**1 j**	**C2,S2**	**TAMIK, C1,S1**	**U**	

Annexe 3-5

X. TROUBLES DE L'EQUILIBRE, VERTIGES

Ils concernent 5 hommes (Age moyen: 64 ans) et 11 femmes (Age moyen : 60,5 ans)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
VERTIGE, TROUBLE DE L'EQUILIBRE						
BX9500092	M,34	3 mois	C3,S2		A	
MA8800356	F,60	1 j	C2,S2		A	
MA8800929	F,47	1 cp	C2,S2	DAFLON, C1,S1	A	
NC9000297	F,58	15 j	C3,S2		A	
LL9200133	F,63	2 j	C1,S1		U	
NY9306790	F,77	2 j	C1,S2		A	
LM9500091	F,84		C2,S1	SOTALEX, C1,S1 LOXEN, C1,S1 ALDACTONE, C1,S1 CORDIPATCH, C1,S1 PREVISCAN, C1,S1	U	
TS9600227	**F,64**	**4 sem.**	**C3,S1**	**RENITEC, C1,S1** **LIPANTHYL, C1,S1**	**A**	
BX9701040	**M,74**	**4 sem.**	**C2,S1**	**PREVISCAN, C1,S1** **DAONIL, C1,S1** **CAPTOLANE, C1,S1** **GLUCOPHAGE, C1,S1**	**A**	
BX9701041	**M,78**	**10 j**	**C2,S1**	**DAONIL** **CORDARONE** **ASPEGIC** **GLUCOR**	**A**	
NC8900097	F,60	1 cp	C2,S2		A	
MA8700143	F,66	?	C1,S1	FLUVERMAL, C1,S1	F	
BX9701023	**F,63**	**9 sem.**	**C2,S1**	**AVLOCARDYL** **DAFLON** **DAONIL** **LASILIX** **GLUCOR** **TRANXENE** **IMOVANE**	**A**	
BX9700381	**M,63**	**4 sem.**	**C2,S1**	**DAONIL**	**A**	
BX9700301	**M,71**	**6 sem.**	**C2,S1**	**LOPRIL** **CORDARONE** **VASTAREL** **PRAXILENE** **EUGLUCAN**	**A**	
BX971022	**F,24**	**7 mois**	**C2,S1**	**DIAMICRON** **MOPRAL** **TILDIEM** **ALDACTAZINE** **LYSANXIA**	**A**	

16 cas ont été notifiés: il s 'agit de patients agés,en général, avec une pathologie lourde : diabète, insuffisance cardiaque...

Cet effet indésirable est mentionné dans les RCP.

Annexe 3-5

☆ MEDIATOR®

benfluorex

FORMES et PRÉSENTATIONS

Comprimé enrobé (blanc) : Boîte de 30.
Modèle hospitalier : Boîte de 100, sous plaquette thermoformée unidose.

COMPOSITION

	p cp	*p boîte*
Benfluorex chlorhydrate	150 mg	4,5 g

Excipients : amidon de maïs, carmellose sodique, cire d'abeille blanche, éthylcellulose, stéarate de magnésium, oléate de glycérol, polysorbate 80, povidone, silice colloïdale, saccharose, bicarbonate de sodium, talc, dioxyde de titane.

DC INDICATIONS

- Adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable.
- Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

DC POSOLOGIE et MODE D'ADMINISTRATION

3 comprimés par jour.
Cette posologie peut être prescrite d'emblée ou atteinte progressivement :
- 1 comprimé la première semaine au dîner,
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner,
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois 1 comprimé par jour, en fonction des résultats biologiques.
Coût du traitement journalier : 1,43 à 4,29 F.
En association avec le régime, Mediator constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

DC CONTRE-INDICATIONS

Pancréatites chroniques avérées.

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI

Mises en garde :
Les troubles métaboliques relevant d'un traitement par Mediator sont essentiellement observés chez l'adulte. La prescription de Mediator n'est donc pas justifiée chez l'enfant.
Précautions d'emploi :
Si, après une période d'administration de quelques mois (3 à 6 mois), une réduction satisfaisante des concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.
L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

DC GROSSESSE et ALLAITEMENT

Grossesse : Les résultats des études réalisées chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence de données dans l'espèce humaine, ces résultats expérimentaux ne permettent pas de préjuger un effet malformatif. Cependant, par mesure de prudence, ne pas prescrire pendant la grossesse.
Allaitement : En l'absence de données sur le passage dans le lait maternel, l'allaitement est déconseillé pendant la durée du traitement.

DC EFFETS INDÉSIRABLES

Les effets secondaires suivants ont été observés : digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.

DC SURDOSAGE

Conduite à tenir en cas d'absorption massive : le traitement sera purement symptomatique : lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience, des fonctions respiratoire et cardiaque.

PP PHARMACODYNAMIE

Hypolipémiant :
Il agit sur plusieurs facteurs liés au risque athérogène.
- Actions de Mediator sur le métabolisme lipidique :
  - Mediator diminue l'absorption intestinale des triglycérides (rat). Cet effet, confirmé chez l'homme en pharmacologie clinique, repose sur la diminution d'activité de la lipase pancréatique.
  - Il réduit la synthèse hépatique des triglycérides et du cholestérol in vitro et in vivo (rat).
  - Il diminue la stéatose hépatique induite par des régimes riches en lipides, en glucides chez le rat obèse et au cours du diabète expérimental (rat).
  - Il limite l'incorporation du cholestérol dans la paroi artérielle (lapin).

  Ce mode d'action est susceptible d'expliquer la diminution du cholestérol et des triglycérides chez l'homme.
- Actions de Mediator sur le métabolisme glucidique :
  - Il facilite la pénétration et l'utilisation cellulaires du glucose (rat).
  - Il diminue l'hyperglycémie du rat diabétique (insulinoprive ou non) et l'aire d'HPO chez le lapin.
  - Dans le diabète asymptomatique chez les patients obèses, il entraîne une baisse de la glycémie postprandiale et une amélioration de la courbe d'HPO supérieure à celle qu'on obtient avec un régime identique associé à un placebo.

  Mediator, n'ayant pas d'action sur l'insulinosécrétion, ne peut pas provoquer d'hypoglycémie.
- Effet complémentaire de Mediator :
  Chez des patients obèses hyperuricémiques traités par Mediator et régime, une baisse de l'uricémie d'environ 14 % a été observée.

Aucune interférence indésirable de Mediator avec les traitements associés au cours des études n'a été constatée.
Mediator :
- ne potentialise pas les anticoagulants,
- ne provoque pas d'hypoglycémie,
- n'interfère pas avec la fonction thyroïdienne.

PP PHARMACOCINÉTIQUE

- Absorption gastro-intestinale rapide et totale avec un pic maximal survenant entre 1 et 2 heures après l'administration.
- Élimination rapide et totale par voie urinaire : en 8 heures, une excrétion moyenne d'environ 74 % de la dose administrée est constatée.
  L'élimination se fait en 2 phases :
  - une première phase rapide (60 % en 3 ou 4 heures),
  - une deuxième phase lente, se terminant en 36 heures environ.

LISTE I
AMM 317 557.9 (1974, validée 1987) 30 comprimés.
317 559.1 (1974, validée 1987) 100 comprimés.
PRIX : 42,90 F (30 comprimés).
Remb Séc soc à 65 %. Collect.

BIOPHARMA
Information médicale :
29, rue du Pont. 92200 Neuilly-sur-Seine
Tél : 01 46 41 60 00
Les Laboratoires Servier
22, rue Garnier. 92200 Neuilly-sur-Seine

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RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT
DIRECTION GENERALE
3990

REÇU LE
13 MAI 1998
SERVIER S.A.S.

Saint-Denis le, 11 MAI 1998

M. le Pharmacien Responsable
Laboratoires SERVIER
22 rue Garnier
92200 NEUILLY SUR SEINE

Monsieur,

J'ai l'honneur de vous faire connaître qu'une enquête de pharmacovigilance relative aux effets indésirables observés avec votre spécialité MEDIATOR® (Benfluorex), est officiellement mise en place sous la responsabilité du centre de Pharmacovigilance de Besançon dont le responsable est M. le Pr P. BECHTEL.

Je vous saurais gré, en conséquence, de bien vouloir lui communiquer, si il vous en formulait la demande, tous les renseignements ou dossiers qui pourraient être nécessaires à la bonne conduite de cette enquête.

Je vous prie d'agréer, Monsieur, l'expression de ma considération distinguée.

LE DIRECTEUR DE L'ÉVALUATION

Pr Jean-Michel ALEXANDRE

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le 21 DEC. 1998

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Jeudi 10 septembre 1998)

Etaient présents

M. RICHE : Président
M. LE LOUET (suppléant de Mme ALBENGRES), Mme PENFORNIS (suppléante de M. ALLAIN H), Mme LAINE CESSAC (suppléante de M. ALLAIN P), M. ANDREJAK, Mme RADAL (suppléante de Mme AUTRET), Mme BAVOUX, Mme DAVID- LAROCHE (suppléante de M. BECHTEL), M. BIOUR, M. BLAYAC, Mme CARLHANT, M. CARON, Mme CHICHMANIAN, Melle DIORTE, Mme EFTHYMIOU, M. ESCHALIER, Mme SGRO (suppléante de M. ESCOUSSE), M. VIAL (suppléant de M. EVREUX), Mme GERMAIN, Mme GINISTY, Mme HARAMBURU, Mme HILLAIRE-BUYS, M. IMBS, Mme JEAN-PASTOR, Mme JOUGLARD, Mme KREFT-JAIS, M. LAROUSSE, Mme LAVARENNE, M. LE DOZE, M. MALLARET, M. MERLE, M. MONTASTRUC, M. MOULIN, M. GILLET (suppléant de M. NETTER), Mme NOBLET, M. OLLAGNIER, M. ROYER, Mme SOUBRIE, M. THUILLEZ, M. TRENQUE, Mme PERAULT (suppléante de M. VANDEL),
Mme TUBERT-BITTER (représentant Monsieur le Directeur Général de l'INSERM),
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme BARON (représentant Monsieur le Directeur Général de la Santé),
M. ALEXANDRE (représentant Monsieur le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance

Mme BIDAULT
Mme CASTOT
Melle DELEAU
M. DHANANI
Melle FERVAL
Mme FOSSET-MARTINETTI
M. JACQUET
Melle JULLIAN
Mme LEREBOURS
Mme MORIN
Mme PARIENTE-KHAYAT
Mme WESCHLER

Assistaient à la réunion (D.E.V.) :

Melle AUGUSTE
Mme DUMARCET
Mme DURANTEAU
Mme GRENE
Mme HOOG-LABOURET
Mme LANFRANCHI
Mme LELAN
Mme MIGNON
Mme MORER
Mme MORGENSZTEJN
Mme PICON
M. REYNIER
Mme REY-QUINIO
Mme SAINT-RAYMOND
M. SAWAYA
Mme VINAS

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

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Etaient excusés

M. BEGAUD (Vice-Président)
M. BECHTEL
M. VANDEL

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I - ADOPTION DU PROCÈS-VERBAL DES COMITÉS TECHNIQUES DU 25 JUIN 1998 ET DU 23 JUILLET 1998

Le procès-verbal de la séance du 25 juin 1998 a été adopté avec les modifications suivantes :

- Page 4 — 8ème ligne : remplacer "1/2474 unités" par "1/2474 seringues". Remplacer "1/10160 unités" par "1/10160 seringues".

  10ème ligne : remplacer "1/11544 unités" par "1/11544 comprimés".

- Page 18 — 3ème ligne : remplacer "percutanée" par "sous-cutanée".

- Page 20 — 7ème ligne : remplacer "Par ailleurs, ... collègues toxicologues" par "Le CRPV de Strasbourg a fait parvenir à l'Agence le détail des notifications reçues de la part du Dr Kintz avec leur chronologie. Par ailleurs, le Dr Kintz estime, à partir de discussions avec ses collègues toxicologues,...".

Le procès-verbal de la séance du 23 juillet 1998 a été adopté avec les modifications suivantes :

- Page 13 — Observation "vaccin BCG Pasteur®" : remplacer "chez un enfant" par "chez 8 enfants"

- Page 16 — "Antirétroviraux et grossesses - projet de suivi" : remplacer le texte entier par le texte suivant :

François MEYER (Direction de l'Evaluation / Agence du Médicament) et Françoise BAVOUX (CRPV de Saint-Vincent de Paul) ont présenté l'état actuel de la pharmacovigilance "antirétroviraux et grossesse" et les possibilités d'améliorations à venir.

En 1995, l'analyse des résultats de l'essai ACTG 076/ANRS 024 a mis en évidence une diminution du taux de transmission materno-foetale (TMF) du virus de l'immunodéficience humaine (VIH) de 25% chez les femmes non traitées à 8% chez les femmes traitées par la zidovudine durant la grossesse. La mise sur le marché des antiprotéases en 1996 a modifié la stratégie thérapeutique antirétrovirale et l'évolution de la maladie. Les patientes font des projets de vie et les cliniciens se trouvent confrontés de plus en plus fréquemment à une situation difficile : désir de grossesse, prévention de la transmission materno-foetale, exposition du foetus et de l'enfant à des médicaments nouveaux n'ayant pas fait l'objet d'évaluation en clinique.

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Le nombre de femmes atteintes par l'infection à VIH/sida menant à terme leur grossesse est de l'ordre de **600 par an**. Plusieurs structures sont actuellement engagées dans le suivi de ces grossesses en France.

- **L'Etude Périnatale Française** (EPF) de Unité INSERM 292 assure un suivi épidémiologique de la TMF du VIH, et des enfants séronégatifs jusqu'à l'âge de 18 mois. Il faut souligner que l'EPF n'enregistre pas les effets indésirables des médicaments.
Environ 450 enfants nés de mères atteintes par l'infection à VIH sont inclus par an dans l'EPF.

- **Des essais cliniques ayant pour objectif l'évaluation de la TMF du VIH**. L'évaluation des effets indésirables réalisée dans le cadre de l'essai ANRS 075 (seul essai actuellement en cours) doit être améliorée.
Chaque année, approximativement 150 nouveau-nés de mères séropositives ne sont inclus ni dans l'EPF ni dans un essai clinique de TMF et échappent donc a ce type de suivi.

- un "**registre**" destiné au repérage des enfants dont la mère a reçu de la zidovudine pendant la grossesse est tenu au niveau de la Direction des hôpitaux ; son fonctionnement est actuellement en cours de modification.

Enfin, une **enquête officielle de pharmacovigilance** relative aux issues des grossesses des femmes traitées par les antirétroviraux et les effets indésirables chez le nouveau-né, le nourrisson et l'enfant après exposition *in utero* aux antirétroviraux, dont le CRPV responsable est Paris Saint-Vincent de Paul, est mise en place depuis février 1998.

Aucune structure n'assure un recueil correct des effets indésirables survenant chez les femmes atteintes par le VIH traitées par antirétroviraux durant la grossesse et leurs nouveau-nés. La situation actuelle est caractérisée par une sous-notification extrême et l'absence d'analyse globale de ces effets indésirables alors que le nombre de femmes enceintes traitées par multithérapie augmente.

Il est nécessaire **d'inciter, par un monitorage actif, les praticiens concernés à déclarer au système national de pharmacovigilance les effets indésirables** survenant chez des femmes inclues ou non dans l'EPF ou un essai clinique de TMF du VIH. L'envoi d'une lettre associée à une "fiche de recueil d'effets indésirables survenant au cours de la grossesse" est prévu. Il est important que les praticiens soient contactés régulièrement afin de maintenir intact leur vigilance (relances téléphoniques, visites dans les maternités). Une attention particulière devra être portée sur les praticiens suivant les femmes en dehors de l'EPF ou d'un essai clinique.

Une analyse globale des données de tolérance doit être réalisée par le système national de pharmacovigilance, si possible en collaboration avec les structures existantes (EPF, Agence nationale de recherche sur le sida, Direction des hôpitaux), afin de permettre un échange d'informations. Actuellement, les responsables de l'EPF souhaitent que les effets indésirables soient d'abord notifiés à la cohorte puis au système de pharmacovigilance. Cette proposition

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de circuit de déclaration des effets indésirables n'est pas conforme au décret de pharmacovigilance de 1995. Les notifications d'effets indésirables recueillies par les CRPV seront centralisées par le CRPV de Saint-Vincent de Paul. Les données de pharmacovigilance émanant des CRPV seront complétées par celles déclarées dans le cadre des essais cliniques à l'Agence du médicament et présentées par les laboratoires pharmaceutiques dans les rapports périodiques de sécurité.

Une demande de subvention auprès du Conseil scientifique et du Conseil d'Administration de l'Agence du Médicament sera présentée le 14 octobre 98.

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II - TOUR DE TABLE DES CAS MARQUANTS

ALLOPURINOL MSD®
(allopurinol)
: Vertiges, troubles visuels, lésions dermatolologiques , céphalées, epistaxis survenus chez un homme de 48 ans, traité par ZYLORIC® depuis 23 ans, puis depuis 10 jours par ALLOPURINOL MSD®.
(CRPV de REIMS)

ARCALION® 200 mg
(sulbutiamine)
+ BREXIN®
(pyroxicam,
β-cyclodextrine) : Malaise avec hypotension (pression artérielle systolique : 7cm Hg) et troubles digestifs chez une femme de 48 ans. Réadministration positive de l'ARCALION®(CRPV de LIMOGES)

ARTOTEC®
(diclofénac +
misoprostol) : Douleurs angineuse chez un homme de 43 ans, 20 minutes après chaque prise d'ARTOTEC® (antécédents coronariens). Pas de récidive après l'arrêt du traitement.
(CRPV de RENNES)

BEFIZAL®
(bézafibrate) : Réaction de photosensibilité chez une femme de 50 ans.
(CRPV de MARSEILLE)

CUROSURF®
(fraction phospholipidique
de poumon de porc)
+ CLAROFAN®
(céfotaxime sodique)
+RANIPLEX®
(ranitidine)
+ CLAMOXYL®
(amoxicilline)
+ NETROMICINE®
(nétilmicine - sulfate de) : Hémorragie pulmonaire importante avec malaise, bradycardie, et défaillance multiviscérale chez un nouveau-né de 2 jours.
(CRPV d'AMIENS)

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DIAMOX® 250 mg
(acétazolamide)
+ ASPEGIC® 1000 mg
(acétylsalicylate de DL-lysine)
+ CYTOTEC®
(misoprostol)
+ HEPT-A-MYL®
(heptaminol)
+ ZYRTEC® 10 mg
(cétirizine)
+ SILOMAT®
(clobutinol) : Confusion, syndrome cérébelleux, désorientation temporo-spatiale et polypnée, acidose métabolique compensée avec alcalose respiratoire et hyperchlorémie chez une femme de 50 ans.
(CRPV de TOURS)

ENDOXAN®
(cyclophosphamide)
+ fluoro-uracile
+ tamoxifène : Colite hémorragique ischémique avec diminution de l'anti-thrombine III à 43 % chez une femme de 72 ans. Evolution favorable à l'arrêt du traitement. Réintroduction négative du fluoro-uracile et de l'ENDOXAN®.
(CRPV de STRASBOURG)

GENTALLINE®
(gentamicine) : Vertiges à J3 d'un traitement par GENTALLINE® chez une femme de 80 ans. Pas d'insuffisance rénale. Syndrome vestibulaire isolé (cf. Questions diverses).
(CRPV de MARSEILLE)

INTRONA®
(interféron alfa 2b recombinant)
+ DEROXAT®
(paroxétine)
+ XANAX®
(alprazolam) : Dépression, agressivité et homicide chez un homme de 32 ans.
(CRPV de MARSEILLE)

ISOBAR®
(méthyclothiazide,
triamtérène) : Pancréatite aiguë chez une femme de 73 ans.
(CRPV d'AMIENS)
Le CRPV d'Amiens présentera un point sur diurétiques thiazidiques et pancréatites lors du Comité Technique du 21 janvier 1999.

KETUM®
(kétoprofène gel) : - Eczéma et phlycthènes volumineuses chez un homme de 43 ans.
- Eczéma étendu et oedème chez une femme de 21 ans.
(CRPV de RENNES)

LIPANTHYL®
(fénofibrate) : - Réactions de photosensibilité chez un homme de 67 ans et trois femmes de 58 ans, 63 ans et 72 ans. Cet effet indésirable, bien connu des spécialistes, n'est pas mentionné dans le RCP des médicaments de la classe des fibrates.
(CRPV de MARSEILLE)
Le CRPV de Marseille présentera un point sur photosensibilisation et fibrates lors du Comité Technique du 21 janvier 1999.
- Eczéma aigu photoallergique chez un homme de 46 ans qui avait présenté 9 mois plus tôt un eczéma aigu bulleux au KETUM GEL® (kétoprofène).
(CRPV de STRASBOURG)
Le CRPV de Nantes fera un point lors du Comité Technique du 21 janvier 1999 sur les réactions croisées photoallergiques avec le kétoprofène administré par voie cutanée.

MALOCIDE®
(pyriméthamine)
+ QUINIMAX®
(quinine, quinidine, cinchonine,
cinchonidine) : Syndrome de Stevens-Johnson chez un homme de 37 ans. Antécédents de lésions de la muqueuse génitale sous FANSIDAR® (sulfadoxine, pyriméthamine) et FANSIMEF® (méfloquine, sulfadoxine, pyriméthamine).
(CRPV de RENNES)

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MIGWELL® (ergotamine, caféine, cyclizine) + CRIXIVAN® (indinavir) + EPIVIR® (lamivudine) + ZERIT® (stavudine)	:	Ergotisme chez un homme de 34 ans. (CRPV d'AMIENS)
PENTASA® (mésalazine)	:	- Pancytopénie et agranulocytose chez un nouveau-né (1 jour), la mère ayant été traitée pendant toute la grosssesse. (CRPV de RENNES) - Malformation cardiaque chez un foetus de 22 semaines, la mère ayant été traitée pendant toute la grossesse. (CRPV de ROUEN) Ces observations seront transmises au groupe de travail "grossesse"
RETROVIR® (zidovudine) + EPIVIR® (lamivudine) + ZOVIRAX® (aciclovir)	:	Augmentation isolée de la lipase chez un enfant de 10 mois. (CRPV de PARIS SAINT-VINCENT DE PAUL)
RIMIFON® (isoniazide) +LASILIX® (furosémide) + CORDARONE® (amiodarone) + AMLOR® (amlodipine) + NITRIDERM® (trinitrine) + EFFERALGAN® (Paracétamol)	:	Syndrome de Lyell d'évolution fatale chez un homme de 73 ans. (CRPV de CLERMONT-FERRAND)

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SAVARINE® (chloroquine proguanil)	:	Crise tonicoclonique chez un enfant de 14,5 ans. (CRPV de CLERMONT-FERRAND)
SPASFON-LYOC® (phloroglucinol) + EFFIPREV® (norgestimate, éthinylestradiol)	:	Choc anaphylactique chez une femme de 23 ans après la prise de phloroglucinol per-os. (CRPV de LYON)
STAMARIL® (vaccin amaril vivant, stabilisé)	:	2 cas graves de méningite aseptique après une vaccination par STAMARIL® ont été déclarés à l'unité de Pharmacovigilance par le laboratoire. Le CRPV de TOULOUSE présentera un point sur ce sujet lors du Comité Technique du 19 novembre 1998.
VIDEX® (didanosine) + CRIXIVAN® (indinavir) + ZERIT® (stavudine)	:	Pancréatite et acidose lactique traité par LEVOCARNIL® (lévocarnitine)) chez un homme de 33 ans. (CRPV de PARIS SAINT-VINCENT DE PAUL) Les CRPV de Paris Saint-Antoine et Paris Saint-Vincent de Paul feront un point sur analogues nucléosidiques, acidoses lactiques et pancréatites lors du Comité Technique du 21 janvier 1999.
VOLTARENE® injectable (diclofénac) + COLTRAMYL® injectable (thiocolchicoside)	:	Malaise avec perte de connaissance et d'urine, hypotension à 8 cm Hg de maximale chez un homme de 83 ans. Bilan négatif et EEG normal (diagnostic d'épilepsie éliminé). (CRPV de LIMOGES)

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ZOMIG® (zolmitriptan) + DEROXAT® (paroxétine)	:	Syndrome sérotoninergique entraînant l'hospitalisation après 2 jours de traitement par ZOMIG® pour migraine chez une femme de 26 ans, traitée depuis 6 mois par DEROXAT®. (CRPV de LILLE) L'unite de Pharmacovigilance transmettra cette observation au Groupe de Travail "interactions médicamenteuses"

III - POINT SUR LE SILDÉNAFIL (VIAGRA®)

Un point sur les données de pharmacovigilance du sildénafil (Viagra®) a été présenté par le Centre Régional de Pharmacovigilance de Rouen.

Le sildénafil agit par inhibition sélective et puissante de la phosphodiestérase de type 5 (PDE 5) dans les corps caverneux de la verge. Le sildénafil et son métabolite principal (N déméthyl) sont liés à 96% aux protéines plasmatiques. Le métabolisme hépatique du sildénafil fait intervenir la voie du CYP 3A4 (voie principale) et la voie du CYP 2 C9 (voie secondaire).
Le sildénafil est indiqué chez l'homme de plus de 18 ans dans le traitement de la dysfonction érectile.

Viagra® a été mis sur le marché aux Etats-Unis le 7 avril 1998. D'après les données IMS, jusqu'au 17 juillet 1998, le nombre de prescriptions a été estimé à 3 208 000 aux Etats-Unis.

Dans l'Union européenne, ce médicament enregistré selon une procédure centralisée avec les Pays-Bas comme pays rapporteur, a été autorisé par la Commission Européenne le 15 septembre 1998. Dans l'attente de la décision de la Commission Européenne, le Comité des Spécialités Pharmaceutiques a demandé au laboratoire de soumettre un rapport périodique d'évaluation sur les données de sécurité non pas sur une base semestrielle mais sur une base mensuelle. 2 rapports ont été soumis par le laboratoire.

Données internationales de sécurité d'après les rapports périodiques de tolérance

Le Centre Régional de Pharmacovigilance de Rouen a analysé les données contenues dans les 2 rapports de sécurité disponibles à ce jour.
Dans le dernier rapport de tolérance, sur la période du 16 juin 1998 au 15 juillet 1998, 761 événements ont été signalés par des professionnels de santé correspondant à 386 cas répartis en 150 cas graves et 236 cas non graves.

● Parmi les effets graves, 40 décès ont été rapportés dont 24 d'origine cardiaque probable et 16 de cause inconnue ; l'âge, connu dans 18 cas, est en moyenne de 60 ans avec des extrêmes compris entre 39 ans et 74 ans ; la posologie, connue dans 10 cas est en moyenne de 55 mg avec des extrêmes compris entre 50 et 100 mg.

La plupart des décès et des effets indésirables graves rapportés sont d'origine cardio-vasculaire ou cérébro-vasculaire. La notion de facteurs de risque cardio-vasculaire et/ou de prise concomitante de dérivés nitrés est retrouvée dans 2/3 des cas de décès dans le 1er rapport mais est difficile à évaluer dans le 2ème rapport.

Selon le rapporteur, il est nécessaire de mieux préciser les caractéristiques cliniques des patients traités en terme de facteurs de risque et d'antécédents cardio-vasculaires afin d'évaluer de façon précise le non-respect des contre-indications et de mieux identifier les patients à risque.

● De rares cas d'hypotension ont été rapportés.

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● Des troubles hématologiques divers ont été rapportés, à type d'hémolyse aiguë, C.I.V.D., épistaxis... L'effet antiagrégant plaquettaire potentiel du sildénafil mérite d'être gardé en mémoire.

● Les effets indésirables visuels sont à surveiller.

Données françaises

Deux effets indésirables ont été rapportés en France : un décès chez un patient de 78 ans traité par inhibiteurs calciques et dérivés nitrés et un cas d'agressivité chez un patient de 52 ans sans antécédent psychiatrique qui a pris en 1 semaine 3 comprimés de Viagra®. L'évolution a été favorable en 2 jours

Conclusion

Dans l'ensemble, les effets indésirables rapportés sont attendus compte-tenu de la pharmacologie du produit et de la population traitée.

Le Centre Régional de Pharmacovigilance de Rouen propose d'élaborer une fiche spécifique des effets indésirables destinée à standardiser le recueil des données et accepte d'analyser les rapports périodiques successifs de tolérance.

IV - POINT SUR LE BENFLUOREX (MÉDIATOR ®)

Le Centre Régional de Pharmacovigilance de Besançon a présenté, à la demande de l'Agence du Médicament, des données sur les chiffres de ventes et des données de cinétique du Benfluorex. L'Agence est en effet régulièrement interrogée par des pharmaciens inspecteurs de la santé sur la possibilité d'usage détourné de ce produit.

- Evolution des chiffres de vente

Depuis 1991, les ventes progressent régulièrement. Aucun pic n'a été observé au cours des mois qui ont suivi les mesures prises à l'encontre des anorexigènes. Il est toutefois, à noter que les ventes de ce produit sont d'environ 5 millions de boîtes, ce qui est loin d'être négligeable.

Il est en fait, difficile au vu des seuls chiffres de ventes de mettre en évidence un mésusage du produit. Il est donc indispensable pour affiner l'analyse de :

- disposer des données Dorema
- de pouvoir distinguer les nouvelles prescriptions des renouvellements
- de saisir l'observatoire des prescriptions

- Données cinétiques et de métabolisme

Les concentrations plasmatiques du Benfluorex sont atteintes en 1 à 2 heures, l'absorption est complète et le volume de distribution est faible de 0,37 l/kg. La fixation plasmatique est de 77 %. Le métabolite majeur est le 1-(3-trifluoromethylphenyl)-2N-2-(carboxymethyl)aminopropane. L'élimination est rénale avec 75 % du produit éliminé dans les 8 premières heures. Le Benfluorex est totalement métabolisé.

La norfenfluramine, métabolite du Benfluorex est retrouvée en faible quantité (2 %) dans les urines. Il est surprenant de constater que les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60 ng/ml). En effet, la Norfenfluramine formée à partir de la Fenfluramine, n'est plus transformée et se retrouve intacte dans les urines de 24 h à l'état d'équilibre à 7,4 % de la dose administrée. Alors que la norfenfluramine formée à partir du Benfluorex, est transformée en produit désaminé et oxydé.

Il n'y a aucune explication actuellement pour cette différence.

Le Comité Technique juge que ces informations sont insuffisantes et ne permettent pas d'être entièrement rassuré. En particuliers, le rapporteur devrait pouvoir disposer d'une analyse correcte des AUC.

Enfin, une question relative à la parenté chimique du Benfluorex avec les amphétaminiques est posée. Il a été rapporté qu'un patient âgé traité par MEDIATOR® avait présenté un test urinaire positif ; cette recherche avait été faite chez ce dernier dans le cadre d'une procédure judiciaire, son fils étant toxicomane. Les CEIP pourrait être interrogés à ce sujet.

Etude volontaires sains.
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Reference cité dans AFSSAPS 18 Juin 99

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V - POINT SUR LES ATTEINTES DÉMYÉLINISANTES DU SYSTÈME NERVEUX CENTRAL APRÈS VACCINATION CONTRE L'HÉPATITE B CHEZ L'ENFANT DE MOINS DE 15 ANS.

Le Centre Régional de Pharmacovigilance de Strasbourg a présenté le suivi de l'enquête relative aux affections démyélinisantes du système nerveux chez des enfants âgés de 15 ans au moins au cours d'une vaccination contre l'hépatite B.

Ce point fait état des observations rapportées depuis la date de commercialisation des vaccins jusqu'au 31 mars 1998.

Les propositions de critères d'atteintes démyélinisantes du système nerveux central survenant après une vaccination et validés par deux experts en neurologie ont été longuement exposées.Le comité technique a pris connaissance des difficultés rencontrées pour l'interprétation des IRM chez l'enfant.

Trente huit observations d'affections démyélinisantes (centrales et périphériques) ont été retenues, après élimination des doublons et avis de l'expert neuropédiatre. Vingt sept cas de ces 38 observations touchent le système nerveux central. Elles correspondent à 6 premières poussées de SEP, 1 SEP connue, 10 atteintes ophtalmologiques (névrite optique, névrite optique rétrobulbaire, diplopie, papillite), 4 myélites, 1 encéphalomyélite, 3 encéphalites, 2 "autres" atteintes démyélinisantes (paresthésie, hémiparésie, ...). Ces cas sont survenus chez 17 filles (62,9 %) et 10 garçons. Les âges des patients varient de 7 à 15 ans. 7 observations concernent des enfants de moins de 10 ans et 20 cas des enfants âgés de 11 à 15 ans. Des antécédents familiaux de sclérose en plaques sont retrouvés dans 4 dossiers.Un cas d'antécédent personnel de sclérose en plaques a été signalé. Le délai de survenue est inférieur ou égal à 2 mois dans 59,2 % des cas. La fréquence de survenue de ces effets ne semble pas dépendre du rang de vaccination (3 cas après P1, 9 cas après P2, 3 cas après P3, 10 cas après un rappel et 2 cas où le rang n'est pas indiqué). Les années de survenue s'échelonnent entre 1993 et 1997. En 1993, il y a eu 1 cas, en 1994 : 2 cas, en 1995 : 3 cas, en 1996 : 13 cas et en 1997 : 8 cas. Les profils de tolérance des vaccins ne semblent pas être différents : 18 cas sont rapportés avec l'ENGERIX B® et 8 cas avec le GENHEVAC B®. Dans 1 cas, le nom du vaccin en cause n'est pas précisé. Il n'existe aucun cas avec réadministration positive et avec rechallenge négatif.

A la suite de ce bilan, le comité technique a relevé l'absence de notifications chez le nourrisson.

Par ailleurs, le CRPVde Strasbourg a présenté une étude épidémiologique réalisée en milieu scolaire du Bas-Rhin auprès de collégiens vaccinés. Cette enquête consiste en un suivi de la tolérance du vaccin contre l'hépatite B (réactions locales, troubles visuels,...) par des médecins-scolaires. Ainsi, au niveau de ce département, 10.000 élèves des classes de 6ème ont été inclus dans cette étude. Cependant, au bout de 3 ans (à leur entrée en 3ème), on ne dénombrait plus que 100 lycéens par rapport à l'échantillon initial de 10.000. Le comité technique a trouvé cette initiative intéressante tout en soulignant deux problèmes majeurs : d'une part, les difficultés d'ordre pratique pour développer de telles études dans d'autres départements et d'autre part, le nombre de perdus de vue qui représente plus de 90% de l'échantillon initial.

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VI - ENQUÊTE OFFICIELLE SUR LA NÉVIRAPINE (VIRAMUNE®)

Le Centre Régional de Pharmacovigilance de Créteil a présenté un bilan des effets indésirables avec VIRAMUNE® (néviparine) dans le cadre de l'A.T.U. de cohorte pour la période 1er novembre 1997 - 2 juin 1998.

VIRAMUNE® a obtenue une Autorisation de Mise sur le Marché Européenne (procédure centralisée) en février 1998.

L'analyse des données de tolérance confirme la toxicité cutanée prédominante.

Le premier rapport périodique de tolérance comprend, en effet, un nombre important d'effets indésirables cutanés graves : syndrome de Lyell, syndrome de Stevens-Johnson, érythème polymorphe. Ce point sera présenté au CSP des 20-22 octobre 1998.

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VII - ENQUÊTE OFFICIELLE SUR LE GLIMÉPIRIDE (AMAREL®)

Les Centres Régionaux de Pharmacovigilance de Bordeaux et de Montpellier ont présenté un point sur les effets indésirables notamment à type d'atteintes hépatiques et d'hypoglycémies, au cours de la prise d'AMAREL®, sulfamide hypoglycémiant commercialisé en France par les Laboratoires Hoechst-Houdé depuis septembre 1997.

1) Atteintes hépatiques et glimépiride :

* Le Centre Régionnal de Pharmacovigilance de Bordeaux a présenté 15 observations d'atteinte hépatique rapportées en France chez des patients traités par AMAREL® (à la date du 8 août 1998).

Ces observations se répartissent de la façon suivante :
- 5 observations déclarées aux Centres de Pharmacovigilance
- 15 observations déclarées aux laboratoires, dont 5 doublons

Parmi ces 15 observations, 7 ont été exclues en raison d'une autre explication (une lithiase avec dilatation du cholédoque, une hépatite C, 3 cancer du pancréas, une angiocholite, une lithiase avec dilatation des voies biliaires et fistule).

Parmi les huit observations retenues (4 hommes, 3 femmes, 1 genre non précisé), l'âge moyen était de 63,5 ans. Sept observations ont été enregistrées comme graves. Il s'agissait d'une hépatite fulminante (ALAT à 583N, insuffisance rénale aiguë anurique, ictère et encéphalopathie), de 4 cytolyses (dont une avec des ALAT à 382N) et de 2 cholestases. L'évolution a été favorable pour 7 observations et fatale pour un cas (hépatite fulminante).
Le taux d'incidence des atteintes hépatiques a été estimé à 1 cas notifié pour 10 000 patients traités (pour une période de 10 mois).

* Au cours des essais cliniques en France, 2 cas d'atteinte hépatique ont été enregistrés. Une observation a été exclue (hépatite C). L'autre observation rapportait une augmentation modérée des enzymes hépatiques d'évolution inconnue.

* A l'étranger :
En mars 98, le glimépiride était commercialisé dans 22 pays (en Europe, Amérique du Nord, Centrale et du Sud, Asie). Le glimépiride a été commercialisé pour la première fois en Suède en Octobre 1995. 15 observations d'atteintes hépatiques graves ont été rapportées à l'étranger. Mais 2 ont été exclues (cancer du foie, cancer des voies biliaires), 3 étaient non documentées et 3 trop succintes. Parmi les 7 observations restantes, 4 au moins comportaient une autre explication (non médicamenteuse). Le seul décès était à priori lié à une insuffisance hépatique sur insuffisance cardiaque, compliquée d'infection respiratoire aiguë.

Au total, concernant les atteintes hépatiques, il n'y a guère d'élément nouveau par rapport au bilan présenté en Mars 98. La mention figurant dans le RCP et transcrite dans le Vidal 1998 parait suffisamment claire et explicite : "Des cas isolés d'augmentation des enzymes hépatiques ont été rapportés au cours du traitement avec les sulfonylurées, ainsi qu'une altération de la fonction hépatique accompagnée d'une cholestase avec ictère et d'une hépatite. Les symptômes disparaissent généralement après arrêt du traitement mais une hépatite sévère peut évoluer vers une insuffisance hépatique."

Il est nécessaire de continuer à surveiller le glimépiride pour avoir un recul d'un an par rapport au début de sa commercialisation en France (septembre 1997).

2) Hypoglycémies et glimépiride :

Le Centre Régional de Pharmacovigilance de Montpellier a présenté 90 cas d'hypoglycémies rapportés en France chez des patients traités par AMAREL® (à la date du 24 août 1998).

Ces observations se répartissent de la façon suivante :
- 10 cas d'hypoglycémie au cours des essais cliniques dont 3 cas graves. L'évolution a été favorable dans tous les cas (après "resucrage" intraveineux dans 2 cas et oral dans 1 cas, non précisé pour les autres observations).
- 8 observations déclarées aux Centres de Pharmacovigilance dont 5 graves. L'âge moyen était de 69,8 ans (extrêmes : 49-87 ans). La posologie de glimépiride était de 1 mg/j dans 3 cas, 2 mg/j dans 4 cas et 4 mg/j dans 1 cas. Le délai d'apparition par rapport au début du traitement était de 1 jour pour une observation, compris entre 1 à 4 jours dans 3 observations et supérieur à 3 jours dans 4 observations. Dans 5 observations, la valeur de la glycémie était connue et inférieure à 0,5 g/l. L'évolution a été favorable dans tous les cas (après "resucrage" intraveineux dans 3 cas et oral dans 2 cas). Hormis l'âge, il existait dans la plupart des dossiers d'autres facteurs de risque (insuffisance rénale dans 2 observations, interactions médicamenteuses dans 4 cas). Dans 3 observations graves sur 5, l'indication d'un traitement anti-diabétique oral était probablement excessive.
- 72 observations déclarées au laboratoire dont 17 enregistrés comme graves.
L'âge moyen était de 66,7 ans (extrêmes : 55-91 ans). Pour les cas graves, la posologie de glimépiride était de 1 mg/j dans 8 cas, 2 mg/j dans 3 cas et supérieure à 2 mg pour les 6 autres observations. Le délai d'apparition par rapport à la dernière prise du traitement était précisé dans 3 observations (1, 2 et 18 heures). Dans 8 observations, la valeur de la glycémie était connue et inférieure ou égale à 0,5 g/l. L'évolution a été favorable dans 12 cas et non précisée dans 2 autres. Un patient est décédé 6 mois plus tard d'une fibrose pulmonaire préexistante. Il existait des interactions médicamenteuses validées dans 11 observations sur 17 graves, et suspectées dans 2 autres observations. Hormis l'âge, il existe dans la plupart des dossiers d'autres facteurs de risque (insuffisance rénale dans 2 observations, interactions, effort physique inhabituel, anorexie dans 4 cas, pour une observation l'indication d'un traitement anti-diabétique oral était excessive, non-indication également suspectée dans un autre cas).

L'incidence a été estimée à 11-11,5 cas pour 10 000 patients traités quelque soit la gravité de l'hypoglycémie (3-3,2 cas pour 10 000 patients traités pour les hypoglycémies graves).

Au total, le nombre et la gravité des hypoglycémies semblent actuellement en accord avec ce qui est décrit dans la littérature pour les autres sulfonylurées. Etant donné la longue durée d'action de cet analogue du glibenclamide, le respect des contre-indications et l'évaluation des terrains à risque doit rester de mise. Le maniement de ce type de produit, surtout chez la personne âgée, doit être très prudent et une grande partie des hypoglycémies pourrait être évité par un bon respect des règles de bon usage. Les facteurs de risque sont tous repris dans le Résumé des Caractéristiques du Produit. Il est nécessaire de continuer à surveiller le glimépiride pour avoir au moins 1 an de recul par rapport au début de sa commercialisation en France (septembre 1997). Compte-tenu de la longue durée d'action du glimépiride, le Comité Technique de Pharmacovigilance souhaite la mise en place d'une réflexion sur le problème de l'utilisation de ce médicament ainsi que des autres hypoglycémiants oraux chez les personnes âgées.

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3) Autres effets et glimépiride :

Le Centre Régional de Pharmacovigilance de Montpellier a présenté 28 cas d'autres effets rapportés en France chez des patients traités par AMAREL® (23 provenant des Centres de Pharmacovigilance et 5 provenant du laboratoire).

Ces observations se répartissent de la façon suivante :
- Effets cutanés : 8 observations
- Effets hématologiques : 4 observations
- Effets digestifs : 5 observations (dont une pancréatite très peu documentée)
- Effets oculaires : 2 observations
- Effets divers : 9 observations

La plupart des effets notifiés sont connus et mentionnés dans le Résumé des Caractéristiques du Produit.

En conclusion, la ré-évaluation des données de pharmacovigilance du glimépiride ne montre pas de nouveauté en terme de nature, fréquence ou sévérité des effets rapportés. L'Autorisation de Mise sur le Marché a été enregistrée dans le cadre d'une reconnaissance mutuelle dont l'état membre de référence sont les Pays-Bas auxquels la France transmettra les résultats de cette analyse. La surveillance de ce médicament doit être poursuivie pour avoir un an de recul par rapport au début de sa commercialisation en France.

VIII - POINT SUR LES MÉDICAMENTS GÉNÉRIQUES

Lors du tour de table des cas marquants du comité technique du 27 mai 1998, le problème de la pharmacovigilance des génériques avait été abordé et les CRPV de Limoges et de Saint-Etienne, chargés de rassembler des exemples de cas marquants d'inefficacité ou d'effets indésirables survenus avec des génériques. Ce point a été discuté en présence du président du groupe de travail "médicaments génériques".

Le Directeur de l'évaluation a tenu à rappeler quelques définitions.

Le texte de référence concernant les médicaments génériques est l'article L601-6 du Code de la Santé Publique qui précise que "on entend par spécialité générique d'une autre spécialité une spécialité qui a la même composition qualitative et quantitative en principes actifs, la même forme pharmaceutique, et dont la bioéquivalence avec l'autre spécialité a été démontrée par des études appropriées de biodisponibilité".

Ainsi, le **médicament générique** est une copie conforme à l'original, équivalent sur le plan thérapeutique et dont l'intérêt majeur est un coût moins important par rapport au médicament original.
Cependant, des différences peuvent exister au niveau des principes actifs qui peuvent contenir des impuretés différentes suivant la voie de synthèse choisie. Il faut également vérifier que l'étude de bioéquivalence est fiable et extrapolable.
A l'échelle européenne, ces médicaments sont nommés **médicaments essentiellement similaires.** Les études de bioéquivalence ne sont pas, selon les textes européens et contrairement à la réglementation française, systématiques : elles sont faites en complément du dossier pharmaceutique afin de mettre en évidence des différences qui pourraient avoir des conséquences sur le plan clinique.
En France, le terme d'**équivalent thérapeutique** est également employé : il concerne des médicaments identiques en tout point, disposant parfois de la même chaîne de fabrication mais commercialisés par des laboratoires différents.

Le CRPV de Limoges s'est heurté à des difficultés lors de la recherche des observations : d'une part, les médicaments, produit de référence ou générique, sont souvent codés dans la banque selon leur dénomination commune internationale et d'autre part le droit de substitution dans les hôpitaux est déjà effectif compte tenu des listes limitatives des médicaments disponibles à la pharmacie. Généralement, les prescriptions et le dossier du patient mentionnent le produit de référence, plus connu que le générique mais la pharmacie délivre le produit dont elle dispose. Ceci conduit à des confusions faisant attribuer les effets indésirables au produit de référence plutôt qu'au générique.

Dans le cadre de l'enquête, 6 médicaments ont été retenus : acébutolol, allopurinol, furosémide, nifédipine, propranolol, trimébutine. La période d'interrogation de la base s'étendait jusqu'au 31 décembre 1997.
Concernant l'allopurinol, 18 observations ont été recensées. Dans 14 cas, le générique était administré en remplacement d'un traitement par ZYLORIC bien toléré et dans 9 cas, le ZYLORIC était repris sans problème après échec du générique (survenue d'un effet indésirable). Les effets étaient généralement bénins, surtout cutanés et digestifs.
Pour les autres produits retenus pour l'enquête, seulement 5 observations impliquent spécifiquement le générique.

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Globalement, deux types d'effets sont rencontrés : soit une modification de l'effet du générique par rapport au produit de référence (augmentation ou diminution de l'effet), soit des effets spécifiques du générique qui pourraient impliquer les excipients. La comparaison des compositions du produit de référence et du générique ne permet pas de donner une explication rationnelle de l'effet indésirable. De plus, il s'agit de cas isolés et aucune extrapolation n'est possible actuellement.

Le Comité technique a souhaité que les problèmes de traçabilité des produits réellement administrés aux malades puissent être résolus de la meilleure manière possible afin que les CRPV puissent disposer des données fiables pour la constitution des dossiers de pharmacovigilance susceptibles d'impliquer des génériques.

Enfin, il a été rappelé qu'un signal concernant la pharmacovigilance d'un médicament générique (effet indésirable, inefficacité) peut entraîner l'intervention de l'Inspection et qu'il pourra être procédé à la vérification de la qualité des principes actifs et des modes de fabrication.
Enfin, le Comité technique a proposé que le répertoire des génériques soit distribué aux CRPV.

IX - ENQUÊTE OFFICIELLE SUR LA GEMCITABINE (GEMZAR®)

Résultats de l'enquête officielle sur la tolérance du GEMZAR (gemcitabine) associée à la radiothérapie.

La gemcitabine est enregistrée en France selon une procédure nationale et est commercialisée depuis **juin 1996** sous le nom de GEMZAR® par les laboratoires Lilly.
Cet analogue nucléosidique de la déoxycytidine est indiqué par voie parentérale dans le traitement du cancer non métastatique du poumon non à petites cellules (NSCLC), de l'adénocarcinome du pancréas et dans le cancer du pancréas résistant au 5FU. La gemcitabine peut être associée à la radiothérapie de façon concomitante ou successive (gemcitabine pouvant alors être administrée avant ou après la radiothérapie).

Les résultats de l'enquête sur les effets indésirables de l'association gemcitabine-radiothérapie ont été présentés par le Centre Régional de Pharmacovigilance de Poitiers qui avait déjà étudié la cardiotoxicité de la gemcitabine (résultats de l'enquête officielle présentés lors du Comité Technique du 27 mai 1998).
Les observations ont été rapportées dans le cadre d'essais cliniques ou de la notification spontanée.

1. Association concomitante gemcitabine - radiothérapie

Lors d'essais cliniques dans le cancer du poumon, associant 1000 mg/m² de gemcitabine et 60Gy de radiothérapie sur 6 semaines, et dans le cancer tête et cou, associant 300 mg/m² par semaine de gemcitabine et 70Gy de radiothérapie sur 7 semaines, cette association a donné lieu à une toxicité inacceptable (fibroses pulmonaires et/ou oesophagiennes) qui a motivé l'arrêt de ce type d'essai. D'autres essais dans le cancer du poumon et du pancréas sont en cours et il n'a pas été rapporté à ce jour de toxicité excessive avec des doses de gemcitabine plus réduites.

En janvier 1996 et suite au deuxième rapport périodique, les laboratoires Lilly ont déposé une demande de modification de l'information pour ajouter dans le RCP le risque d'apparition de fibroses pulmonaires et oesophagiennes sévères lors de l'association concomitante gemcitabine et radiothérapie curative (rubriques "interactions médicamenteuses" et "mises en garde").

2. Association successive

- **Radiothérapie puis gemcitabine**

Au niveau mondial, 25 cas (9 cas français) évoquant un **phénomène de rappel** ont été signalés. Un phénomène de rappel est suspecté lorsque la localisation des événements survenus au décours du traitement par la gemcitabine, correspond aux territoires irradiés.

Chez 5 patients, la radiothérapie avait induit des complications post-radiques, suggérant que l'existence d'une **intolérance à la radiothérapie** facilite la survenue du phénomène de rappel.
Dans 3 cas, la **posologie** de la gemcitabine était supérieure à la dose recommandée de 1000mg/m²; la dose cumulée allait de 1 à 15,6 g/m².

Dans 7 cas, le **délai** entre la radiothérapie et la gemcitabine n'était pas documenté mais dans 11 cas sur 18, il existait une corrélation entre le délai radiothérapie et gemcitabine et le délai gemcitabine et apparition de l'effet indésirable.

Hormis les manifestations neurologiques chez les patients ayant reçu une radiothérapie cérébrale (5 cas), la **symptomatologie** est très homogène avec des manifestations cutanées à type de dermato-polymyosite. Elle est grave dans 19 cas sur 25.

Selon l'expert radiothérapeute, un mécanisme histopathologique possible serait l'existence d'une microartériopathie oblitérante inflammatoire induite par la gemcitabine.

L'évolution est favorable dans 10 cas sur 25 ; dans 12 cas, la symptomatologie a persisté ou s'est aggravée (fibrose pulmonaire, épaississement cutané avec douleurs persistantes) ; dans 3 cas, l'évolution était inconnue.

❒ **Gemcitabine puis radiothérapie**

Deux cas pouvant évoquer un **phénomène de radiosensibilisation** ont été rapportés.

Le rapporteur serait d'avis de **contre-indiquer l'association concomitante de la gemcitabine et de la radiothérapie à visée curative et palliative.**

Selon l'expert radiothérapeute, l'administration successive de la radiothérapie et de la gemcitabine pourrait être raisonnablement envisagé avec un délai d'un mois entre les deux thérapeutiques.

En conclusion, le Comité technique souhaite que les résultats de l'enquête officielle sur "gemcitabine et radiothérapie" et "gemcitabine et cardiotoxicité" soient présentés à la Commission Nationale de Pharmacovigilance du 22 septembre 1998.

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X - DEMANDE DE MODIFICATION DE L'INFORMATION MÉDICALE SUR LE CISAPRIDE (PREPULSID®)

Les données de sécurité actualisées et la demande de modification d'information de la spécialité Prépulsid® déposée par les laboratoires Janssen Cilag ont été présentées par le Centre de Pharmacovigilance de Lille.

1 - Contexte

a) Demande de modification de l'information

Le 30 juin 1998, l'Unité de Pharmacovigilance a reçu des laboratoires Janssen Cilag une demande de modification de l'information pour Prépulsid®.

Cette demande de modification a été déposée dans tous les pays de l'Union Européenne et concerne les rubriques 4.3 "contre-indications" et 4.5 "interactions médicamenteuses" (extension de la contre-indication actuelle (formes orales ou parentérales de kétoconazole, d'itraconazole, de miconazole, de fluconazole, macrolides (exceptée la spiramycine), antiprotéases et diphémanil") à la contre-indication de classe pour les antifongiques azolés et les macrolides, ajout de la néfazodone en contre-indication). A la rubrique 4.4 "mises en garde", les facteurs devant être évalués avant l'administration de cisapride afin d'évaluer le rapport bénéfice-risque sont énumérés. A la rubrique 4.6 "Grossesse et allaitement", une information sur l'utilisation du cisapride pendant la grossesse a été ajoutée. Au niveau de la rubrique 4.8 "effets indésirables", les effets de type cardio-vasculaire sont détaillés. De plus, les symptômes pouvant survenir en cas de réactions d'hypersensibilité sont décrits. Il est précisé dans la rubrique 4.9 "surdosage" que la bradycardie, facteur de risque de survenue de torsades de pointes, doit être recherchée et corrigée.

b) Information de la F.D.A.

En juin dernier en raison des effets arythmogènes du produit, la F.D.A. a pris la décision de réserver l'utilisation du cisapride au traitement de deuxième intention du reflux gastroesophagien avec un renforcement des rubriques "contre-indications et "mises en garde et précautions particulières d'emploi" du Résumé des Caractéristiques du Produit.
Ce sujet a été abordé au Comité des Spécialités Pharmaceutiques de juillet dernier où il a été demandé que le rapport bénéfice-risque de la spécialité soit réévalué au niveau national.

2 - Données de sécurité actualisées

En France, les données de sécurité cardiaque ont été évaluées à plusieurs reprises par la Commission Nationale de Pharmacovigilance et la Commission d'AMM et ont abouti à des modifications successives du RCP avec information des prescripteurs par une lettre aux prescripteurs en février 1995, janvier 1996 et juin 1997.

Du 31 mars 1996 au 31 mars 1998, 30 observations d'effets cardiaques ont été rapportées chez 11 enfants et 19 adultes. Ces observations se répartissent en 6 malaises, 4 syncopes, 3 sensations dysrythmiques, 8 morts subites, 3 arrêts circulatoires et/ou respiratoires.

Annexe 3-7

L'évolution a été fatale dans 11 observations chez 6 enfants et 5 adultes. Chez l'enfant, 4 décès correspondent à des tableaux de mort subite du nourrisson et 2 sont survenus chez des enfants âgés respectivement de 10 mois et 15 ans, porteurs d'antécédents et/ou des pathologies associées graves associées, cardiaques ou non cardiaques.

Après analyse de ces dossiers, aucun lien direct ne peut être établi entre la prise de cisapride et ces décès.
Les données électrocardiographiques étaient documentées dans 16 observations et comprenaient 4 cas d'extrasystoles auriculaires ou ventriculaires, 1 cas d'asystole, 1 cas d'élargissement de QRS, 4 cas de fibrillation ou tachysystolie auriculaire et 9 allongements de QTc dont 2 cas s'accompagnaient de torsades de pointes. Une hypokaliémie était présente dans ces 2 dernières observations. L'évolution a été favorable dans ces 16 observations.

En terme d'interaction médicamenteuse, une seule observation de syncopes itératives avec allongement de QTc sans enregistrement de trouble du rythme ventriculaire peut être retenue. Elle peut correspondre à une interaction pharmacodynamique avec le disopyramide, antiarythmique capable à lui seul de provoquer un tel effet indésirable.

3 - Données bibliographiques

Depuis la dernière Commission de Pharmacovigilance, 2 publications concernant les données cliniques chez l'enfant ont été analysées.

Levine et coll 1998[1] n'ont pas mis en évidence de modification du QTc par rapport au QT de base après un mois de traitement par cisapride à la dose de 0,8 mg/kg/j chez 30 enfants dont 10 prématurés.

En revanche, *Hill et coll 1998*[2] ont comparé l'intervalle QTc d'enfants âgés de 5 mois à 18 ans traités par cisapride à la dose moyenne de 0,67 ± 0,23 mg/kg/j [0,3 -1,68] à une population témoin de 1000 enfants normaux et ont mis en évidence une valeur de QTc moyen à 0,43 dans le groupe cisapride versus 0,42 dans le groupe témoin. Onze enfants sur 35 soit 31% ont eu un allongement de QT supérieur à 0,45. De plus 2 enfants ont développé une torsade de pointes lors d'un traitement associé à de l'érythromycine ou de la clarithromycine.

4 - Données de vente

Du 31 mars 1996 au 31 mars 1998, l'exposition au Prépulsid® en France a été estimée à 4 300 000 traitements-patients ou 5 744 000 mois de traitements.

---

[1] Levine A, Fogelman R, Sirota L et al. QT interval in children and in infants receiving cisapride (abstract E9). Pediatrics 1998; 101 : 464.

[2] Hill SL, Evangelista JAK, Pizzi AM et al. Proarrhythmia associated with cisapride in children. Pediatrics 1998 ; 101 : 1053-1056.

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5 - Conclusion

Selon le rapporteur, la demande de modification de l'information paraît acceptable sous réserve de quelques amendements.

Cependant, les données de sécurité cardiaque du cisapride doivent servir de base à la réévaluation du rapport bénéfice-risque.

Annexe 3-7

XI - QUESTIONS DIVERSES

a) Techniques :

- Point sur les antibiotiques de la famille des aminosides et atteintes vestibulaires isolées :

Le CRPV de Marseille a réalisé un point sur les atteintes vestibulaires isolées survenant avec les aminosides, après avoir rapporté un cas survenu après une dizaine de jours de traitement par gentamicine et ayant laissé des séquelles graves et invalidantes. L'audiogramme de cette patiente était normal.

La rubrique "effets indésirables" du Résumé des Caractéristiques du produit (RCP) des aminosides mentionne la possibilité de survenue d'"atteintes cochléo-vestibulaires".

Après consultation d'experts, il s'avère que les atteintes vestibulaires isolées sont bien connues des spécialistes en ORL. Les vertiges qui en sont la principale manifestation peuvent être durables et invalidants. Par ailleurs, ces symptômes étant mal connus des médecins hors de cette spécialité, le patient est souvent orienté vers une consultation psychiatrique.
La gentamicine donne davantage d'atteintes vestibulaires que cochléaires. Les autres aminosides sont aussi concernés par les effets vestibulaires mais dans des proportions moindres et ceux-ci sont plus rarement isolés.
Dès l'apparition des premiers symptômes, les patients doivent être rapidement orientés vers une consultation spécialisée. La position allongée des patients ne permet pas ou limite l'expression clinique du vertige.
Les examens par Vidéo Nystagmométrie apportent une beaucoup plus grande sensibilité, ce qui permet de quantifier l'atteinte vestibulaire et de suivre son évolution.

Il paraît donc indispensable de modifier le RCP de ces produits afin d'attirer l'attention du prescripteur sur la symptomatologie.
Le Comité Technique souhaite la mise en enquête officielle des antibiotiques de la famille des aminosides concernant les atteintes cochléo-vestibulaires. Le CRPV de Marseille est désigné comme responsable de cette enquête.

- **ROACCUTANE® (isotrétinoine)** : le CRPV de Fernand-Widal a rapporté un cas d'usage criminel du ROACCUTANE® fort insolite. Le conjoint ne souhaitant pas avoir d'enfant, administrait à sa partenaire, actuellement enceinte de 8 semaines 1/2, une capsule de ROACCUTANE® par voie vaginale avant chaque rapport sexuel.

- **QUINIMAX® (quinine, quinidine, cinchonine, cinchonidine)** : les infectiologues du CHU de Strasbourg ont observé une fréquence importante d'effets indésirables connus de la quinine chez des malades traités par QUINIMAX®.
→ Les CRPV doivent interroger leur(s) service(s) d'infectiologie et rapporter les effets indésirables survenus avec ce médicament au CRPV de Strasbourg qui présentera un rapide bilan lors du CT du 22 octobre 1998.

- DEPAKINE® (acide valproïque) / DEPAMIDE® (valpromide) et grossesse / CRPV de Clermont-Ferrand : Le valpromide (Depamide®) a pour métabolite actif l'acide valproïque, or la rubrique "grossesse" du RCP de Depamide® est totalement différente de celle de Depakine®. Le CRPV de Clermont-Ferrand adressera un courrier concernant cette remarque à l'unité de pharmacovigilance qui le transmettra au Groupe de Travail "grossesse".

- Effets délictueux des médicaments / soumission chimique médicamenteuse :

Dans le cadre du dossier relatif à l'usage criminel des produits psycho-actifs, l'Agence du Médicament a été chargée par la Direction Générale de la Santé :

- d'assurer le fonctionnement d'un groupe de travail pluridisciplinaire et interministériel. Ce groupe coordonné par le Professeur Lagier, doit d'une part élaborer des recommandations de prise en charge clinique des victimes droguées à leur insu et d'autre part se charger de l'aspect analytique de ce dossier.
- de mener une réflexion sur les actions préventives à mettre en oeuvre au niveau de l'Autorisation de Mise sur le Marché de ces molécules, tant sur le plan des études à mener au cours du développement (potentiel amnésiant et désinhibiteur des produits) que sur la recherche de solutions galéniques.

Sur l'aspect préventif, l'Agence du Médicament a décidé d'effectuer un état des lieux afin de compléter la liste des produits cités dans le rapport. L'ensemble des 3 réseaux (Centres Régionaux de Pharmacovigilance, Centres Anti-poisons et Centres d'évaluation et d'information sur les Pharmacodépendances) sera donc sollicité. Par conséquent, il est demandé aux CRPV de recenser les observations de soumission chimique médicamenteuse dont ils auraient pu avoir connaissance.

b) Administratives :

- <u>Nouveaux points (récapitulatif)</u> :

- Analogues nucléosidiques / acidose lactique et pancréatite : CRPV de St-Antoine et St Vincent de Paul : Comité Technique du 21 janvier 1999.
- Thiazidiques et pancréatite : CRPV d'Amiens : Comité Technique du 21 janvier 1999.
- Stamaril® (vaccin amaril) / méningite aseptique : CRPV de toulouse : Comité Technique du 19 novembre 1998,
- ELOHES® (hydroxyéthylamidon) / complications hépatiques : CRPV de Paris St-Antoine : Comité Technique du 22 octobre 1998.
- Fibrates et photosensibilisation : CRPV de Marseille :Comité Technique du 21 janvier 1999.

- <u>Nouvelles enquêtes officielles (récapitulatif)</u> :

- Aminosides / atteintes cochléo-vestibulaires : CRPV de Marseille : Comité Technique du 17 décembre 1998.

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- Divers :

- Le CRPV de Limoges présentera lors du CT du 21 janvier 1999 un point sur TICLID® et, en particulier, l'évaluation de l'efficacité des mesures prises.

- Documents distribués :

- Relevé d'avis du groupe de travail "Interactions médicamenteuses" n° 27 du 11 mai 1998

- Liste des événements indésirables graves inattendus notifiés à l'Unité Essais Cliniques (Période du 30/06/98 au 28/08/98)

- Décret n°98-578 du 9 juillet 1998 (JORF du 11 juillet 1998) relatif aux autorisations d'importation et aux autorisations temporaires d'utilisation de médicaments à usage humain et modifiant le Code de la Santé Publique.

- Liste des antiretroviraux (AMM ou ATU) au 2 septembre 1998

- Calendrier des demandes de modification en cours - septembre 1998 -

- Circulaire de la Direction des Hôpitaux sur les solutions d'irrigation stérile à base de glycocolle 1,5 % du 4 août 1998

- 3 publications du *New England Journal of Medicine* Volume 339, number 11 (10 septembre 1998) concernant les anorexigènes et atteintes valvulaires.

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XII - TOUR DE TABLE DE LA LITTÉRATURE

Anti-ulcéreux - Pharmacocinétique - Interactions.
"Pharmacokinetic drug interactions with anti-ulcer drugs."
R. DAL NEGRO.
Clin. Pharmacokinet. 1998, 35 (2) : 135-50.
(CRPV de CLERMONT-FERRAND)

Bloqueurs des canaux calciques : nouveautés sur leur (in)efficacité et leur (in)sécurité.
Bulletin du CRPV de Barcelone.
(CRPV de TOULOUSE)

Contraceptifs oraux - Risque de cancer ovarien héréditaire.
"Oral contraceptives and the risk of hereditary ovarian cancer."
S.A. NAROD, H. RISCH, R. MOSLEHI & al.
N. Engl. J. Med. 1998, 339 (7) : 424-28.
(CRPV d'ANGERS)

Corticoïdes inhalés - Cataracte - Sujets âgés.
"Association of inhaled Corticosteroïd use with cataract extraction in elderly patients."
E. GARBE, S. SUISSA, J. LELORIER.
JAMA 1998, 280 (6) : 539-43.
(CRPV de PARIS-BROUSSAIS)

Déféripone - Sécurité et efficacité à long terme.
"Long term safety and effectivness of iron-chelation therapy with deferiprone for thalassemia major."
N. OLIVIERI, G.M. BRITTENHAM, C.E. McLAREN & al.
N. Engl. J. Med. 1998, 339 (7) : 417-23.
(CRPV d'ANGERS)

Déféripone - Toxicité ou manque d'efficacité.
"Iron-chelation therapy with oral deferiprone. Toxicity or lack of efficacy."
K.V. KOWDLEY.
N. Engl. J. Med. 1998, 339 (7) : 468-9.
(CRPV d'ANGERS)

Effet du pamplemousse sur la pharmacocinétique du vérapamil administré par voie orale.
"The effect of grapefruit juice on the pharmacokinetics of orally administered verapamil."
R. ZAIDENSTEIN & al.
Eur J Clin Pharmacol 1998, 54 : 337-40.
(CRPV de LIMOGES)

Immunoglobulines intraveineuses - Pseudohyponatrémie.
"Intravenous immune globulin and pseudohyponatremia."
N. LAWN, E.F.M. WIJDICKS, M.F. BURRITT.
N. Engl. J. Med. 1998, 339 (9) : 632.
(CRPV d'ANGERS)

Annexe 3-7

Inhibiteurs calciques - Cancer.
"Is the use of some calcium antagonists linked to cancer ? Evidence from recent observational studies."
M. PAHOR & al.
Drugs & Aging 1998, 13 : 99-108.
(CRPV de LIMOGES)

Montelukast.
"Montelukast."
A. MAEKHAM, D. FAULDS.
Drugs 1998, 56 (2) : 251-6.
(CRPV de CLERMONT-FERRAND)

Oestrogènes et progestatifs - Prévention secondaire des maladies coronariennes chez la femme ménopausée.
"Randomized trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women."
S. HULLEY, D. GRADY, T. BUSH, C. FURBERG, D. HERRINGTON, B. RIGGS, E. VITTINGHOFF.
JAMA 1998, 280 (7) : 605-13.
(CRPV de PARIS-BROUSSAIS)

Périndopril - Surveillance après commercialisation.
"Perindopril postmarketing surveillance : a twelve-month study in 47351 hypertensive patients."
C. SPEIRS, F. WAGNIART, L. POGGI.
Br J Clin Pharmac 1998, 46 (1) : 63.
(CRPV de CAEN)

Polymédication - Etude de correlation avec sexe, âge et traitement.
"Polypharmacy : correlations with sex, age and drug regimen. A prescription database study."
L. BJERRUM & al.
Eur J Clin Pharmacol 1998, 54 : 197-202.
(CRPV de LIMOGES)

Prévention secondaire de l'infactus du myocarde.
"Trends of prescribing patterns for the secondary prevention of myocardial infarction over a 13-year period study."
M. MARTINEZ & al.
Eur J Clin Pharmacol 1998, 54 : 203-8.
(CRPV de LIMOGES)

Prion - Troubles psychiatriques.
"A prion-linked psychiatric disorder."
HELENA B. SAMAIA, HOMERO P. VALLADA, RICARDO P. MOURA, ANDREW J.G. SIMPSON, RICARDO R. BRENTANI.
Nature 1997, 390, n° 6657 : 241.
(CRPV de MARSEILLE)

Quinte de toux causée par *Bordetella pertussis* et *Bordetella parapertussis*.
"Whooping cough caused by *Bordetella pertussis* and *Bordetella parapertussis* in an immuzed population."
Q. HE, M.K. VILJANEN, H. ARVILOMMI, B. AITTANEN, J. MERTSOLA.
JAMA 1998, 280 (7) : 635-7.
(CRPV de PARIS-BROUSSAIS)

Répaglinide.
"Repaglinide"
J.A. BALFOUR.
Drugs & Aging 1998, 13 : 173-80.
(CRPV de LIMOGES)

Sotalol - Effets indésirables d'une dose unique administrée chez des patients asthmatiques.
"Adverse effects of a single dose of (+)- sotalol in patients with mild stable asthma."
G. DEVERAUX, K. FISHWICK & al.
Br J Clin Pharmac 1998, 46 (1) : 79.
(CRPV de CAEN)

Traitement antithrombotique prophylactique et curatif - Personnes âgés immobiles.
"Rational antithrombotic therapy and prophylaxis in elderly immobile patients."
E.C.M. VAN GORP & al.
Drugs & Aging 1998, 13 : 145-157.
(CRPV de LIMOGES)

Vaccin contre la rougeole - Déficience de la réponse immune chez des enfants vaccinés à l'âge de 6 mois.
"Deficiency of the Humoral Immune Response to Measles Vaccine in Infants immunized at age 6 months."
H.A. GANS, A.M. ARVIN, J. GALINUS, L. LOGAN, R. DEHOVITZ, Y. MALDONADO.
JAMA 1998, 280 (6) : 527-532.
(CRPV de PARIS-BROUSSAIS)

Vaccins Hépatite B - Effets indésirables graves.
"Major adverse reactions to yeast-derived hepatitis B vaccines - a review."
I. GROTTO, Y. MANDEL, M. EPHROST, I. ASHKENAZI, J. SHEMER.
Vaccine 1998, 16 (4) : 329-34.
(CRPV de NANCY)

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DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 22 octobre 1998)

Etaient présents

M. RICHE : Président
M. LE LOUET (suppléant de Mme ALBENGRES), M. ESCOFIER (suppléant de M. ALLAIN H), Mme LAINE (suppléante de M. ALLAIN P), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET), Mme BAVOUX, Mme DAVID- LAROCHE (suppléante de M. BECHTEL), M. BIOUR, M. BLAYAC, Mme CARLHANT, M. CARON, Mme CHICHMANIAN, Mme DJEZZAR, M. FIALIP (suppléant de M. ESCHALIER), Mme SGRO (suppléante de M. ESCOUSSE), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR (suppléante de Mme JOUGLARD), Mme KREFT-JAIS, Mme LACOTTE, Mme LAGARCE,
M. LAROUSSE, M. MERLE, Mme LAPEYRE-MESTRE (suppléante de M. MONTASTRUC),
M. MOULIN, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme RADAL, Mme SOUBRIE, Mme TANASESCU, M. THUILLEZ, M. THOMAS, M. TRENQUE, M. VANDEL, M. VIAL,
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme BARON (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance

Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Mme JOUSSELIN-PAUTROT
Melle JULLIAN
Mme LEREBOURS
M. MAIGNEN
Mme MORIN
Mme PARIENTE-KHAYAT
Melle PIERRON
M. ROPERS
Mme WECHSLER

Assistaient à la réunion (D.E.V.) :

Mme BAUMELOU
Mme GRENE
Mme KONOPKA
Mme LORENCE

Experts :

M. CHAPLAIN

M. DONADIEU

Etaient excusés

M. BEGAUD (Vice-Président)
M. MALLARET
Monsieur le Directeur Général de l'INSERM

Annexe 3-8

I - ADOPTION DU PROCÈS-VERBAL DU COMITÉ TECHNIQUE DU 10 SEPTEMBRE 1998

Le procès-verbal de la scéance du 10 septembre 1998 a été adopté avec les modifications suivantes :

Page 6 : Observation ALLOPURINOL MSD® : supprimer le mot "intracrânienne".

Page 14 : Paragraphe "Données cinétiques et de métabolisme", 6e ligne : remplacer "métabolisme" par "métabolite".

Page 15 : 4é paragraphe : remplacer "Parmi les 48 observations.... (paresthésie, hémiparésie, ...)" par "Trente huit observations d'affections démyélinisantes (centrales et périphériques) ont été retenues, après élimination des doublons dans de l'expert neuropédiatre. Vingt sept cas de ces 38 observations touchent le système nerveux central. Elles correspondent à 6 premières poussées de SEP, 1 SEP connue, 10 atteintes ophtalmologiques (névrite optique, névrite optique rétrobulbaire, diplopie, papillite), 4 myélites, 1 encéphalomyélite, 3 encéphalites, 2 "autres" atteintes démyélinisantes (parestbésie, hémiparésie, ...). Ces cas sont survenus ... entre 1993 et 1997. En 1993, il y a eu 1 cas, en 1994 ..."

Remplacer "La majorité des cas est apparue en 1993 (1 cas) ... 1997 (8 cas) par "En 1993, il y a eu 1 cas, en 1994 : 2 cas, en 1995 : 3 cas, en 1996 : 13 cas et en 1997 : 8 cas."

5è paragraphe : remplacer "nouveau-né" par "nourrisson".

Page 16 : Titre : remplacer "néviparine" par "névirapine".

Page 18 : 11è ligne : remplacer "88 ans" par "87 ans".

31è ligne : remplacer le paragraphe par "L'incidence a été estimée à 11-11,5 cas pour 10000 patients traités quelque soit la gravité de l'hypoglycémie (3-3,2 cas pour 10000 patients traités pour les hypoglycémies graves)".

Page 20 : 4è paragraphe, 3è ligne : remplacer "substilution" par "substitution".

Page 24 : 2è paragraphe, 3è ligne : remplacer "dear doctor letter" par "une lettre aux prescripteurs".

Annexe 3-8

II- PRÉSENTATION DU REGISTRE FRANCAIS DES NEUTROPÉNIES CHRONIQUES SÉVÈRES

Le Dr Jean DONADIEU, hématologue dans le service d'Hématologie et d'Oncologie Pédiatrique à l'hôpital d'enfants Armand-Trousseau à Paris a présenté le Registre **Français** des neutropénies chroniques sévères, fichier regroupant une centaine d'observations. Par ailleurs et indépendamment de ce Registre Français, il existe un Registre **International** incluant 531 patients atteints également de neutropénies chroniques sévères.

Le G-CSF est un facteur de croissance de la lignée granulocytaire commercialisé par les laboratoires Amgen sous le nom commercial de Neupogen ® et également par les laboratoires Bellon- RPR sous le nom de Granocyte®. Seul le Neupogen® a une Autorisation de Mise sur le Marché dans l'indication des neutropénies chroniques sévères.
Il est à noter que les neutropénies chroniques sévères sont les seules pathologies où le G-CSF est administré **au long cours.**

D'après les résultats des deux registres, plusieurs effets indésirables sont suspectés :

- **Transformations leucémiques** :
La question de la responsabilité du G-CSF dans la survenue de leucémies secondaires est actuellement soulevée. La fréquence de survenue de ces transformations leucémiques diffère dans les deux registres (2% dans le Registre Français, 10% dans le Registre International). Selon le Dr Donadieu, cette différence s'expliquerait par le fait que, dans le Registre International, certaines neutropénies initialement non classées en syndrome précis étaient en fait des états pré-leucémiques (absence d'analyse cytogénétique médullaire initiale).
- **Ostéoporose** : peu de données concernant l'ostéodensité des patients sont cependant disponibles.
- **Carcinome rénal** : un cas chez une patiente du Registre Français, porteuse d'une glycogénose Ib.
- **Protéinurie**
- **Splénomégalie** :
Selon le Dr Donadieu, on n'assiste pas actuellement à une flambée des leucémies secondaires au cours de l'utilisation chronique du G-CSF ; par conséquent, une modification de l'indication du G-CSF dans les neutropénies chroniques sévères n'est pas justifiée.
Pour plus de clarté, il souhaiterait voir rassembler **dans un seul paragraphe** du RCP tous les examens à effectuer dans le cadre de la surveillance du traitement. Il propose : un examen cytogénétique médullaire annuel, une densité osseuse tous les 2 ans environ, une recherche annuelle de splénomégalie, une recherche par bandelette d'une hématurie et d'une protéinurie. Il s'interroge également sur l'intérêt de l'ajout d'une surveillance rénale échographique tous les 2 ans.

Au total, afin de faire le point sur toutes ces données et de situer le Registre Français par rapport au Registre international, une rencontre technique réunissant le Dr Donadieu, le Système National de Pharmacovigilance (qui sera représenté par le CRPV de Caen), l'Unité de Pharmacovigilance et l'Unité AMM Cancérologie Immunologie s'avère nécessaire.

Annexe 3-8

III - TOUR DE TABLE DES CAS MARQUANTS

ARTOTEC®
(diclofénac,
misoprostol) : Pancréatite aiguë chez un homme de 41 ans, alcoolique.
(CRPV de Nantes)

BUFLOMEDIL RATIOPHARM®
(buflomédil) : Crises comitiales généralisées (4 crises en 48 heures) 36 heures après la première prise de 2 comprimés du générique en remplacement du FONZYLANE® (buflomédil) chez une femme de 75 ans diabétique et angoreuse.
(CRPV de Nantes)

CLARITYNE®
(loratadine) : Extrasystoles et palpitations chez un homme de 49 ans. Réadministration positive.
(CRPV de Caen)

CRIXIVAN®
(indinavir) : - Dysfonctionnement et raideur articulaires chez un homme de 61 ans.
(CRPV de Nancy)
- 3 cas de gynécomastie, débutant par un syndrome inflammatoire très douloureux ; absence d'atteintes endocriniennes.
(CRPV de Paris - Pitié-Salpétrière)

DEROXAT®
(paroxétine) : 4 observations d'hématome chez 4 femmes âgées de 22, 30, 39 et 54 ans. Les résultats de l'enquête officielle sur les syndromes hémorragiques des inhibiteurs de la recapture de la sérotonine seront présentés lors du Comité technique du 17 décembre 1998.
(CRPV de Paris - Créteil)

DISULONE®
(dapsone, oxalate
de fer) : Agranulocytose chez une femme de 69 ans. Les rubriques du RCP "mises en garde" et "effets indésirables" sont à revoir. Ouverture d'une enquête officielle placée sous la responsabilité du CRPV de St-Etienne.
(CRPV de Saint-Etienne)

EFFEXOR®
(venlafaxine)
+ HUMORYL®
(toloxatone) : Syndrome sérotoninergique chez une femme de 52 ans.
(CRPV de Limoges)

ENGERIX B®
(Ag HBs)
+ DT POLIO®
(anatoxine diphtérique,
anatoxine tétanique,
vaccin poliomyélitique) : Myélite aiguë chez un homme de 34 ans.
(CRPV de Montpellier)

FORENE® I.M.
(isoflurane) : Relâchement utérin excessif, source d'hémorragies post abortum chez deux femmes de 15 ans et 34 ans.
(CRPV de Rouen)

FONZYLANE®
(buflomédil) : 3 observations de tentative de suicide lors de la prise de FONZYLANE® à fortes doses, entraînant des convulsions et des troubles du rythme cardiaque. La précédente information sur la gravité majeure de ces intoxications n'a pas eu l'impact souhaité auprès des médecin-urgentistes. Une réévaluation de l'efficacité des mesures prises sera effectuée par le CRPV de Limoges.
(CRPV de Lyon)

FUCIDINE®
(acide fusidique)
+ MINISINTRON®
(acénocoumarol) : Thrombopénie chez une femme de 80 ans.
(CRPV de Rennes)

Héparine sodique : Thrombopénie et thrombose veineuse et artérielle chez un homme de 83 ans, chez deux femmes âgées de 72 et 78 ans.
Dans deux cas la surveillance des plaquettes n'avait pas été faite.
(CRPV de Marseille)

HOLOXAN®
(ifosfamide)
+ UROMITEXAN®
(mesna) : Infarctus du myocarde, angor et syndrome de menace chez une femme de 48 ans.
(CRPV de Tours)

HYZAAR®
(losartan potassique,
hydrochlorothiazide) : Toxidermie bulleuse chez une femme de 79 ans.
(CRPV de Strasbourg)

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INNOHEP®
(tinzaparine sodique) : Plusieurs cas de décès et d'accidents hémorragiques survenus lors de l'utilisation de ce médicament. Les précautions d'emploi mentionnées dans le résumé des caractéristiques du produit paraissent insuffisantes. Il existe une confusion dans l'esprit des médecin-prescripteurs entre les doses préventives et curatives confirmant leur manque d'information sur ce médicament. Ouverture d'une enquête officielle placée sous la responsabilité des CRPV de Toulouse et Rouen.
(CRPV de Rouen)

LAROXYL®
(amitriptyline)
+ DEROXAT®
(paroxétine) : Syndrome sérotoninergique chez une femme de 59 ans (décès).
(CRPV de Limoges)

LOVENOX®
(énoxaparine sodique)
+ ORGARAN®
(danaparoïde) : Thrombopénie et thromboses multiples chez une femme de 75 ans (décès). Test d'agrégabilité positif avec ces 2 médicaments.
(CRPV de Saint-Etienne)

MABTHERA®
(rituximab)
+ STABLON®
(tianeptine)
+ SOLU-MEDROL® 40 mg/2 ml
(méthylprednisolone) : Hypertension, tachycardie auriculaire, dyspnée et oedème pulmonaire chez un homme de 66 ans (décès).
(CRPV de Nice)

METHOTREXATE®
(méthotrexate) : - Rupture hémorragique lors d'une grossesse extra-utérine chez une femme de 28 ans (utilisation hors AMM).
- Avortement spontané à 17 semaines de gestation chez une femme de 27 ans (utilisation hors AMM).
Un point sur l'utilisation du méthotrexate dans les grossesses extra-utérines sera effectué par les CRPV de Rouen et Paris-Broussais.
(CRPV de Rouen)

Nitrate de propyl : Malaise lipothymique et névrite optique ischémique transitoire chez un homme de 28 ans.
(CRPV de Strasbourg)

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OXEOL®
(bambutérol)
+ RISORDAN®
(isosorbide dinitrate)
+ LOXEN®
(nicardipine)
+ LASILIX® faible
(furosémide)
+ DIFFU K®
(chlorure de potassium)
+ ROVAMYCINE®
(spiramycine)
+ SOLUPRED®
(prednisolone) : L'augmentation de posologie de l'OXEOL® (1 à 2 comprimés) a entraîné un coma diabétique chez une femme de 89 ans (décès).
(CRPV de Nantes)

PRIMOBOLAN®
(méténolone)
DANABOL®
(méthanediénone) : 1 observation de diminution du taux d'HDL, à 20 fois inférieure à la normale chez un homme de 29 ans prenant des produits anabolisants et pratiquant du culturisme. Le CRPV de St Etienne enverra un courrier à l'Agence du médicament. Le CRPV de Saint-Etienne transmettra cette observation au C.E.I.P. correspondant.
(CRPV de St Etienne)

PROGRAF®
(tacrolimus)
+ CORTANCYL®
(prednisone) : 3 cas de diabète sucré survenus chez des hommes de 21 ans, 22 ans et 52 ans.
(CRPV de Paris - Broussais)

RETROVIR®
(zidovudine)
+ EPIVIR®
(lamivudine) : Acidose isolée persistante à 6 semaines de vie chez un prématuré.
(CRPV de Paris - Saint-Vincent de Paul)

RETROVIR®
(zidovudine)
+ CRIXIVAN®
(indinavir)
+ EPIVIR®
(lamivudine) : Dysfonctionnement et raideur articulaires chez un homme de 61ans.
(CRPV de Nancy)

ROACCUTANE®
(isotrétinoïne) : Lésions chéloïdiennes chez un homme de 24 ans.

(CRPV de Paris Fernand-Widal)

SALAZOPYRINE®
(sulfasalazine)
+ INDOCID®
(indométacine)
+ Sels d'Or : Hypoacousie chez un homme de 47 ans.
(CRPV de Limoges)

TAZOCILLINE®
(pipéracilline, tazobactam)
CLINOMEL®
(solutions d'acides aminés
avec électrolytes) : Plusieurs cas de rupture de poche plastique avec projection de liquide lors de la reconstitution du médicament . Le CRPV de Nantes enverra un courrier à l'Agence du médicament en mentionnant le N° de lot du médicament incriminé. L'Unité de Pharmacovigilance transmettra cette observation à l'Unité Accidents de la Direction de l'Inspection des Etablissements de l'Agence du médicament.
(CRPV de Nantes)

TECHNESCAN MAG 3®
(solution injectable de
technetium 99mTc) : Urticaire chez un nourrisson de 6 semaines.
(CRPV de Saint-Etienne)

TENORDATE®
(nifépidine, aténolol) : Dépression et idée suicidaire chez une femme de 50 ans. Régression à l'arrêt du traitement. Pas de symptôme sous TENORMINE® (aténolol).
(CRPV de Toulouse)

TERALITHE® 250
(lithium)
+ DEPAMIDE®
(valpromide) : Augmentation de la lithiémie chez un homme de 45 ans. Cette interaction n'est pas mentionnée dans les RCP de ces spécialités. L'observation sera transmise au Groupe de Travail "Interactions".
(CRPV de Caen)

TRIFLUCAN®
(fluconazole) : Agranulocytose chez un homme 42 ans. La modification du RCP est en cours.
(CRPV d'Angers)

VIDORA®
(indoramine)
+ ACTAPULGITE®
(attapulgite de Mormoiron
activée)

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+ DOLIPRANE®
(paracétamol)
+ SPASFON®
(phloroglucinol,
triméthylphloroglucinol)
+ VOGALENE®
(métopimazine)
+ RHINUREFLEX®
(ibuprofène,
pseudoéphédrine) : Malaise, somnolence, allongement du QT et torsade de pointes chez un enfant de 12 ans ayant pris accidentellement 15 comprimés de VIDORA®.
(CRPV de Clermont-Ferrand)

VIRACEPT®
(nelfinavir) : 1 cas de gynécomastie a été rapporté, sans atteinte endocrinienne.
(CRPV de Paris - Pitié-Salpétrière)

VIRACEPT®
(nelfinavir) : Hypercholestérolémie à 17,85 mmol/l chez un homme de 47 ans.
(CRPV de Saint-Etienne)

YU PING FENG SANG
(plante chinoise importée
illégalement en France,
présentée sous forme
de gouttes buvables) : Gynécomastie chez un enfant de 15 mois. Cette observation a été transmise à la D.G.S.
(CRPV de Saint-Etienne)

ZELITREX®
(valaciclovir) : Syndrome confusionnel chez une femme (âge inconnu). Plusieurs cas sont rapportés dans la Banque nationale de pharmacovigilance. Cette spécialité a fait l'objet d'une DMI. Cet effet indésirable devrait donc prochainement apparaître dans le RCP.
(CRPV de Marseille)

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ZELITREX®
(valaciclovir)
+ DI-ANTALVIC®
(paracétamol, dextropropoxyphène)
+ ASPEGIC® 250
(acétylsalicylate de lysine)
+ AMLOR®
(amlodipine)
+EUPANTOL®
(pantoprazole)
+ LASILIX®
(furosémide) : Syndrome confusionnel, nausées et vomissements chez un homme de 75 ans.
(CRPV de Montpellier)

ZELITREX®
(valaciclovir)
+ HALDOL®
(halopéridol)
+ PARKINANE®
(trihexyphénidyle)
+ GLUCOPHAGE®
(metformine)
+ ZOVIRAX®
(aciclovir)
+ RENITEC®
(énalapril) : Confusion mentale, coma et insuffisance rénale chez une femme de 72 ans.
(CRPV de Montpellier)

ZERIT®
(stavudine)
+ EPIVIR®
(lamivudine)
+ CRIXIVAN®
(indinavir) : Acidose lactique et stéatose hépatique chez une femme de 34 ans.
(CRPV de Toulouse)

ZOMIG®
(zomitriptan)
+ DESERNIL®
(méthysergide)
+ PROZAC®
(fluoxétine) : Accident ischémique transitoire, hémiparésie et paralysie faciale chez une femme de 49 ans. Cette observation sera transmise au Groupe de Travail "Interactions".
(CRPV de Tours)

IV - POINT SUR INHIBITEURS DE L'ENZYME DE CONVERSION ET HYPONATRÉMIES

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Le Centre Régional de Pharmacovigilance de Créteil a présenté un point sur les hyponatrémies associées à la prise d'inhibiteurs de l'enzyme de conversion.

Après recherche dans la banque de données du Système National de Pharmacovigilance, 42 cas ont été retrouvés. 30 d'entre eux mentionnaient un diurétique associé et 9 observations mentionnaient également la prescription d'un inhibiteur de la recapture de la sérotonine.

L'imputabilité a été jugée douteuse dans 30 observations, plausible dans 4 cas, vraisemblable dans 1 cas et n'a pas été évaluée dans 6 cas.

Au total, devant une incidence faible, un mécanisme mal connu, des traitements hyponatrémiants associés dans la plupart des cas, aucune modification de l'information ne semble actuellement justifiée.

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V - ENQUÊTE OFFICIELLE SUR LES SYNDROMES D'HYPERSENSIBILITÉ ET LES TOXIDERMIES A L'ALLOPURINOL

Le Centre de Pharmacovigilance de Rouen a présenté les résultats de l'enquête officielle relative aux syndromes d'hypersensibilité et toxidermies à l'allopurinol.

L'allopurinol est un uricofreinateur empêchant la formation de l'acide urique par inhibition de la xanthine-oxydase. Il est commercialisé depuis de nombreuses années (première AMM obtenue en 1967).

La notification en 1997, de 2 cas de vascularite et de 3 cas de décès consécutifs à des syndromes de Lyell a conduit à la réalisation d'un point sur les atteintes cutanées graves dont les résultats ont été présentés au Comité Technique du 26 février 1998 où il a été décidé l'ouverture d'une enquête officielle.

Cette enquête a été réalisée à partir de toutes les observations d'effets indésirables cutanés et de syndromes d'hypersensibilité notifiées aux Centres Régionaux de Pharmacovigilance et aux laboratoires concernés[1] entre janvier 1993 et décembre 1997.

Un total de 265 observations d'effets secondaires cutanés survenus en Francea été analysé. Il s'agit de 29 cas de syndrome d'hypersensibilité, 37 cas de toxidermies bulleuses, 152 cas d'autres toxidermies, 30 cas d'urticaire et 17 cas de prurit.

1- Syndrome d'hypersensibilité : 29 observations
Il s'agit de 17 femmes et 12 hommes dont la moyenne d'âge est de 62 ans.
L'imputabilité est plausible dans 10 cas et vraisemblable dans 3 cas.
Le délai d'apparition de l'effet est inférieur à 1 mois dans 14 cas, compris entre 1 et 6 mois dans 7 cas, supérieur à 6 mois dans 6 cas et inconnu dans 2 cas.
Dans 12 cas, le traitement par allopurinol a été poursuivi pendant plus de 10 jours après la survenue de l'effet indésirable.
L'évolution a été fatale dans 4 cas (dont 3 cas où le décès est du à l'effet indésirable). Dans l'un de ces 3 cas, le décès est survenu à la suite de la réintroduction de l'allopurinol.
Dans 24 cas, l'évolution a été favorable, sans séquelle et dans 1 cas, elle est inconnue.

2- Toxidermies bulleuses : 37 observations
Il s'agit de 17 femmes et 20 hommes dont la moyenne d'âge est de 65 ans.
L'imputabilité est plausible dans 14 cas et vraisemblable dans 6 cas.
Le délai d'apparition de l'effet est inférieur à 1 mois dans 21 cas, compris entre 1 et 6 mois dans 7 cas, supérieur à 6 mois dans 1 cas et inconnu dans 8 cas.
L'évolution a été fatale dans 7 cas (dont 6 cas où le décès est lié à l'effet indésirable). Dans l'un de ces 6 cas, le traitement par allopurinol a été continué pendant encore 3 semaines après la survenue de l'effet indésirable.
Aucun des décès n'est lié à une réintroduction du produit.

[1] Les laboratoires ayant une AMM pour une spécialité à base d'allopurinol et commercialisée sur la période étudiée sont les suivants :
Glaxo Wellcome (Zyloric®), GNR Pharma (Allopurinol GNR®), Merck Sharp Dohme Chibret (Allopurinol MSD®), Lafon Ratiopharm (Allopurinol Ratiopharm®), Sanofi (Desatura®), Bayer (Allopurinol Bayer®).

Dans 22 cas, l'évolution a été favorable et sans séquelle, dans 2 cas il y a eu guérison avec séquelles, dans 2 cas, le sujet n'est pas encore rétabli et dans 4 cas, l'évolution est inconnue.
La réintroduction de l'allopurinol a abouti dans 1 cas à un syndrome de Lyell, dans 3 cas à un syndrome de Stevens-Johnson et dans 1 cas à une éruption bulleuse.

3- Autres toxidermies : 152 observations
Il s'agit de 56 femmes et 94 hommes (dans 2 cas, le sexe n'est pas précisé) dont la moyenne d'âge est de 65,5 ans.
L'imputabilité est plausible dans 25 cas, vraisemblable dans 25 cas et très vraisemblable dans 5 cas.
Le délai d'apparition de l'effet est inférieur à 30 jours dans 61 cas, compris entre 1 et 6 mois dans 35 cas, supérieur à 6 mois dans 36 cas et inconnu dans 20 cas.
Dans 124 cas, l'évolution a été favorable et sans séquelle, dans 2 cas il y a eu guérison avec séquelles, dans 8 cas le sujet n'est pas encore rétabli et dans 18 cas, l'évolution est inconnue.

Durant les 5 dernières années, les ventes d'allopurinol correspondent à plus de 458 millions de mois de traitement, ce qui correspond à une fréquence d'effets indésirables de :
- 1 cas de syndrome d'hypersensibilité pour 16 millions de mois de traitement,
- 1 cas de toxidermie bulleuse pour 12,07 millions de mois de traitement,
- 1 cas de toxidermie sans facteur de gravité pour 3 millions de mois de traitement.

Plusieurs points ont été soulignés par le rapporteur :
- l'importance du nombre de réintroductions positives (15 cas sur 218 dossiers de toxidermie et syndromes d'hypersensibilité), ce qui a conduit au décès dans 1 cas et à la survenue de toxidermies bulleuses dans 5 cas,
- l'importance du délai entre la survenue de l'effet et l'arrêt du traitement (de 1 à 5 semaines dans 9 cas),
- dans 20% des cas, les effets indésirables surviennent plus de 6 mois après le début du traitement,
- aucune observation de syndrome d'hypersensibilité ou de syndrome de Lyell n'est rapportée avec les spécialités autres que le Zyloric®, ce qui peut s'expliquer par les chiffres de vente nettement supérieurs du Zyloric®.
3 observations de toxidermie ont été rapportées avec des génériques après substitution du Zyloric® par ceux-ci (Allopurinol Ratiopharm® et Allopurinol MSD®).

En conclusion, le rapporteur propose de modifier le RCP des spécialités contenant de l'allopurinol:

- **rubrique "indications"** : ajout de "l'hyperuricémie modérée asymptomatique (uricémie < 90 micro-mol/l) n'est pas une indication au traitement par allopurinol"
- **rubrique "posologie"** : le rapporteur propose une table d'adaptation de la posologie chez l'insuffisant rénal et le sujet âgé, en fonction de la clairance de la créatinine, qui ne figure pas dans le RCP actuel de l'allopurinol. Cette adaptation permettrait d'empêcher l'accumulation d'oxypurinol, qui semble être le facteur déclenchant de la majorité des syndromes d'hypersensibilité.
- **rubrique "effets indésirables"** : Les laboratoires GLAXO WELLCOME ont déposé une demande de modification de la rubrique "effets indésirables" de Zyloric®. Le texte proposé par le rapporteur, en accord avec les laboratoires GLAXO WELLCOME est le suivant :

"*Les réactions cutanées sont rares, mais peuvent être graves. Elles peuvent se manifester par des éruptions prurigineuses, érythémateuses, papuleuses, vésiculeuses ou bulleuses.*

Les délais d'apparition peuvent être longs, parfois de plusieurs années. L'apparition de ces manifestations cutanées doit faire cesser le traitement et contre-indique définitivement sa reprise en cas de toxidermie bulleuse. Si l'éruption a été bénigne et après guérison, une réintroduction à doses très faibles et progressivement croissantes peut être envisagée si nécessaire. Toute nouvelle manifestation cutanée doit faire interrompre définitivement le traitement. De façon exceptionnelle, des éruptions cutanées plus graves telles que des

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syndromes de Lyell ou Stevens-Johnson ont été signalées.

Manifestations hépatiques *:*

Les atteintes hépatiques, exceptionnellement graves, observées au cours des syndromes d'hypersensibilité peuvent être cytolytiques ou cholestatiques. Quelques cas d'hépatite granulomateuse isolée, réversible à l'arrêt du traitement, ont été signalés.

Hypersensibilité généralisée *:*

Ce syndrome, associe à divers degrés fièvre, altération de l'état général, éruption cutanée (parfois sévère avec syndrome de Lyell ou de Stevens-Johnson, vascularite), polyadénopathie, atteinte hépatique, altération de la fonction rénale, hyperéosinophilie. Il est rare mais peut être fatal. Il survient principalement chez des sujets insuffisant rénaux, où âgés, chez lesquels une adaptation de la posologie à la clearance de la créatinine n'a pas été effectuée (cf. posologie). Il doit être recherché chez tout patient présentant un ou plusieurs des signes cités. Il impose l'arrêt immédiat du traitement et contre-indique formellement sa reprise. Ces manifestations peuvent survenir à n'importe quel moment du traitement mais le plus souvent dans les 4 premières semaines.
L'arrêt précoce du traitement est la condition essentielle à une évolution favorable en quelques semaines."

Le Comité Technique a souhaité que le rapporteur sollicite l'avis d'experts néphrologues, dermatologues et allergologues sur ses propositions de modification du RCP, avant la présentation du dossier à la Commission Nationale du 10 novembre 1998.

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VI - POINT SUR L'HÉPATOTOXICITÉ DE EULEXINE® (FLUTAMIDE) ET ANANDRON® (NILUTAMIDE)

Le centre de pharmacovigilance de Tours a présenté les résultats de l'enquête officieuse concernant les effets indésirables hépatiques rapportés avec Anandron® (nilutamide) et Eulexine® (flutamide).
Ces 2 spécialités sont des anti-androgènes non stéroïdiens, agonistes du LH-RH qui bloquent les récepteurs androgéniques prostatiques.

Anandron® (comprimé à 50 mg et à 150 mg) est une spécialité indiquée dans le traitement du cancer de la prostate métastasé en association avec la castration chirurgicale ou chimique. Cette spécialité est autorisée depuis 1986 et commercialisée par les laboratoires Cassenne.

Eulexine® (comprimé à 250 mg) est une spécialité indiquée dans le traitement du cancer de la prostate métastasé, autorisée depuis 1986 et commercialisée par les laboratoires Schering Plough.

Cette enquête officieuse a été motivée par la survenue en avril 1996 d'un cas d'hépatite fulminante d'évolution fatale chez un patient de 64 ans traité par Eulexine® et Zoladex® depuis 6 mois, associés à Haldol®, Nozinan®, Artane® et Pervincamine® depuis 20 ans.

Cas rapportés avec Anandron® (nitulamide)

Tous les effets indésirables hépatiques déclarés aux centres de Pharmacovigilance depuis la mise sur le marché de cette spécialité jusqu'au 27 août 1998 ont été pris en compte.

21 effets indésirables hépatiques ont été déclarés aux centres de pharmacovigilance chez des patients âgés en moyenne de 70 ans ± 11 ans [43-89 ans]. Dans 5 observations, il s'agissait d'une atteinte de type cytolytique, dans 3 cas d'une atteinte cholestatique, dans 2 cas d'une atteinte mixte, dans 10 cas d'une atteinte hépatique sans précision, et dans 1 cas d'une hépatite fulminante. Le délai de survenue est en moyenne de 21 semaines avec des extrêmes compris entre 1 semaine et 2 ans ; dans 12 observations le délai de survenue était inférieur à 6 mois.

La dose était inférieure ou conforme à la dose préconisée dans le Résumé des Caractéristiques du Produit dans 11 observations, supérieure dans 6 observations et non documentée dans 4 observations. Dans 10 observations sur 21 (48%), l'atteinte a été considérée comme sévère. Le degré de gravité, documenté dans 7 observations, a été noté grave dans 6 d'entre elles.

L'évolution a été favorable dans 12 observations, en cours dans 2 observations, fatale dans 1 observation et n'était pas connue dans 6 observations.

Cas rapportés avec Eulexine® (flutamide)

Une enquête officielle de pharmacovigilance sur les effets hépatiques de l'Eulexine® ayant été réalisée par le centre de Pharmacovigilance de Clermont-Ferrand en mai 1991 ; seuls les cas déclarés après cette date et avant le 27 août 1998 ont été pris en compte.

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Depuis 1991 38 effets indésirables hépatiques ont été déclarés aux centres de pharmacovigilance chez des patients âgés en moyenne de 72 ans ± 8 ans [57-89 ans]. Ces effets se répartissent en 10 atteintes de type cytolytique, 8 atteintes cholestatiques, 3 atteintes mixtes, 14 atteintes sans précision et 3 hépatites dont 1 nécrose hépatique et 2 cirrhoses. Le délai de survenue est en moyenne de 30 semaines avec des extrêmes compris entre 5 jours et 5 ans ; dans 17 observations le délai de survenue était inférieur à 6 mois. La dose était inférieure ou conforme à la dose préconisée dans le Résumé des Caractéristiques du Produit dans 32 observations, supérieure dans 1 observation et non documentée dans 5 observations. Dans 13 observations sur 38, l'atteinte a été considérée comme sévère. Le degré de gravité, documenté dans 23 observations, a été noté comme grave dans 17 d'entre elles.

L'évolution a été favorable dans 25 observations, "en cours" dans 6 observations, "guérison avec séquelles" dans 1 observation, "fatale" dans 4 observations (décès sans rapport avec l'effet dans 1 observation et décès dû à l'effet dans 3 observations) et n'était pas connue dans 2 observations.
A la rubrique "Mises en garde" de l'actuel Résumé des Caractéristiques du Produit, un contrôle périodique de la fonction hépatique est préconisé.

Le nombre de cas rapportés d'atteintes hépatiques est plus faible pour la spécialité Anandron® que pour la spécialité Eulexine®. En revanche, les atteintes hépatiques paraissent plus sévères avec Anandron®. Ceci laisse supposer soit que Eulexine® est à l'origine d'atteintes hépatiques moins sévères soit qu'une surveillance régulière des transaminases préconisée seulement dans le Résumé des Caractéristiques du Produit Eulexine® pourrait en limiter la sévérité.

Selon le rapporteur il paraît nécessaire de modifier la rubrique "effets indésirables" du Résumé des Caractéristiques du Produit de l'Anandron® afin de faire apparaître la possibilité d'hépatite sévère. De plus, la pertinence d'une surveillance systématique des transaminases devra être discutée.
La rubrique "effets indésirables" du Résumé des Caractéristiques du Produit de l'Eulexine® paraît adaptée. La périodicité du contrôle de la fonction hépatique préconisé dans le Résumé des Caractéristiques du Produit devra être discutée.

Au total, le comité technique a proposé de mettre en place une enquête officielle de pharmacovigilance pour les spécialités contenant le nilutamide ou le flutamide.
Le dossier sera examiné à la Commission Nationale de Pharmacovigilance de décembre 1998 en présence d'experts hépatologues.

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VII - POINT SUR L'HÉPATOTOXICITÉ DE LA CÉTIRIZINE (ZYRTEC®, VIRLIX®)

A la suite de l'examen d'une demande de modification et d'une demande d'éxonération relatives à la Cétirizine, le Centre Régional de Pharmacovigilance de Reims avait souhaité revoir la tolérance hépatique de ce produit. Un bilan des effets hépatiques notifiés avec la cétirizine est donc présenté en Comité Technique.
Cette évaluation s'est appuyée sur les données du Système National de Pharmacovigilance et les données des rapports périodiques de tolérance (PSUR) fournis par les laboratoires.

La Cétirizine est commercialisée par les laboratoires Synthélabo et UCB, respectivement sous les noms de spécialités Virlix® et Zyrtec®.

Les chiffres de ventes connus pour des périodes différentes sont les suivants :
- 14 972 405 boîtes de 15 cp pour Virlix® entre le 01/01/93 et 31/12/97
- 28 922 892 boîtes de 15 cp pour le Zyrtec® entre le 01/07/88 et le 31/12/94

L'analyse de la base nationale permet de retenir seulement 6 observations ; pour 5 d'entre elles, la chronologie est évocatrice et un cas de rechallenge positif a été publié par le CRPV de Tours.

Les cas rapportés par les laboratoires sont peu documentés, une cholestase associée à une cytolyse (transaminases à 5 N) chez un patient présentant une lithiase biliaire est décrite.

Les données de la littérature sont pauvres, HEPATOX signale trois publications dont le cas publié par le CRPV de Tours.

Les données de pré clinique et les essais cliniques ne montraient pas d'hépatotoxicité. Quelques cas ont été signalés en "postmarketing". Toutefois le caractère exceptionnel de ces derniers ne permet pas de modifier le libellé du Résumé des Caractéristiques du Produit.

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VIII - POINT SUR LA PHARMACOVIGILANCE EUROPÉENNE.

Compte-rendu du groupe de travail de Pharmacovigilance de l'Agence Européenne des 7 et 8 octobre 1998.

- **Terfénadine (article 12)** : les décisions de la Commission Européenne doivent être appliquées par les Etats Membres avant le 22 octobre 1998. En France, la suspension de l'AMM est effective jusqu'au 11 février 1999.

- **Anorexigènes (article 15a)** :
- fenfluramine / dexfenfluramine et amfépramone / phentermine : Les réponses aux questions adressées aux firmes sont attendues pour le 1er mars 1999 au plus tard et seront examinées par le Comité des Spécialités Pharmaceutiques (CSP) de mars 1999, en présence des firmes. L'opinion du CSP est attendue pour le mois d'avril 1999.
- Clobenzorex, fenbutrazate, fenproporex, mazindol, méfénorex, norpseudoéphédrine, phendimétrazine, propylhexédrine : initiation d'un article 15a (Autriche rapporteur, France et Allemagne co-rapporteur) afin de réévaluer le rapport bénéfice / risque de tous ces anorexigènes amphétaminiques. Le rapport d'évaluation circulera parmi les Etats Membres à partir du 30 janvier 1999 et sera discuté au CSP du mois de février 1999. L'opinion du CSP est attendue pour le mois d'avril 1999.
  L'Italie pose le problème du MEDIATOR® (benfluorex) en raison de l'analogie structurale avec la fenfluramine et craint la survenue de valvulopathies associées à l'utilisation de ce médicament. Ce problème sera discuté au prochain groupe de travail des 24 et 25 novembre 1998.

- **Sparfloxacine (ZAGAM®) (article 12, France rapporteur)** : le rapport d'évaluation de la France concernant le protocole de l'étude d'efficacité a circulé parmi les Etats Membres pour information et sera discuté lors du CSP du mois d'octobre 1998.

- **Kétorolac (TORADOL®) / risque hémorragique et augmentation de la mortalité** : le Royaume-Uni a présenté son rapport d'évaluation. Deux études italiennes et une synthèse espagnole ont été distribuées. Le Royaume-Uni analyse et prépare ses commentaires sur les trois études publiées adressées par la firme. Ce sujet sera de nouveau discuté lors du groupe de travail du mois de novembre 1998.

- **Sildénafil (VIAGRA®)** : le groupe de travail a jugé nécessaire la réalisation d'une étude post-marketing par la firme. Par ailleurs, l'infofax de l'Allemagne concernant les interactions avec les nitrates sera discuté lors du Working Party du mois de novembre 1998.

- **Inhibiteurs des protéases / lipodystrophies, hyperlipidémies, altération du métabolisme du glucose, pancréatites, complications cardio-vasculaires** : un libellé commun pour la classe des inhibiteurs des protéases a été finalisé pour adoption lors du CSP du mois d'octobre 1998 où sera choisie la procédure à appliquer (mesure de restriction urgente ou variation de type II). Les prescripteurs seront informés par le biais d'une lettre d'information où d'un bulletin national selon les Etats Membres. Il a, par ailleurs, été jugé nécessaire que les firmes ré-analysent les données cliniques et mettent en place des études de tolérance. Désormais, les produits de cette classe seront revus ensembles.

- **Analogues nucléosidiques / lipodystrophies, acidoses lactiques, stéatoses hépatiques** : la révision du libellé commun concernant les acidoses lactiques a été jugées nécessaire. La Suède adressera sa proposition de libellé commun aux Etats-Membres avant le CSP du mois d'octobre 1998. Il a par ailleurs été demandé aux firmes de revoir le problème des lipodystrophies dans le prochain rapport périodique actualisé de tolérance.

- **Tolcapone (TASMAR®) / hépatotoxicité** : Ce médicament est enregistré selon une procédure européenne

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centralisée avec l'Irlande comme pays rapporteur. A la suite de 2 notifications d'hépatite fulminante mortelle, la firme a fait une présentation orale lors du Working Party. Celui-ci a adopté un libellé pour le RCP et la notice qui seront modifiés dans le cadre d'une mesure urgente de restriction avec envoi d'une lettre d'information aux prescripteurs. Au total, 60 000 patients dans le monde dont 1500 en France ont reçu un traitement par TASMAR®. Lors des essais cliniques de phase III (pré-AMM), des observations d'élévations de transaminases hépatiques ont été signalées mais il n'y avait pas de différence statistiquement significative entre le groupe placebo et le groupe tolcapone. Ces atteintes hépatiques avaient fait l'objet d'une précaution d'emploi signalée dans le RCP.

- **Thiomersal (dérivé mercuriel) / hypersensibilité et neurotoxicité** : Le groupe de travail a approuvé les conclusions du pays rapporteur (Irlande) : inscription comme excipient à effet notoire, mise en garde dans le RCP concernant la neurotoxicité et la sensibilisation au produit (la neurotoxicité n'a cependant pas été retenue lors de l'utilisation de cet excipient dans les vaccins). Par ailleurs, l'OMS en 1990 avait recommandé de ne pas dépasser une exposition de 200 µg/semaine de mercure organique (correspondant environ à 400 µg de thiomersal) chez l'adulte (excepté chez la femme enceinte). En septembre 1998, le groupe de travail a recommandé de ne pas dépasser une exposition de 200 µg/an de mercure organique chez l'enfant quelque soit l'apport (alimentaire ou médicamenteux). Par ailleurs, la dose maximale pouvant être administrée chez l'enfant, dans le cadre du schéma vaccinal est de 500 µg de thiomersal pour les 2 premières années.

- **Contraceptifs oraux de troisième génération / risque cardio-vasculaire** : Le rapport de l'étude MICA a circulé parmi les Etats Membres pour information. Le groupe de travail a été informé de la création d'un groupe *ad hoc* d'experts sur les contraceptifs oraux et le risque cardio-vasculaire à compter du 15 octobre 1998.

- **Vaccins contre l'hépatite B / Atteintes démyélinisantes et pathologies auto-immunes**
la France a exposé les résultats des dernières études épidémiologiques et les mesures prises par le Secrétariat d'Etat à la Santé. La France et l'Allemagne ont envisagé la nécessité de modifier la rubrique "mise en garde et précautions d'emploi" du RCP, ce qui n'a pas été approuvé par les autres Etats Membres. Le groupe de travail de pharmacovigilance a proposé au CSP de réunir un groupe *ad hoc* d'experts pour une évaluation complète du problème.
La France fera circuler un rapport d'évaluation parmi les Etats Membres en novembre 1998.

- **Cisapride (PREPULSID®) / cardiotoxicité** : certains Etats Membres ont contre-indiqué l'utilisation du cisapride chez l'enfant de moins de 3 mois. Dans d'autres Etats Membres, il s'agit uniquement d'une contre-indication relative.
Dans la plupart des Etats Membres, le cisapride est utilisé dans cette tranche d'âge.
La France adressera un infofax afin de recueillir les indications du cisapride dans chaque Etat Membre puis adressera un rapport d'évaluation sur le bénéfice / risque du produit pour discussion en novembre 1998.

- **Albumine / augmentation de la mortalité** : le Royaume-Uni a présenté son rapport d'évaluation sur l'article de Cochrane paru dans le BMJ 1998 (Human albumin administration in critically ill patients : systelatic review of randomized controlled trials. Brit Med J ; 317 : 235-240). L'Allemagne a également fait circuler un rapport d'évaluation concernant cet article. Il existe également des études non citées dans l'article du BMJ. Ce sujet sera de nouveau discuté en janvier 1999 après réunion d'experts dans chaque Etat Membre.

- **Anti-histaminiques non sédatifs / révision des mises en garde sur les risques cardio-vasculaires** : le groupe de travail a approuvé l'ajout de recommandations dans le RCP de l'astémizole sous forme d'un libellé commun à tous les Etats Membres. L'utilisation chez l'enfant âgé de 2 à 6 ans est jugée acceptable si les firmes fournissent des données de sécurité rassurantes.

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Les données concernant l'ébastine seront discutées en novembre 1998.
Les Etats Membres doivent adresser à la Finlande leurs commentaires sur le projet de RCP de la loratadine. Le projet de RCP révisé sera discuté en novembre 1998.

- **Aprotinine (TRASYLOL®) / infarctus du myocarde, thrombose du greffon, augmentation de la mortalité** : les Pays-Bas doivent adresser un rapport d'évaluation actualisé prenant en compte les données des laboratoires BAYER, pour discussion en novembre 1998.

- **Isotrétinoine / dépression, psychose, suicide, effets indésirables cutanés** : les modifications de RCP relatives aux réactions psychologiques sont en cours de réalisation ou déjà réalisées dans les différents Etats Membres. La France a informé le groupe de travail que des réactions cutanées après épilation à la cire ont été rapportées. Cet effet indésirable est déjà mentionné dans le RCP de plusieurs Etats Membres et doit faire l'objet d'une variation de type II en France.

- **Lamotrigine (LAMICTAL®)** : La suède adressera un rapport d'évaluation sur l'utilisation du lamictal® en pédiatrie pour discussion en novembre 1998.

- **Traitements substitutifs hormonaux contenant des oestrogènes / augmentation du risque de cancer du sein** : le groupe de travail a jugé nécessaire d'introduire un libellé harmonisé dans le RCP de ces spécialités. Le libellé ainsi que la procédure a suivre seront discutés en novembre 1998.

- **Propacétamol (PRO-DAFALGAN®) / eczéma de contact** : une reformulation de ce médicament est en cours.

- **Inhibiteurs sélectifs de recapture de la sérotonine / syndrome de sevrage** : en juin 1998, le Royaume-Uni a proposé un libellé afin d'harmoniser le RCP de ces produits. Ce sujet sera discuté en novembre 1998.

- **Sertindole (SERDOLECT®) / cardiotoxicité / demande de modification par la firme** : le Royaume-Uni a adressé un rapport d'évaluation dans le cadre de la procédure de reconnaissance mutuelle. Les pays commercialisant cet anti-psychotique sont extrêmement inquiets en raison de notifications de morts subites (en rapport avec l'effet proarythmique) et envisagent de prendre rapidement des mesures. La France n'est pas concernée par cette procédure de reconnaissance mutuelle , il y a cependant quelques essais cliniques en cours.

- **Vigabatrin (SABRIL®) / atteinte du champ visuel** : une évaluation globale du rapport bénéfice / risque a été jugée nécessaire. Une procédure d'arbitrage dans la cadre d'un article 12 de la Directive 75/319/CEE à été engagée auprès du CSP par la Finlande.

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IX - ENQUETE OFFICIELLE SUR LA CARDIOTOXICITE DE LA NAVELBINE® (VINORELBINE)

La vinorelbine (Navelbine®) est un oncostatique du groupe des vinca-alcaloïdes. Elle est commercialisée en France depuis 1989, par les laboratoires Pierre Fabre Médicament avec pour indication première, le traitement des cancers du poumon non à petites cellules et depuis 1992, le traitement du cancer du sein métastatique. A la suite de la notification de 2 accidents ischémiques, une enquête sur les effets indésirables cardiaques a été réalisée par le centre de pharmacovigilance de Caen.
Les données de la littérature (8 publications), des centres régionaux de pharmacovigilance (28 dossiers) et de la firme (27 dossiers, doublons exclus) recueillies entre 1er janvier 1989 et le 21 juin 1998 ont été évaluées. Les données internationales de la firme ont finalement été exclues de l'analyse car elles étaient insuffisamment informatives et/ou n'apportaient rien de nouveau par rapport aux données françaises.
Les notifications spontanées comprennent 42 observations d'accidents ischémiques, 8 troubles du rythme et 5 accidents cardiaques divers.

Les accidents ischémiques.
Il s'agit de 12 infarctus du myocarde, 9 cas d'angine de poitrine et 21 douleurs thoraciques.
Le délai d'apparition était inférieur à 60 minutes dans 27 cas. L'évolution a été fatale dans 5 cas et favorable dans 32 cas. La notion de réintroduction positive est présente dans 18 dossiers. Aucun antécédent cardio-vasculaire n'a été signalé pour 20 dossiers (sur 35 où cette donnée a pu être renseignée), aucun antécédent de tabagisme pour 3 dossiers (sur 14 dossiers), les patients avaient eu une irradiation médiastinale dans 12 cas (sur 34 dossiers) ou une chimiothérapie cardiotoxique pour 15 patients (sur 34). Il n'existe pas de donnée sur le volume perfusé et la durée de perfusion.

Les troubles du rythme.
Il s'agit d'un arrêt cardio-circulatoire, de 5 tachycardies, d'un bloc auriculoventriculaire, d'un flutter auriculaire.

Les autres manifestations sont : 2 chocs cardiogéniques, une défaillance cardiaque congestive et un cas de péricardite.
Il pourrait s'agir d'une toxicité indirecte (induction d'un spasme coronarien) ou d'une toxicité directe (la vinorelbine exerçant son action sur les myofibrilles).
Une estimation de l'incidence des cas notifiés a été calculée à partir d'une posologie totale moyenne arbitrairement fixée à 400 mg par patient. Il existe très probablement une sous notification des cas (bien connue avec ce type de médicament). On peut remarquer aussi que le tabagisme n'est renseigné que pour 25% des observations alors que 65% des patients sont traités pour cancer broncho-pulmonaire non à petites cellules.

Au total, les accidents ischémiques représentent 67% de l'ensemble des cas avec une évolution fatale pour 12 % des cas.
Il doit être envisagé de mentionner une information sur ces effets indésirables cardiaques (douleurs précordiales, infarctus du myocarde, modifications transitoires de l'ECG symptomatique d'une ischémie coronaire ou d'un trouble du rythme) figure dans la rubrique effets indésirables du RCP. De plus une précaution d'emploi devrait être indiqué pour les patients présentant une pathologie cardiaque ischémique.
Ce dossier sera présenté à la prochaine Commission Nationale de Pharmacovigilance.

Il a été rappelé que le centre devra étendre cette enquête aux autres médicaments du groupe des vinca-alcaloïdes.

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X - POINT SUR LES LEUCÉMIES INDUITES PAR NOVANTRONE® (MITOXANTRONE)

La mitoxantrone est un cytostatique de la famille des anthraeènediones apparentée aux anthracyclines. Elle est commercialisée par les laboratoires Wyeth-Lederlé (A.M.M. obtenue en 1985) sous le nom de Novantrone®. Elle est indiquée dans le traitement du cancer du sein et particulièrement dans les cancers avancés du sein métastatiques, dans les leucémies aiguës myéloïdes et dans les lymphomes non hodgkiniens. La Novantrone® est également commercialisée dans 7 autres pays européens (Allemagne, Portugal, Grèce, Danemark, Suède, Norvège et Finlande).

La mitoxantrone est utilisée dans le traitement adjuvant du cancer du sein en per-opératoire en perfusion unique quel que soit le type de thérapeutique postérieure, ou dans les protocoles de type FMC (fluoro-uracile, mitoxantrone et cyclophosphamide) à la dose de 12 mg/m² en alternance avec la radiothérapie à raison de 4 à 6 cures successives.

Le Dr Catherine SGRO (CRPV de Dijon) et le Dr Gilles Chaplain (Registre des cancers gynécologiques de la Côte d'Or) ont présenté les résultats d'une enquête officieuse sur la hémopathies induites par la mitoxantrone.

Un total de 11 observations d'hémopathies survenues après l'administration de mitoxantrone ont été rapportées aux Centres Régionaux de Pharmacovigilance. Il s'agit de 9 cas de leucémies aiguës non lymphocytaires et de 2 myélodysplasies. En raison de la difficulté d'établir le diagnostic cytologique de myélodysplasie, seules les observations de leucémies aiguës non lymphocytaires ont été analysées dans cette enquête.

Concernant les 9 leucémies aiguës non lymphocytaires, l'âge moyen des patients lors du diagnostic du cancer du sein est de 45 ans, l'âge moyen des patients lors du diagnostic de la leucémie aiguë non lymphoblastique (LANL) est de 48 ans. Dans les deux cas cet âge moyen serait inférieur à l'âge moyen des patients dans la population générale chez qui un cancer du sein ou une LANL sont diagnostiqués. Le délai moyen de survenue entre le début de l'administration de la mitoxantrone et de la découverte de la LANL est de 23 mois. La dose cumulée moyenne de mitoxantrone administrée aux patientes est de 108 mg, ce qui semble indiquer que ces patientes ont bénéficié d'un traitement adjuvant non intensifié de leur cancer du sein (soit une dose de 12 mg/m² de mitoxantrone par cycle). Les LANL observées chez les patientes sont dans 50 p. cent des cas des LAM 3 selon la classification FAB. L'évolution a été fatale dans 4 cas sur 9.

6 observations d'hémopathies malignes ont été rapportées aux cours d'essais cliniques. Seules 2 observations de myélodysplasies n'ont pas été notifiées au système national ou publiées. Un total de 19 observations ont été rapportées au laboratoires Wyeth-Lederlé, 2 observations ont également été rapportées aux CRPV. Il s'agit de 18 LANL et de 1 myélodysplasie. Enfin, 21 cas de LANL ainsi que 2 cas de myélodysplasie ont été publiés.

Le Dr Gilles Chaplain a présenté les résultats d'une étude réalisée avec les données des registres de la Côte d'Or (registre des hémopathies malignes et registre des cancers gynécologiques).

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Dans ce département pour lequel le recueil peut être considéré comme exhaustif, 15 cas d'hémopathies ont été identifiés dans une cohorte de 3600 femmes ayant un premier cancer du sein entre 1982 et 1996 ; il s'agit de 10 cas de LANL et de 5 myélodysplasies.

Les résultats moutrent que :

- le risque de LANL dans cette cohorte est approximativement 12 fois celui de la population du département,
- le risque de LANL chez les femmes n'ayant pas reçu un protocole incluant la mitoxantrone est approximativement 4 fois celui de la population du département,
- le risque de LANL chez les femmes ayant bénéficié d'une traitement adjuvant incluant la mitoxantrone est approximativement 175 fois celui de la population du département,
- enfin, 7 des 10 cas de LANL dans cette cohorte sont survenus chez les 350 patientes ayant bénéficié d'un protocole incluant de la mitoxantrone.

Les données de la littérature confirment que les hémopathies survenant après une chimiothérapie sont habituellement des LANL et des myélodysplasies. Le risque relatif de développer une LANL ou une myélodysplasie après un cancer du sein serait multiplié par 1,5 par rapport à la population générale.

Le rapporteur a demandé un financement public ou privé afin de poursuivre cette étude.

Au vu de ces résultats le Comité Technique de Pharmacovigilance souhaite que :

1 - une enquête officielle de pharmacovigilance visant à évaluer la survenue d'hémopathies malignes après l'administration de mitoxantrone soit ouverte et que la suvenue d'hémopathies malignes après l'administration des anthracyclines soit étudiée,

2 - ce dossier soit présenté au groupe immunohématologie de l'Agence du 23 octobre 1998,

3 - un avis sur la qualité méthodologique de l'étude soit demandé.

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XI - DEMANDE DE MODIFICATION ET POINT SUR LA NÉPHROTOXICITÉ DE HOLOXAN® (IFOSFAMIDE).

Le centre de pharmacovigilance de Paris Saint-Vincent-de-Paul a présenté les compléments des résultats de l'enquête officieuse et de l'examen de la demande de modification de l'information de la spécialité Holoxan®.

En effet, à la suite de la présentation de ce dossier au comité technique du 16 octobre 1997, celui-ci avait demandé au centre de pharmacovigilance de compléter le travail par une analyse des effets neurologiques de l'ifosfamide et des interactions médicamenteuses et de recueillir l'avis d'experts. Un avis d'experts cancérologues, néphrologues et pédiatres a donc été sollicité.

Dans l'Application nationale de pharmacovigilance, entre 1985 et le 31 octobre 1997, 161 observations ont été enregistrées avec le principe actif ifosfamide. Parmi ces observations seuls les effets neurologiques associés ou non à une atteinte rénale, les effets rénaux et les effets urologiques ont été analysés représentant un total de 76 observations.

31 observations d'effets rénaux isolés ont été enregistrées. L'effet indésirable le plus fréquemment rapporté est l'insuffisance rénale aigüe. Le délai d'apparition précisé dans 23 observations se situe entre 1 et 30 jours dans 20 d'entre elles. L'évolution a été favorable dans 19 observations, inconnue dans 5 observations, "séquellaire" dans 3 observations (persistance d'une insuffisance rénale à distance) et fatale dans 4 observations.

20 observations d'effets neurologiques centraux sans atteinte rénale associée ont été signalées entre 1992 et 1997. Ces effets neurologiques ont été considérés comme sévères dans tous les cas. Les signes cliniques ont été une encéphalopathie dans 7 observations, un syndrome confusionnel dans 5 observations, un coma dans 2 observations, un syndrome cérébelleux dans 2 observations, et un accident vasculaire cérébral dans 1 observation. L'évolution a été favorable dans 10 observations, fatale dans 3 observations, avec séquelles dans 1 observation et inconnue dans 3 observations.

21 observations d'effets neurologiques associés à une atteinte rénale ont été rapportées. Dans toutes ces observations, l'atteinte a été considérée comme sévère. Ces effets se répartissent en 5 observations de coma avec insuffisance rénale ou anurie, 7 observations d'encéphalopathie avec insuffisance rénale, 2 observations de convulsions avec hyponatrémie ou hypokaliémie, 1 observation de myoclonie, 5 observations de syndrome confusionnel avec une insuffisance rénale ou une hyponatrémie et 1 observation d'hallucinations avec insuffisance rénale. Dans 15 observations, le délai d'apparition était inférieur à 5 jours. L'évolution a été favorable dans 13 observations, fatale dans 6 observations et inconnue dans 2 observations.

4 effets urologiques ont été enregistrés entre 1985 et 1992. Il s'agit de 3 cystites hémorragiques et d'une rétention urinaire. Dans aucune des observations, un traitement par mesna n'a été associé. L'évolution a été favorable dans 3 observations et notée "en cours" dans 1 observation.

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Pour les effets indésirables rénaux, selon le rapporteur, il paraît nécessaire de compléter l'information avec des modifications au niveau des rubriques "effets indésirables" et "mises en garde spéciales et précautions d'emploi" en insistant sur le risque de développer des lésions rénales chroniques plusieurs années après l'arrêt du traitement par ifosfamide et donc l'intérêt de surveiller les marqueurs de toxicité tubulaire rénale à distance.

Pour les effets indésirables neurologiques, selon le rapporteur, il paraît aussi nécessaire de modifier le libellé des rubriques "effets indésirables" et "mises en garde et précautions d'emploi".

Le rapporteur a fait des propositions de modifications de libellé des rubriques "mises en garde et précautions d'emploi", "effets indésirables", "interactions médicamenteuses" et "pharmacocinétique".

Au total, le comité technique a demandé de mettre les spécialités Holoxan® en enquête officielle de pharmacovigilance sous la responsabilité du centre de pharmacovigilance de Paris Saint-Vincent-de-Paul.

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XII - ENQUÊTE OFFICIELLE SUR L'ALVERINE (SPASMAVERINE®, HEPATOUM®, METEOSPASMYL®, SCHOUM®)

A la suite de la notification d'un choc anaphylactique sous METEOSPASMYL® avec réintroduction positive et après un bilan préliminaire sur cette spécialité, le CRPV de Bordeaux a été chargé d'une enquête officielle de pharmacovigilance concernant l'ensemble des spécialités contenant de l'alvérine.

L'alvérine est un antispasmodique musculotrope, proche de la papavérine et de la mébéverine. Quatre spécialités contenant de l'alvérine sont actuellement commercialisées : HEPATOUM® solution buvable (laboratoires Hépatoum), METEOSPASMYL® (laboratoires Mayoli-Spindler), SCHOUM® solution buvable (laboratoires Pharmygiène-Scat), SPASMAVERINE® (laboratoires Théraplix).

56 observations d'effets indésirables ont été retenues concernant uniquement les spécialités METEOSPASMYL® et SPASMAVERINE®, aucun effet indésirable n'ayant été notifié pour les deux autres spécialités. Il s'agit essentiellement d'observations de réactions allergiques et d'atteintes hépatiques. Les autres effets indésirables notifiés étaient notamment des effets neurologiques (10 cas) et cutanés (6 cas).

1. Réactions allergiques

18 cas de réactions allergiques ont été retenues : urticaire ou urticaire géante (5 cas), urticaire avec oedème et/ou oedème de la face et/ou gêne respiratoire (7 cas), oedème de la langue ou laryngé (2 cas), choc (4 cas) dont 3 avec réintroduction positive. Ces réactions sont survenues le plus souvent lors d'une première prise. Le délai d'apparition des symptômes après la prise est dans la majorité des cas inférieur à 2 heures. L'évolution a toujours été favorable. Les tests cutanés pratiqués chez trois patients ont été négatifs. 16 observations ont une imputabilité I3 (C3S1) et 2 cas une imputabilité II (C2S1).

2. Atteintes hépatiques

11 cas d'atteintes hépatiques sous METEOSPASMYL® ont été retenues. Dans 9 cas, un ictère ou un signe d'appel (prurit, douleur abdominale, asthénie) avaient motivé un bilan hépatique. Dans 6 cas, le bilan hépatique a mis en évidence une élévation à 20 N des ALAT. L'atteinte hépatique était le plus souvent cytolytique (8 cas). Dans 9 cas, la durée de traitement était inférieure ou égale à 3 mois. Dans 7 cas, l'effet était grave (6 hospitalisation, 1 décès d'étiologie inconnue). Un cas de réintroduction positive a été notifié. L'imputabilité des observations a été C3S2 dans 1 cas, C2S2 dans 5 cas, C2S1 dans 2 cas et C1S2 dans 1 cas et C1S1 dans 2 cas. Deux de ces cas ont été publiés en 1997.

L'analyse des observations montrent que l'alvérine entraîne rarement des réactions anaphylactoïdes et des atteintes hépatiques. Le Comité technique estime qu'il est nécessaire de créer une rubrique effets indésirables dans le RCP de l'ensemble des spécialités contenant de l'alvérine afin de mentionner la survenue de ces effets indésirables.

Le dossier sera présenté à la Commission Nationale de Pharmacovigilance du 10 novembre 1998.

XIII - POINT SUR ELOHES® (HYDROXYÉTHYLAMIDON) ET HÉPATOXICITÉ

L'ELOHES® 6 p. cent est une spécialité commercialisée par les Laboratoires Fresenius France, qui a obtenu une A.M.M. le 29 novembre 1990. Il s'agit d'une spécialité contenant un substitut du plasma, l'hydroxyéthylamidon (poids moléculaire de 200 KD) à 6 p. cent. L'ELOHES® est indiqué :

- dans le traitement des défaillances circulatoires aiguës lors de chocs hypovolémiques, hémorragiques, toxi-infectieux, traumatiques ou au cours des brûlures étendues,

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- dans le traitement des échanges plasmatiques en association avec l'albumine,

- en cas d'hémodilution normovolémique.

Sept observations de surcharge des cellules de Kupffer ont été rapportées entre Avril et Août 1998 au Centre Régional de Pharmacovigilance de Saint-Antoine. Les patients ont reçu une dose moyenne d'hydroxyéthylamidon de 1200 g (690 - 1800) pendant une période moyenne de 5,2 mois (1 mois 1/2 - 18 mois). Un examen histopathologique d'un fragment de parenchyme hépatique réalisé chez chacun des 7 patients a montré la présence de microvacuoles dans le cytoplasme des cellules de Kupffer. Cliniquement, les patients présentaient une anorexie associée à une altération de l'état général s'accompagnant d'une augmentation des GammaGT à 1,5 - 2 N.

Au vu de ces données, le Comité Technique de Pharmacovigilance a décidé d'ouvrir une enquête officielle concernant les atteintes hépatiques associées à l'administration d'hydroxyéthylamidon.

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XIV - QUESTIONS DIVERSES

a) Techniques :

- **DOXIUM® (dobésilate) :** Lors de l'examen de la DMI, 5 observations graves d'agranulocytose ont été signalés avec ce médicament. La gravité de ces effets indésirables nécessite l'ouverture d'une enquête officielle placée sous la responsabilité du CRPV de Brest.

- **Vaccins contre l'hépatite B :** Une réunion d'experts s'est tenu le 21 septembre 1998 à l'Agence du médicament. L'analyse des deux principales études montrent une tendance à l'augmentation du risque mais non significatif. De ce fait, aucune relation de causalité n'a pu être démontré entre la vaccination contre l'hépatite B et la survenue d'atteintes démyélinisantes du système nerveux central. L'incidence de l'hépatite B a fortement diminué, mais on estime à 100.000, le nombre de porteurs sains de l'hépatite B avec un risque de passage à la chronicité et d'apparition de cirrhose ou cancer du foie. La décision du Secrétaire d'Etat à la Santé, s'appuyant sur le principe de précaution, est de suspendre la vaccination systématique (mais non obligatoire) chez les pré-adolescents sans prise en compte du risque individuel. C'est un réaménagement de la stratégie vaccinale sans remettre en cause la vaccination pour la population à risque et les nourissons. A la demande du Secrétaire d'Etat à la Santé, la rubrique "précautions d'emploi" du RCP des vaccins sera étendue aux antécédents familiaux et personnels de pathologies auto-immunes. La dernière réunion de l'OMS conteste la décision de la France concernant la suspension de la vaccination systématique chez les pré-adolescents, arguant qu'il n'y a aucune raison de remettre en cause la stratégie vaccinale et que cette décision peut avoir des conséquences graves sur la population non protégée. La Communauté européenne demande à la France d'apporter des données supplémentaires pour inclure éventuellement ces nouvelles précautions d'emploi dans le RCP des 2 vaccins contre l'hépatite B enregistrés selon une procédure européenne de reconnaissance mutuelle :
  - HB VAX DNA® : France, Etat membre de référence ;
  - ENGERIX B® : Belgique, Etat membre de référence.

Il est demandé à tous les CRPV d'informer l'Agence du médicament avant la transmission de toute communication écrite à l'ensemble des professionnels de santé, différente du dossier de presse fourni par le Ministère de la Santé.

- **UTROGESTAN® (progestérone)** : à la suite de la survenue d'hépatites chez des femmes enceintes prenant ce médicament au cours du 2ème ou 3ème trimestre de grossesse dans le but de prévenir un accouchement prématuré, alors même que son utilisation est formellement contre-indiquée pendant cette période, et compte tenu du fait que ce médicament ne nécessite pas de prescription, une réévaluation du rapport bénéfice/risque de ce médicament sera effectuée . Une information des professionnels de santé avait été diffusée en juin et septembre 1998 par le laboratoire pharmaceutique commercialisant ce médicament.

- **EQUANIL® (méprobamate) :** une note sera envoyée à l'ensemble du réseau de toxicovigilance afin que soit évaluée l'efficacité des mesures prises depuis septembre 1997 (diminution de la taille des conditionnements : 30 et 50 comprimés) afin de limiter la toxicité de ce médicament lors des surdosages.

- **CLOMID® (clomifène) / Point sur l'utilisation détournée dans la stérilité masculine** (CRPV de Limoges) :
2 observations figurent dans la Banque nationale de pharmacovigilance concernant l'utilisation de ce médicament chez l'Homme (en dehors des indications mentionnées dans l'AMM) dans le but de stimuler la spermatogénèse. A ce jour, ce médicament n'est pratiquement plus utilisé pour traiter la stérilité masculine en raison du manque d'efficacité.

- **SUBUTEX® (buprénorphine)** : l'utilisation de ce médicament, déconseillée mais pourtant largement

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répandue chez la femme enceinte provoque des phénomènes de sevrage chez le nouveau-né. Ces phénomènes de sevrage semblent être moins importants lorsque l'administration du SUBUTEX® n'est pas associée à la méthadone. Mais il est difficile de savoir ce que la femme enceinte toxicomane a réellement aborbé : pour le savoir, des prélèvements sanguins et urinaires peuvent être réalisés. Des services de néonatalogie ont mis en place une étude pour mieux cerner les phénomènes de sevrage chez le nouveau-né dont la mère prenait des médicaments de substitution. Les CRPV pourraient être amenés à collaborer à ce propos. Ce sujet sera réexaminé lors de la présentation relative à l'élixir Parégorique dans le traitement du syndrome de sevrage du nouveau-né.

- **Grossesses et antirétroviraux** : le projet de suivi des enfants dont les mères ont été traitées pendant leur grossesse par des antirétroviraux sera à nouveau soumis au prochain Conseil scientifique de l'Agence du Médicament du 16 novembre 1998. Un compte-rendu sera fait lors du prochain CT du 19 novembre 1998.

- **HEMOCLAR® pommade (polyester sulfurique de pentosane)** : un point sur les risques de sensibilisation liés à l'application de la pommade HEMOCLAR® sera présenté par le CRPV de Limoges lors du prochain CT du 19 novembre 1998.

- **Vente illégale de millepertuis** : Une société commercialise et fait de la publicité auprès des psychiatres concernant un produit à base de millepertuis présenté comme ayant des propriétés antidépressive et anxiolytique, c'est-à-dire comme un médicament. L'Agence du médicament n'a reçu aucun dossier de demande d'AMM pour un produit composé de millepertuis, cité dans cette publicité. Le millepertuis ne fait pas parti des 34 plantes autorisées à la vente libre. Le dossier a été transmis à la DGS.

- **Radiopharmaceutiques** : ces produits ne figurent pas dans le dictionnaire des spécialités VIDAL, il est donc impossible de prendre connaissance du résumé des caractéristique du produit. A priori, les produits radiopharmaceutiques figureront dans le référentiel de l'Agence du médicament. Ce problème sera soumis à Monsieur Oustrin, Président du groupe des médicaments radiopharmaceutiques. Il sera notamment invité lors d'un prochain Comité technique pour discuter de la pharmacovigilance des produits radiopharmaceutiques.

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- **Suivi des vasoconstricteurs en pédiatrie** : Au vu des données de pharmacovigilance, le rapport bénéfice/risque des spécialités contenant des vasoconstricteurs a été considéré comme défavorable chez l'enfant de moins de 30 mois (Commission d'AMM du 04/07/97). De plus, il a été demandé aux laboratoires titulaires d'une autorisation de mise sur le marché de spécialités à base de vasoconstricteurs indiquées chez l'enfant de moins de 12 ans de fournir toutes les données actualisées permettant d'évaluer le rapport bénéfice-risque chez l'enfant de 30 mois à 12 ans.

L'ensemble des données disponibles permettant la réévaluation du rapport bénéfice-risque chez l'enfant de 30 mois à 12 ans ont été fournies par les laboratoires en mai 1998. Elles ont alors été analysées par la Commission d'Autorisation de Mise sur le Marché. Ses conclusions ont été les suivantes:

- concernant la spécialité SUDAFED® sirop, il n'a pu être conclu à un rapport bénéfice/risque favorable en l'absence de données d'efficacité fournies par le laboratoire mettant en évidence un bénéfice dans cette tranche d'âge et du risque de survenue de troubles neurologiques décrits plus fréquemment chez l'enfant en particulier au cours d'épisodes fébriles ou lors de surdosage.
Une contre-indication chez l'enfant de moins de 12 ans a donc été décidée.

- pour les spécialités ACTIFED® solution buvable et ACTIFED® comprimés, les données fournies dans le dossier ne permettaient pas d'établir le bénéfice chez l'enfant de moins de 12 ans. Il est apparu légitime à la Commission d'Autorisation de Mise sur le Marché conformément à la demande des laboratoires Warner Lambert de contre-indiquer les spécialités ACTIFED® solution buvable et comprimé chez l'enfant de moins de 12 ans.

- pour la spécialité RINUTAN®, solution buvable, le rapport bénéfice/risque a été jugé favorable chez l'enfant de plus de 30 mois.

- **Paracétamol et atteintes hépatiques :** il y a 2 ans, une observation d'hépatite fulminante avait été signalée chez un enfant ayant reçu du paracétamol à des doses supérieures à la posologie maximale recommandée. La littérature faisait également état de plusieurs publications concernant des atteintes hépatiques plus ou moins sévères chez des enfants recevant des doses supra-thérapeutiques. Une étude sur l'hépatatotoxicité du paracétamol à doses subnormales avait alors été mise en place sous la responsabilité des CRPV de Paris-St-Antoine et Tours mais n'a jamais aboutie. Le Comité Technique a décidé de clôturer cette étude.

- **QUINIMAX® (quinine, quinidine, cinchonine, cinchonidine) :** le CRPV de Strasbourg, lors du CT du 10 septembre 1998, signalait que les infectiologues du CHU de Strasbourg avaient observé un nombre important d'effets indésirables connus de la quinine avec le QUINIMAX®. Après consultation des différents CRPV, il semble qu'il n'y ait pas de problèmes particuliers en France concernant la tolérance de ce médicament.

- **EPITOMAX® (topiramate)** : 1 observation d'hépatite fulminante a été publiée dans la littérature. Ouverture d'une enquête officielle confiée aux CRPV de Toulouse et Paris-St Antoine.

- **SABRIL®** (vigabatrin) : plusieurs cas d'atteintes visuelles (rétrécissement du champ visuel) ont été rapportés. Ouverture d'une enquête officielle confiée au CRPV de Paris-Pitié Sapêtrière.

b) Administratives :

- **Procédure officielle de gestion des DMI** : cette procédure est en cours d'élaboration à l'Unité. Le schéma final concernant cette procédure sera présenté lors du prochain CT du 19 novembre 1998. Cette procédure imposera lors de la DMI, la soumission par l'entreprise pharmaceutique d'un rapport d'expert dans lequel

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figure une revue complète des données de tolérance ainsi qu'un argumentaire justifiant la demande.

- Une journée de pharmacovigilance aura lieu à la Cité des Congrès de Nantes, le lundi 15 mars 1999, organisée par le CRPV de Nantes.

- Nouveaux points (récapitulatif) :

- Méthotrexate / utilisation dans les grossesses extra-utérines : CRPV de Rouen et Paris-Broussais.
- Hémoclar® pommade / sensibilisation : CRPV de Limoges : CT du 19 novembre 1998.
- Benzodiazépines / accidents de la route : CRPV de St Etienne et Paris-Fernand Widal.

- Nouvelles enquêtes officielles (récapitulatif) :

- Vinca-alcaloïdes : extension de l'enquête officielle de la Navelbine® (vinorelbine) à tous les vinca-alcaloïdes / cardiotoxicité : CRPV de Caen.
- Novantrone® (mitoxantrone) / leucémies : CRPV de Dijon.
- Disulone® (dapsone, oxalate de fer) / agranulocytose : CRPV de St-Etienne.
- Innohep® (tinzaparine sodique) / accidents hémorragiques : CRPV de Toulouse et Rouen.
- Eulexine® (flutamide) - anandron® (nilutamide) / hépatotoxicité : CRPV de Tours.
- Holoxan® (ifosfamide) / néphrotoxicité : CRPV de Paris-St Vincent de Paul.
- Elohes® (hydroxyethylamidon) / hépatotoxicité : CRPV de Paris-St Antoine.
- Doxium® (calcium dobésilate) / agranulocytose : CRPV de Brest.
- Sabril® (vigabatrin) / atteintes visuelles : CRPV de Paris-Pitié Salpêtrière.
- Epitomax® (topiramate) / hépatotoxicité : CRPV de Toulouse et Paris-St Antoine.
- Buflomédil (réévaluation des mesures prises) : CRPV de Limoges.

- Nouveaux dossiers distribués :

- Toprec® sirop pédiatrique (kétoprofène) : demande d'AMM nationale pouvant devenir une reconnaissance mutuelle, France Etat membre de référence : CRPV de Caen.

- Floxyfral® (fluvoxamine) : demande d'extension d'indication aux "TOC chez l'adulte" : CRPV de Montpellier.

- Documents distribués :

- Nouveau calendrier des CT et CN pour l'année 1999 (les CT auront lieu désormais les mardis)

- Liste des événements indésirables graves inattendus notifiés à l'Unité Essais Cliniques

- Extrait du Journal Officiel du 07/07/98 : décision du 23/06/98 portant inscription au répertoire des groupes génériques mentionné à l'article R.5143-8 du code de la santé publique

- Compte-rendu du 20ème meeting OMS (Genève 29 sept - 2 oct 97)

- Calendrier des demandes de modification de l'information en cours - octobre 1998 -

- Liste des ATU cohorte

- Relevé d'avis du GT interactions n°28

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- Contenu du livret "interactions médicamenteuses" du dictionnaire des spécialités Vidal, édition 1999

- Questions relatives à la sécurité du manuel de préparation à l'accréditation (discussion lors du prochain CT du 19 novembre 1998)

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XV - TOUR DE TABLE DE LA LITTERATURE

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"Treatment with calcium antagonists does not increase the risk of fatal or non-fatal cancer in an elderly mid-European population : results from STEPHY II."
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JR. LAPORTE, X. VIDAL et al.
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Br J Clin Pharmac 1998, 46 (3) : 255.
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N. Engl. J. Med. 1998, 339 (13) : 900-5.
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E. TOMA
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(CRPV de Paris - Pitié-Salpétrière)

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"Peripheral neuropathy and lipid - lowering therapy."
PE ZIAJKA et al.
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(CRPV de Saint-Etienne)

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I. LECLERCQ et al.
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"A One-Year Trial of Lamivudine for Chronic Hepatitis B."
C.L. LAI and others.
N. Engl. J. Med. 1998, 339 (2) : 61-8.
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Annexe 3-8

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DIRECTION DE L'EVALUATION Saint-Denis, le
Unité de Pharmacovigilance

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 17 décembre 1998)

Etaient présents

M. RICHE : Président
M. BEGAUD : Vice-Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN H), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BECHTEL, M. BIOUR, Mme CARLHANT (représentant le CRPV de Brest), M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. ESCHALIER, M. ESCOUSSE, Mme GINISTY (représentant le CRPV de Paris - F. Widal), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR (suppléante de Mme JOUGLARD), Mme KREFT-JAIS, Mme LAINE-CESSAC, M. LAROUSSE, M. MERLE, M. MONTASTRUC, Mme LACOTTE (suppléante de M. MOULIN), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), Mme GERMAIN (suppléante de M. TRENQUE), M. VANDEL, M. VIAL.
Mme TUBERT-BITTER (représentant Monsieur le Directeur Général de l'INSERM),
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Assistaient à la réunion (C.R.P.V.) :
Mme BAGHERI, Melle CHAUMERLIAC, Mme CHIFFOLEAU, Mme DAVID- LAROCHE, Melle FERARD, Mme GENESTE, Mme GUY, Mme LAGARCE, M. QUESTEL, Mme RADAL, Melle RICHER, Mme ZENUT.

Unité de pharmacovigilance

Melle DELEAU
Mr DHANANI
Mme FOSSET-MARTINETTI
Mme LEREBOURS
Mme MORIN
Mme PARIENTE-KHAYAT
Melle PIERRON
Melle VERSTUYFT
Mme WECHSLER

Assistaient à la réunion (D.E.V.) :

Mme DEWILDE
Mme DURANTEAU
Mme GUENANECHE
Mme PAVLOVIC
Mme PELANNE
Mme REIDIBOYM
Mme REY QUINIO

Etaient excusés

M. BLAYAC
M. MALLARET
Madame le Directeur des Hôpitaux
Monsieur le Directeur Général de la Santé

I - ADOPTION DES PROCÈS-VERBAUX DES SÉANCES DU 22 OCTOBRE 1998 ET DU 19 NOVEMBRE 1998

- Séance du 22 octobre 1998

Le procès verbal a été adopté avec les modifications suivantes :

Page 4 : 29è ligne : remplacer “un examen annuel de la rate” par “une recherche annuelle de splénomégalie”.

Page 11 : Observation ZOMIG® : supprimer “décès”.

Page 16 : 6è ligne : remplacer “chimique, autorisée depuis 1986" par “chimique. Cette spécialité est autorisée depuis 1986".

Page 20 : 4è ligne : remplacer “Lypodystrophie” par “lipodystrophie”.

Page 21 : Dernière ligne : remplacer “proarythmogène” par “proarythmique”.

Page 23 : Paragraphe “troubles cardiaques” : remplacer “il s’agit d’un arrêt cardiaque, de 5 tachycardie” par “il s’agit d’un arrêt cardio-circulatoire, de 5 tachycardies”.

- Séance du 19 novembre 1998

Le procès verbal a été adopté avec les modifications suivantes :

Page 5 : 8è ligne : ajouter “en hydroxyéthylamidon” après “surcharge Kupfferienne”.

II - TOUR DE TABLE DES CAS MARQUANTS

Seuls sont signalés les cas d'effets indésirables donnant suite à des mesures (mise en enquête, notes, ...) ou faisant l'objet d'une mise au point. La liste complète des cas est jointe en annexe 1.

- **DEPAKINE CHRONO® (valproate de sodium) / CRPV d'Amiens** : 3 observations de syndrome extra-pyramidaux chez deux femmes de 67 et 72 ans et 1 homme de 73 ans.
➔ Un point sur Depakine® et syndromes extra-pyramidaux sera réalisé par le CRPV d'Amiens, pour le Comité technique du 23 février 1999.

- **LOCABIOTAL® (fusafungine) / CRPV de Reims** : oedème de Quincke laryngé majeur chez un jeune homme de 17 ans ayant des antécédents personnels d'allergie médicamenteuse. Décès.
Cette spécialité n'est pas inscrite sur liste. En octobre 1997, les annexes I et II de l'AMM ont été modifiées afin de rajouter la possibilité de survenue d'oedème de Quincke et très exceptionnellement de cas de bronchospasme et de choc anaphylactique nécessitant l'arrêt du traitement. Ces modifications ne figurent pas dans la mise à jour du dictionnaire Vidal 1998.
➔ Une note a été adressée au Directeur de l'Evaluation.

- **TISSUCOL® (colle biologique) / CRPV de Paris - St Vincent de Paul** : bronchospasme, urticaire, chute tensionnelle sans tachycardie puis état de choc chez un homme de 51 ans. Décès malgré l'administration de doses massives d'adrénaline. Ce patient était traité au long cours par du CARTEOL® (cartéolol).
Le TISSUCOL® est utilisé dans le cadre d'une ATU de cohorte. Un avis favorable a été donné récemment à la demande d'AMM. Les annexes I, II et III de l'AMM sont en cours de rédaction. Ce produit contient de l'aprotinine d'origine bovine. Les réactions anaphylactiques semblent fréquentes.
➔ Un point sur les réactions anaphylactiques avec les colles biologiques (TISSUCOL® et BIOCOL®) sera réalisé par le CRPV de Paris-St Vincent de Paul pour le Comité Technique du 23 février 1999.

- **Stallergènes DER PTERONYSSINUS / CRPV de Reims** : choc anaphylactique et arrêt cardiaque survenus 20 minutes après l'injection chez une enfant de 9 ans. Décès.
➔ Aucune autre observation n'a été rapportée avec ce lot de Stallergènes.

- **TOMUDEX® (raltitrexed) / CRPV d'Angers** : aplasie médullaire de stade IV chez un homme de 67 ans. Réadministration positive. Décès. Cet effet n'est pas mentionné dans le Résumé des Caractéristiques du Produit (RCP).
➔ Le CRPV d'Angers contactera le laboratoire afin de savoir s'il envisage de déposer une demande de modification de l'information.

- **VADILEX® (ifenprodil) / CRPV de Limoges** : malaise, perte de connaissance et mouvements cloniques survenant chez un homme de 47 ans, 5 minutes après l'injection de Vadilex®. La présentation de la plaquette d'information de Vadilex®, distribuée par le laboratoire, ne permet pas une lecture correcte de l'information.
➔ Le CRPV de Limoges adressera un courrier à ce sujet à la Commission de la Publicité de l'Agence du Médicament.

III - ENQUÊTE OFFICIELLE INNOHEP® (TINZAPARINE SODIQUE) ET ACCIDENTS HÉMORRAGIQUES : CRPV de Toulouse et Rouen.

Le CRPV de Toulouse a présenté les résultats de l'enquête officielle concernant les accidents hémorragiques

sous tinzaparine sodique, enquête initiée suite à la notification aux CRPV de Toulouse et Rouen de plusieurs cas graves d'hématomes ou d'hémorragies.
Les données de l'enquête révèlent l'existence d'une confusion dans l'utilisation de la tinzaparine par les professionnels de santé : plusieurs cas de mésusage (indications hors AMM) et de surdosage ont pu concourir à la survenue de certains effets indésirables graves hémorragiques. Deux facteurs de risque sont également retrouvés : sujets âgés (plus de 75 ans) et insuffisance rénale. Le rapporteur propose donc :
1) une amélioration du RCP de la tinzaparine par l'ajout, dans la rubrique "Mise en garde et précautions d'emploi" d'une phrase : "Il est impératif de ne pas dépasser les posologies recommandées. Dans le cas contraire, des accidents hémorragiques, parfois graves peuvent s'observer chez des sujets à risque (sujets âgés, insuffisants rénaux ....)"
2) des réunions d'information avec la collaboration des CRPV, réunions organisées par le laboratoire
3) une étude pharmacocinétique chez le sujet très âgé (> 75 ans)

Par ailleurs, le Comité Technique souhaite que l'enquête soit étendue à toutes les héparines de bas poids moléculaire.

Le dossier sera examiné à la Commission Nationale du 22 décembre 1998.

IV - ENQUÊTE OFFICIELLE LAMICTAL® (LAMOTRIGINE) : CRPV de Nantes

Le CRPV de Nantes a présenté les résultats de l'enquête officielle sur le LAMICTAL® (lamotrigine).
Tous les effets indésirables rapportés sont indiqués dans le RCP exceptée la notion de possible aggravation de certaines formes d'épilepsie qui devra être signalée dans la rubrique "effets indésirables".
Le CRPV complétera l'enquête avec les données internationales et les chiffres de vente du laboratoire.
Les nouveaux résultats seront présentés au Comité technique du 23 février 1999 puis en Commission nationale.
Le suivi de ce produit faisant l'objet d'une préoccupation européenne, l'avis de la Commission Nationale sera transmis aux Etats membres.

V - ENQUÊTE OFFICIELLE ZOLOFT® (SERTRALINE) : CRPV de Lyon et Clermont-Ferrand

Les CRPV de Lyon et Clermont-Ferrand ont présenté les résultats de l'enquête officielle sur le ZOLOFT® (sertraline).
Au vue de ces données, les centres rapporteurs proposent de modifier le RCP en ce qui concerne les effets indésirables suivants :
- hépatiques, digestifs, hématologiques, dermatologiques, cardio-vasculaires, endocriniens et génito-urinaires, métaboliques et hydroélectrolytiques, neuropsychiques, syndromes de sevrage, syndromes sérotoninergiques.

Ce dossier sera présenté à la Commission nationale du 10 février 1999.

VI - ENQUÊTE OFFICIELLE SUR LES ANTIGÈNES À VISÉE IMMUNOSTIMULANTE : RÉSULTATS PRÉLIMINAIRES : CRPV de Saint-Etienne

L'enquête officielle de pharmacovigilance sur les antigènes à visée immunostimulante, réalisée par le CRPV de Saint Etienne concerne cinq spécialités : BIOSTIM®, RIBOMUNYL®, IMOCUR®, IRS®19, RHINOPTEN®.

Dans un premier temps, compte-tenu du nombre d'observations très important pour chaque spécialité, seuls les résultats de l'enquête BIOSTIM® ont été présentés.

1190 notifications dans lesquelles apparait BIOSTIM®, quelle que soit sa forme, ont été recensées depuis sa commercialisation jusqu'au mois d'août 1998, seulement 300 observations ont pu jusqu'alors être étudiées. Devant le nombre important de cas graves, avec réintroduction positive, il semble nécessaire de faire apparaître ces effets dans le RCP.

Ces propositions de modification du RCP seront revues au comité technique du 23 février 1999, lors de la présentation des résultats de l'enquête concernant les autres antigènes à visée immunostimulante.

VII - POINT SUR LES ATTEINTES OESOPHAGIENNES SECONDAIRES A LA PRISE DE TETRACYCLINES EN COMPRIME : CRPV de Paris-Créteil

A la suite de la présentation d'un cas d'ulcère de l'oesophage dû à un traitement par Tolexine® (doxycycline) lors du comité technique du 13 novembre 1997, le CRPV de Créteil a été chargé de faire un point sur les atteintes oesophagiennes sous tétracyclines en comprimés.

Ceci fait suite à l'étude réalisée en 1994 par le CRPV de Tours portant sur les complications oesophagiennes secondaires à la prise de doxycycline (forme orale).
Considérant la survenue d'atteintes oesophagiennes et que le risque de ces atteintes était plus élevé avec la forme gélule que la forme comprimé, la Commission nationale de Pharmacovigilance avait proposé, le 06 octobre 1994, de modifier le RCP de toutes les spécialités (forme gélule) contenant de la doxycycline (excepté la VIBRAMYCINE®, sous forme de comprimés pelliculés) aux rubriques "Effets indésirables, Mode d'administration et Précaution d'Emploi" et de réévaluer le dossier pharmaceutique, afin que la forme comprimé pelliculé remplace la forme gélule.

Le comité technique de Pharmacovigilance a décidé de mettre en enquête officielle la doxycycline, sous la responsabilité des CRPV de Créteil et Tours. Les résultats devront être présentés sous la forme d'un récapitulatif des observations rapportées depuis octobre 1994, par forme (gélules, comprimés), par produit (y compris les génériques), par année avec les chiffres de vente.

VIII - ENQUÊTE OFFICIELLE ROACCUTANE® (ISOTRETINOÏNE) : CRPV de Tours, Paris - Broussais et Rouen

Les CRPV de Tours, Paris-Broussais et Rouen ont présenté les résultats de l'enquête officielle concernant le Roaccutane®, portant sur les effets indésirables suivants:

- modifications de la glycémie - diabète
- effets indésirables pleuro-pulmonaires
- effets indésirables visuels
- effets indésirables digestifs
- effets indésirables ostéo-musculaires
- effets sur le métabolisme lipidique
- troubles psychiatriques.

Les rapporteurs ont donc proposé des modifications du RCP au niveau des rubriques "effets indésirables", "mises en garde et précautions d'emploi" concernant les modifications de la glycémie-diabète, les effets indésirables pleuro-pulmonaires, visuels, ostéo-musculaires, et les effets sur le métabolisme lipidique.

Il a été rappelé que la mention de troubles psychiatriques à type de psychose, ainsi que les risques de suicide et de tentative de suicide ont été renforcés dans le RCP, dans le cadre de l'enquête de pharmacovigilance européenne (Royaume-Uni rapporteur).

Par ailleurs, un expert pneumologue sera chargé de revoir les cas d'effet pulmonaire pour faire la part entre un bronchospasme et une crise d'asthme.
Cette enquête officielle sera présentée en Commission Nationale le 10 Février 1999.

IX - ENQUÊTE OFFICIELLE MEDIATOR® (BENFLUOREX) : CRPV de Besançon

Le CRPV de Besançon a présenté les résultats de l'enquête officielle sur le MEDIATOR® (benfluorex) ainsi que les données sur le métabolisme de la molécule.

Bilan des effets indésirables :
Les effets cutanés et / ou allergiques pourraient être rajoutés dans le RCP.

Métabolisme :
La norfenfluramine produite à partir du benfluorex est retrouvée dans les urines avec une concentration de 2 % (contre 7,4 % pour la norfenfluramine produite à partir de la fenfluramine). Il est donc peu probable que le benfluorex induise les mêmes effets que la fenfluramine.

L'Italie qui propose que le benfluorex soit inclus dans l'article 15a européen relatif aux fenfluramines, a en charge une enquête sur cette molécule. Le CRPV de Besançon adressera une copie de son rapport à l'Agence Italienne qui prépare un rapport pour le groupe de travail de pharmacovigilance européen de février 1999.

X - POINT PHARMACOVIGILANCE EUROPEENNE

- Vigabatrin / rapport bénéfice risque / atteintes du champ visuel / article 12 :
Un article 12 a été initié avec la Finlande comme pays rapporteur et le Royaume-Uni comme pays co-rapporteur.
GABITRIL® : La France, en tant qu'Etat membre de référence pour la tiagabine (GABITRIL®) a fait part de son inquiétude quant aux troubles du champ visuel rapportés dans le 4ème PSUR de cette spécialité.
A ce sujet, une réunion à eu lieu à l'Agence du Médicament, en présence du CRPV de Toulouse (responsable de l'enquête officielle) et des laboratoires SANOFI. A l'issu de cette réunion, il a été proposé d'ajouter, dans le RCP de la tiagabine, une précaution d'emploi relative aux troubles du champ visuel.

- Sertindole / morts subites / article 15 :
Alors qu'un article 15 est en cours, la plupart des Etats membres ont suspendu l'autorisation de mise sur le marché du produit. Dans les Etats où il n'est pas autorisé, l'inclusion de patients dans les essais cliniques a été également suspendue.
La France n'est pas concernée par cette procédure de reconnaissance mutuelle.

- Kétorolac (TORADOL®) / risque hémorragique et augmentation de la mortalité :
Un concensus concernant les indications et les doses recommandées a été jugé nécessaire afin que chaque Etat membre concerné effectue ces modifications au niveau national. Le Toradol® n'est pas commercialisé en France.

- Inhibiteurs de protéases (indinavir, nelfinavir, ritonavir, saquinavir) / rhabdomyolyse :
Le libellé commun concernant les rhabdomyolyses, pour la classe des inhibiteurs de protéases sera soumis pour adoption au CSP de décembre 1998.

- Inhibiteurs de la cathécol O-méthyltransférase - Tolcapone (TASMAR®) / suspension de l'AMM -

Entacapone (COMTESS®, COMTAN®) / mesure urgente de restriction :
Comme suite à l'avis donné par le Comité des Spécialités Pharmaceutiques de l'Agence Européenne d'Evaluation des médicaments et la recommandation de la Commission Européenne, l'Agence du Médicament a décidé de suspendre l'utilisation du TASMAR® en France sous toutes ses formes (comprimés dosés à 100 mg et 200 mg à compter du 17 novembre 1998.
Le RCP de l'entacapone a ete modifié dans le cadre d'une mesure urgente de restriction le 23 novembre 1998 afin d'y inclure la possibilité de survenue de rhabdomyolyses et d'un syndrome malin des neuroleptiques.

- Rituximab (MABTHERA®) / mesure urgente de restriction :
A la demande du CSP, les laboratoires sont venus exposer les données concernant les effets allergiques du rituximab aux membres du groupe de travail de pharmacovigilance et aux membres du CSP. Une proposition de modification du RCP, une lettre d'information aux prescripteurs et une liste de questions aux laboratoires ont été finalisées.

- Inhibiteurs sélectifs de recapture de la sérotonine / syndrome de sevrage, dépendance et utilisation au long cours :
Le Royaume-Uni résumera son rapport d'évaluation en tenant compte de la lettre de M. C. Medawar intitulée "SSRIs, EMEA and the CPMP"et des compléments apportés par l'Allemagne et la France. Ce dossier sera de nouveau discuté en février 1999.
Par ailleurs, le groupe de travail de pharmacovigilance demande au groupe de travail "sécurité" d'évaluer les données pré-cliniques sur le potentiel de dépendance de cette classe médicamenteuse.

- Alendronate (FOSAMAX®) / atteintes oesophagiennes et gastro-intestinales :
Malgrès le respect des précautions d'emploi, il existe toujours des notifications préoccupantes d'atteintes digestives, parfois mortelles.
Certains Etats membres ont informé ou vont informer les prescripteurs sur le risque d'atteintes digestives survenant avec l'alendronate. Les données disponibles jusqu'à présent ont été jugées insuffisantes pour modifier le RCP. Le Royaume-Uni demandera au laboratoire les résultats d'un essai clinique et d'une étude épidémiologique en cours aux USA, dès qu'ils seront disponibles. Il sera également demandé au laboratoire de fournir des données sur une étude épidémiologique utilisant le GPRD ainsi qu'un rapport étudiant la possibilité de reformuler la spécialité.

- Anti-histaminiques non sédatifs / mise en garde sur les risques cardio-vasculaires :
Le libellé de la loratadine sera finalisé par procédure écrite. Les données concernant l'ébastine seront discutées en février 1999.

- Produits de contraste iodés de haute osmolarité (HOCM) / réévaluation du risque :
Le risque associé aux HOCM est plus élevé que celui associé aux produits de faible osmolarité. Les allemands veulent retirer ces produits du marché. La majorité des Etats membres souhaitent discuter de ce problème au niveau national. Ce sujet sera de nouveau discuté en mars 1999.

- Traitements substitutifs hormonaux / augmentation du risque de cancer du sein :
Le Royaume-Uni souhaite ajouter les résultats d'une méta-analyse dans la rubrique " mises en garde et précautions d'emploi ". La rédaction d'un libellé commun concernant cette rubrique a été jugée nécessaire. Le Royaume-Uni complète son rapport en tenant compte des RCP des différents Etats membres, pour discussion en février 1999.

- Inhibiteurs de recapture de la sérotonine / risque hémorragique :
La Suède adressera un rapport sur les inhibiteurs de recapture de la sérotonine et le risque hémorragique à tous les Etats membres pour discussion en février 1999. Elle souhaite une harmonisation des RCP car elle considère qu'il s'agit d'un effet de classe.
En France, les résultats de l'enquête officielle seront présentés par le CRPV d'Angers, au Comité technique du 26 janvier 1999.

- Immunoglobulines polyvalentes / atteintes rénales :
A la suite de la diffusion par la FDA de nouvelles recommandations aux professionnels de santé, la France adressera aux Etats membres un rapport sur ce sujet.

XI - QUESTIONS DIVERSES

1) Questions diverses techniques :

- **Psychotropes et usage criminel** : le CRPV de Paris - F. Widal, responsable de l'enquête officieuse, a présenté le modèle de la fiche de recueil des observations de "soumission chimique" (cf. Annexe 3). Il est instamment demandé aux CRPV de transmettre dans les meilleurs délais au CRPV de Paris - F. Widal, les observations dont ils pourraient avoir connaissance.
Psychotropes et troubles comportementaux majeurs : le CRPV de Paris - F. Widal, responsable de l'enquête officieuse, a présenté le modèle de la fiche de recueil des observations qui devra être remplie en plus de la feuille d'observation de pharmacovigilance habituelle (cf. Annexe 4).

- Le CRPV d'Angers a été contacté par un médecin au sujet des suppositoires HEXAPNEUMINE enfant® qui sont désormais contre-indiqués chez l'enfant de moins de 12 ans sans la moindre information des prescripteurs. Seuls les pharmaciens d'officine ont été informés par les laboratoires. Il s'agit en fait d'une modification dans la cadre de la validation de l'AMM de cette spécialité (la dose de pholcodine par prise n'est pas adaptée aux enfants de moins de 12 ans).
Le CRPV de Rennes a été contacté pour le même type de question concernant les suppositoires TRENTADIL enfant® (spécialité validée, désormais contre-indiqués chez l'enfant de moins de 12 ans).
➔ Il est demandé aux CRPV recevant des questions suite à la révision de RCP dans le cadre de la validation, d'adresser un courrier à l'unité de pharmacovigilance qui le transmettra à la Direction de l'évaluation.

- Le CRPV de Limoges souhaite attirer l'attention sur le fait que les monographies des diurétiques dans le dictionnaire Vidal ne sont pas homogènes en ce qui concerne les rubriques "précautions d'emploi" et "contre-indications".
Une note sera adressée à l'évaluateur de la DEV en charge de cette classe thérapeutique.

- Le CRPV de Besançon a proposé de faire une revue de la littérature concernant la pharmacogénétique, lors d'un prochain Comité Technique.

- Le CRPV de Bordeaux a fait remarquer que la monographie de DIMETANE expectorant enfant® dans le dictionnaire Vidal contient quelques incohérences, a savoir des informations non adaptées à l'enfant. En effet, le sirop est contre-indiqué en cas de rétention urinaire liée à des troubles urétro-prostatiques et l'attention des conducteurs de véhicules est attirée sur les risques de somnolence.
Il s'avère que ces informations doivent figurer dans le RCP, dans le cas où le produit serait administré à un adulte, même s'il est destiné à l'enfant.

- Une remarque a été faite quant au problème des médecins qui ne notifient pas dans le cadre de la notification spontanée les effets indésirables liés aux antirétroviraux, notament lorsque les patients sont inclus dans une cohorte.

- Une réunion avec l'ANRS est prévue début 1999 au sujet des troubles du métabolisme glucido-lipidique liés aux antirétroviraux. Par ailleurs, un groupe de travail concernant ce sujet a été créé à l'Agence Européenne.

2) administratives :

- Lorsque les CRPV présenteront en Comité technique un rapport concernant un médicament enregistré selon une procédure européenne (procédure centralisée ou reconnaissance mutuelle), il est proposé que ce rapport soit directement rédigé en anglais et qu'il soit accompagné d'un résumé en français.

- Il est rappelé aux CRPV que malgré les difficultés rencontrées dues au manque de moyens, la saisie et le

recueil des effets indésirables graves est une mission prioritaire (cf. Art. 5144-14 du Décret du 13 mars 1995).

- <u>Nouveaux points (récapitulatif)</u> :

- Colles biologiques et choc allergique : CRPV de Paris St-Vincent de Paul (CT 23/02/99)
- DEPAKINE® et syndromes extra-pyramidaux : CRPV d'Amiens (CT 23/02/99)

- <u>Nouvelles enquêtes officielles (récapitulatif)</u> :

- Héparines de bas poids moléculaire et accidents hémorragiques : CRPV de Toulouse
- Doxycycline et atteintes oesophagiennes : CRPV de Tours et Créteil

- <u>Documents distribués</u> :

- Calendrier des demandes de modification en cours - décembre 1998 -
- Liste des évènements indésirables graves inattendus notifiés à l'Unité Essais Cliniques

Annexe 3-9

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Annexe 3-9

CHU Jean Minjoz 25030 BESANCON Cedex

MEDIATOR (benfluorex)

ENQUETE OFFICIELLE

Comité Technique du 17 Décembre 1998

Confidentiel

M.DAVID-LAROCHE
P.BECHTEL

Annexe 3-9

Le MEDIATOR (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par le laboratoire BIOPHARMA, sous forme de comprimés, dosés à 150 mgL
La posologie recommandée est de 3 comprimés par jour.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène.
(Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Une enquête officieuse a été ouverte, suite à la première mise au point des effets indésirables du benfluorex, présentée lors du Comité Technique du 11 juillet 1995.
Deux mises au point ont été faites :

-le 30 Avril 1998 sur les effets indésirables du benfluorex, rapportés aux CRPV
-le 10 Septembre 1998 sur le métabolisme et les chiffres de vente du benfluorex.

<u>Les effets indésirables rapportés dans les RCP sont :</u>

- effets digestifs : nausées, vomissements, gastralgies, diarrhée
- asthénie
- somnolence
- état vertigineux

2

Annexe 3-9

DONNEES PHARMACOCINETIQUES ET METABOLIQUES
CHLORHYDRATE DE BENFLUOREX

I- Pharmacocinétique.

L'absorption gastro-intestinale du chlorhydrate de benfluforex est complète et rapide, le Tmax est compris entre 1h et 2h.
Le volume de distribution est de 0.37+/- 0.03l/kg chez l'homme.
Chez le rat il est de 1.4l/kg.
Chez le chien de 1.6l/kg.
Chez le singe de 0.36l/kg.
Chez le babouin de 0.31l/kg

On notera que le volume de distribution est identique chez les primates et chez l'homme.

II. Métabolisme.

Le benfluorex est rapidement métabolisé au niveau du foie. Il produit au moins 9 métabolites. (Fig 1). Des données récentes utilisant notamment des méthodes de détection spécifiques et sensibles ont permis de montrer qu'il existait deux métabolites principaux (fig 2) :

- le 1-(3 trifluorométhylphényl)-2N-2-(carboxymethyl)amino propane (S1475)
- la norfenfluramine (S 585)

Une étude réalisée chez 6 volontaires sains qui ont reçu pendant 14 jours une dose quotidienne de 3fois 150mg de benfluorex, a montré que :

- l'état stationnaire était atteint en 4 à 5 jours
- au bout des 14 jours la concentration plasmatique de benfluorex était très faible, autour de 10ng/ml, la concentration plasmatique du métabolite S1475 était très importante, aux alentours de 200ng/ml, la concentration plasmatique du norfenfluramine ne dépassait pas 30ng/ml (fig 3).

Il est très intéressant de comparer les métabolites produits par la biotransformation de benfluorex à ceux produits par la biotransformation de la fenfluramine (fig 4). La norfenfluramine représente la voie principale du métabolisme de la fenfluramine avec des concentrations urinaires de 7,4% de la dose pour la forme libre et de 50,7% pour la forme conjuguée à l'acide glucuronique.

Sans qu'il y ait d'explications à partir de la fenfluramine il semble que la norfenfluramine produite ne subit aucune biotransformation supplémentaire, alors que la norfenfluramine produite à partir de benfluorex est transformée en 3-trifluorométhylphényl-1-hydroxypropanone-2. Ce qui explique qu'on ne trouve pas plus de 2% de norfenfluramine dans l'urine.

Annexe 3-9

I. ATTEINTES HEPATIQUES :

23 cas d'hépatites ou de perturbations de la biologie hépatique ont été notifiés : (le benfluorex est le seul suspect ou d'imputabilité égale ou supérieure aux médicaments associés)

-15 aux CRPV, 9 au laboratoire (dont 1 doublon) .

Elles concernent 15 femmes (âge moyen : 55,1 ans) et 8 hommes (âge moyen (58,6 ans)

Dans 7 cas le benfluorex a une imputation plausible:

DJ9300271 : Femme de 50 ans , traité pendant 2 semaines par MEDIATOR, une préparation d'aubépine, 200mg, et amfépramone 35 mg ,citrarginine, Veinobiase et depuis 1 mois et demi par AXONYL.
ALAT = 625 UI/L, ASAT : 303 UI/L, γGT: 656 UI/L, Ph.Alc. : 198 UI/L.
Evolution favorable 2 semaines après l'arrêt du traitement ,sauf les γGT qui sont encore à 171 UI/L

NY8804047=060K94 (doublon) : homme de 47 ans, traité par MEDIATOR, pendant 6 mois, puis 3 mois (après un arrêt de 3 mois)
ALAT : 375 UI/L , ASAT : 105 UI/L, γGT : 182 UI/L
L'évolution est lentement favorable dans un délai de 2 mois.

DJ9100164 : homme de 61 ans, éthylique chronique, traité depuis 4 ans par RENITEC, DOGMATIL, LASILIX, depuis 1 an par RYHMODAN et depuis 3 ans par MEDIATOR.
ALAT : 1350 UI/L, ASAT : 410 UI/L, γGT : 280 UI/L
La régression de l'hépatite est partielle à l'arrêt de toutes les thérapeutiques, chez ce patient éthylique.

NC9600020 :Femme de 39 ans, traité par MEDIATOR depuis 8 mois.
ALAT: 205 UI/L (4N), ASAT : 89 UI/L (2N), γGT: 134 UI/L
L'évolution est favorable à l'arrêt du MEDIATOR.

NY9608618 : Femme de 36 ans, traité par MEDIATOR, pour cure d'amaigrissement pendant 4 mois.
ALAT : 126 UI/L, ASAT : 41UI/L, γGT : 110 UI/L
L'évolution est favorable à l'arrêt du MEDIATOR.

BX9700024 : Femme de 59 ans, apparition d'un ictère avec prurit, après 4 semaines de traitement par MEDIATOR. (LOXEN et ACUILIX sont pris au long cours)
ALAT: 1017 UI/L (30N), ASAT : 391 UI/L (10N), γGT : 1042 UI/L, Ph. alc. : 907 UI/L (4N)

10010325 : Homme de 42 ans présentant une cytolyse modére et une cholestase discrète 3 semaines après le début d'un traitement par MEDIATOR, pour hypertriglycéridémie et diabète modéré.
L'évolution est favorable à l'arrêt du MEDIATOR.

Dans 1 cas, l'imputation est vraisemblable :

Observation 120039 : observation très succinte du laboratoire, concernant une augmentation des γGT (169 UI/L) , chez une femme de 70 ans, qui était traitée par ailleurs par Diamicron, Icaz et Hypérium. La réintroduction a été positive.

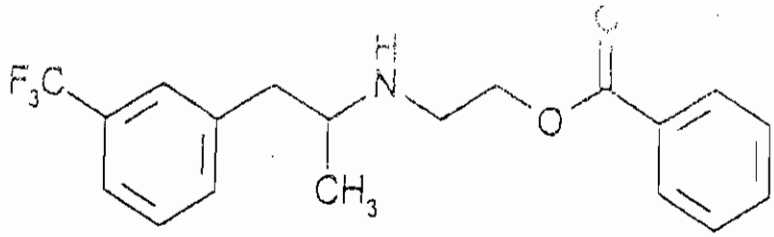
Dans 15 cas, l'imputation est douteuse : dont 10 C2,S1, 5 C1,S1

Annexe 3-9

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
Hépatite mixte						
RE8660098	M,82	1 mois	C2,S1	CORVASAL, DIAMICRON TADENAN	A	
DJ9300271	F,50	2 sem.	C2,S2	Amfépramone, C2,S2	A	γGT↑
10060607	M,61	15 j	C2,S1	GLUCOPHAGE RETARD, C1,S1 DIAMICRON, C1,S1 SECTRAL, C1,S1 RISORDAN, C1,S1	A	
Hépatite cytolytique						
NY8804047 = 060K94	M,47	3 mois	C2,S2		A	γGT↑
DJ9100164	M,61	3 ans	C2,S2	RENITEC, C2,S2 DOGMATIL	A	γGT↑
Hépatite cholostatique						
NC9200360	F,85	3 mois	C2,S1	TENSTATEN, C2,S1	A	
Biologie hépatique perturbée						
NC9600020	**F,39**	**8 mois**	**C2,S2**		**A**	**ALAT↑**
MA9700402	**F,47**	**12 sem.**	**C2,S1**		**A**	**ALAT↑**
MA9400451	F,57	3 mois	C1,S1	Amfépramone, C1,S1	U	ALAT↑
BX9700611	**F,51**	**6 j**	**C2,S1**	**LUTERAN, C2,S1** **LEVOTHYROX , C2,S1** **TENORMINE, C2,S1**	F	**ALAT↑**
PA9803765	**F,66**	**3 mois**	**C1,S1**	**LAROXYL** **GLUCOR** **TEATROIS** **TEALINE...**	**U**	**ALAT↑** **Prep.Magistr.**
PB9300028	M,60	15 j	C1,S1	Prep. magistrale: 15 j Yohimbine Dexfenfluramine Metformine, 2 ans ANAFRANIL, 2 ans	A	ALAT↑
NY9608618	**F,36**	**4 mois**	**C2,S2**		**A**	**ALAT+Bil↑**
PA8851623	M,61	3 ans	C2,S1	(MYOCORIL,C1,S1)	F	ALAT+P.A↑
BX9700024	**F,59**	**4sem.**	**C2,S2**	**LOXEN,C2,S2** **ACUILIX, C2,S2**	**A**	**ALAT+P.A↑** **+γGT↑**
10010325	M,42	3 sem.	C2,S2	(éthylisme)	A	ALAT+P.A↑
10060020	M,55	3 mois	C2,S1		A	ALAT ↑
10060A69	M,?	50 j	C2,S1		A	ALAT ↑ (1,5N)
10540L94	F,48	20 mois	C2,S1	MADECASSOL (C1,S1)	A	ALAT + γGT↑
MP9800161	**F,51**	**5 mois**	**C1,S1**	**ESTREVA, C1,S1** **GESTORAL, C1,S1**	**A**	**ALAT + γGT↑**
10060498	F,50	3 ans	C1,S1		U	γGT↑ dossier succinct
10060038	F,62	> 3 mois	C2,S1		A	γGT↑
120O39	**F,70**	**?**	**C3,S1**	**DIAMICRON** **ICAZ** **HYPERIUM**		γGT↑

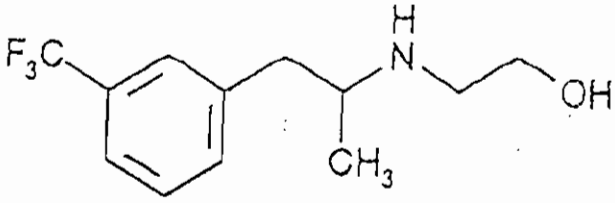
Conclusion : Plusieurs cas d' augmentations de transaminases et/ou de γGT ont été rapportés.
La plupart du temps, le MEDIATOR est en association avec d'autres médicaments qui ont la même imputabilité.
Dans quelques cas, le MEDIATOR est le seul médicament pris par le ou la patiente.
Dans la majorité des dossiers, le délai de survenue est de ≅ 3 mois.

Cet effet indésirable n'est pas mentionné dans les RCP



chlorhydrate de benfluorex

ND



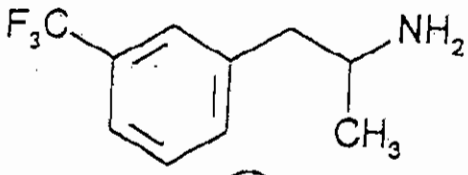
1-(3-trifluorométhylphényl)-2N-(2-hydroxyéthyl)amino propane

12

+ Acide benzoique

conj. gluc.

14



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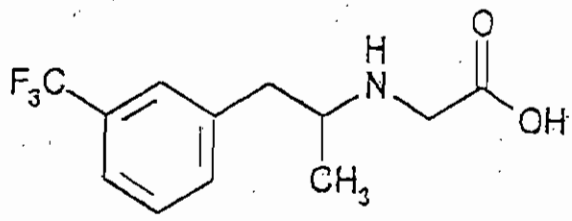
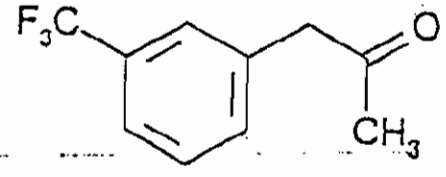
norfenfluramine



63

1-(3-trifluorométhylphényl)-2N-2-(carboxyméthyl)amino propane



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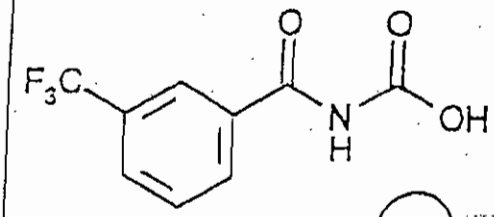

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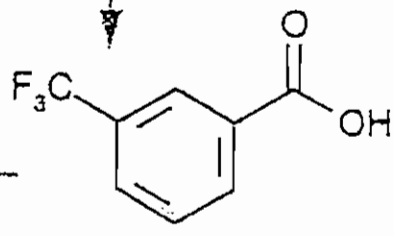
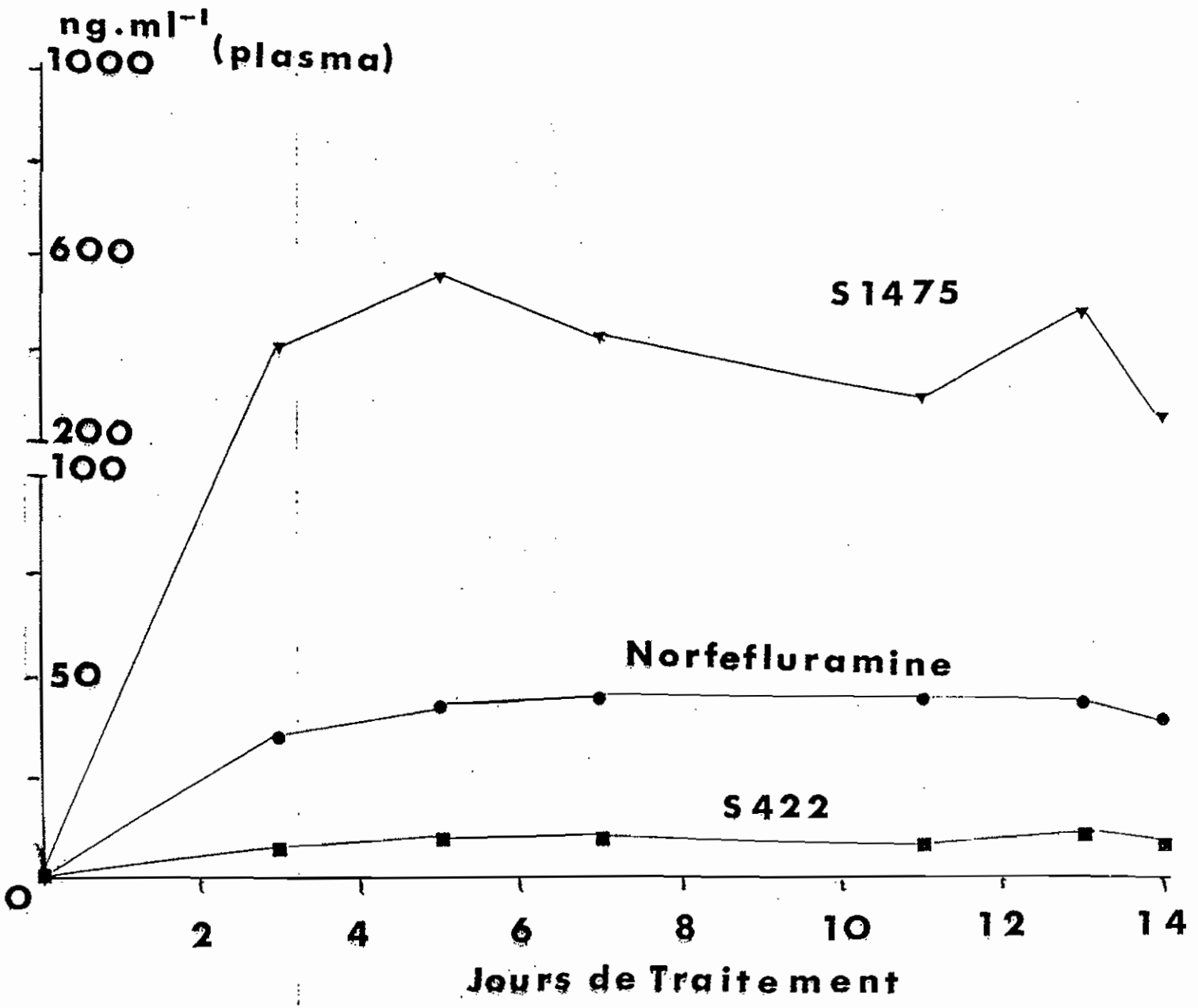
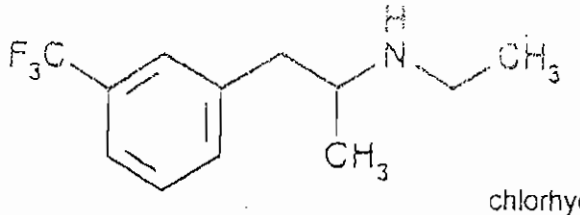


FIG 2



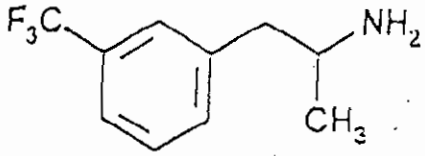
Métabolites du BENFLUOREX



chlorhydrate de fenfluramine

11

norfenfluramine



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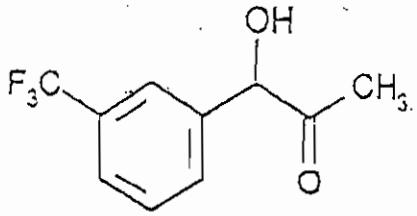

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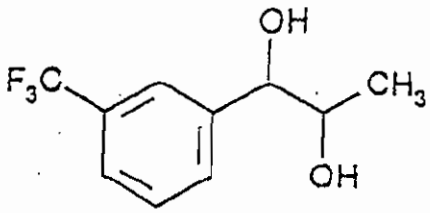

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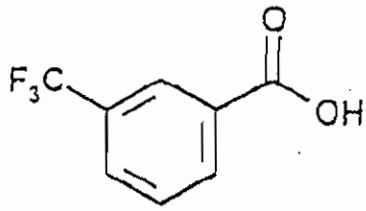

ND

gluc. conj.

50.7

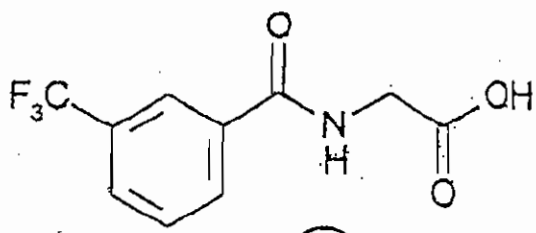

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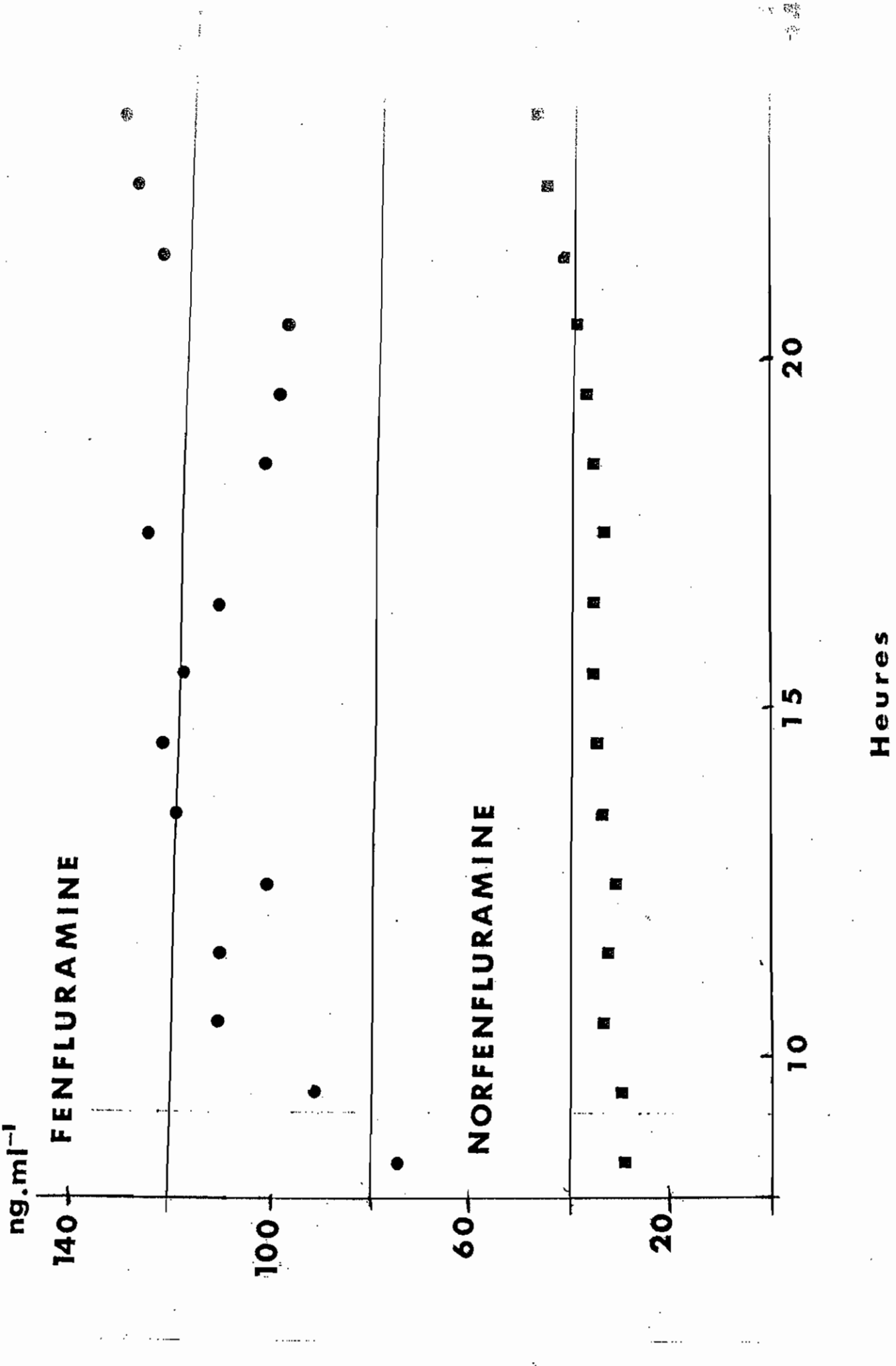
Fig 4

Annexe 3-9


ng.ml⁻¹
FENFLURAMINE
NORFENFLURAMINE
140
100
60
20
10
15
20
Heures

9

Annexe 3-9

A. BILAN GLOBAL

265 notifications nouvelles ont été rapportées

163 aux Centres Régionaux de Pharmacovigilance, 105 au laboratoire.(dont 3 doublons)

Elles concernent 93 hommes et 171 femmes (1 sexe non précisé), dont l'age moyen est de :

- 56,9 ans pour les hommes
- 55,9 ans pour les femmes

Répartition par classe-organe des effets indésirables notifiés :

APPAREIL	Nombre de Notifications CRPV	Nombre de Notifications Laboratoire	TOTAL	Nombre de doublons
FOIE	17	9	25	1
APP. DIGESTIF (sauf foie)	16	5	21	-
HEMATOLOGIE	8	6	14	-
APPAREIL RESPIRATOIRE	10	11	20	1
CARDIO-VASCULAIRE	12	6	18	-
APPAREIL URINAIRE	9	4	13	-
PEAU - ALLERGIE	41	23	64	-
NEURO-PSYCHIATRIE	30	18	48	-
VERTIGES	16	5	20	1
METABOLISME	3	18	21	-
APPAREIL SENSORIEL	1	-	-	-
TOTAL	163	105	265	3

N.B : les nouvelles notifications par rapport à la mise au point de Juillet 1995, sont imprimées «en gras » dans les tableaux suivants.
Dans la colonne, « traitement associé », le médicament est souligné, lorsque l'imputabilité bibliographique est supérieure au MEDIATOR.

10

Annexe 3-9

[illegible] d'hépatites ou de perturbations de la biologie hépatique [illegible] suspect ou d'imputabilité égale ou supérieure aux médicaments associés

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Dans 15 cas, l'imputation est douteuse : dont 10 C2,S1, 5 C1,S1

Annexe 3-9

			Hépatite mixte			
RE8660098	M,82	mois	C2,S1	CORVASAL, DIAMICRON TADENAN	A	
DJ9300271	F,50	2 sem.	C2,S2	Amfépramone, C2,S2	A	γGT↑
10060607	M,61	15 j	C2,S1	GLUCOPHAGE RETARD, C1,S1 DIAMICRON, C1,S1 SECTRAL, C1,S1 RISORDAN, C1,S1	A	
			Hépatite cytolytique			
NY8804047 = 060K94	M,47	3 mois	C2,S2		A	γGT↑
DJ9100164	M,61	3 ans	C2,S2	RENITEC, C2,S2 DOGMATIL	A	γGT↑
			Hépatite cholostatique			
NC9200360	F,85	3 mois	C2,S1	TENSTATEN, C2,S1	A	
			Biologie hépatique perturbée			
NC9600020	**F,39**	**8 mois**	**C2,S2**		A	**ALAT↑**
MA9700402	**F,47**	**12 sem.**	**C2,S1**		A	**ALAT↑**
MA9400451	F,57	3 mois	C1,S1	Amfépramone, C1,S1	U	ALAT↑
BX9700611	**F,51**	**6 j**	**C2,S1**	**LUTERAN, C2,S1** **LEVOTHYROX , C2,S1** **TENORMINE, C2,S1**	F	**ALAT↑**
PA9803765	**F,66**	**3 mois**	**C1,S1**	**LAROXYL** **GLUCOR** **TEATROIS** **TEALINE...**	U	**ALAT↑** **Prep.Magistr.**
PB9300028	M,60	15 j	C1,S1	Prep. magistrale: 15 j Yohimbine Dexfenfluramine Metformine, 2 ans ANAFRANIL, 2 ans	A	ALAT↑
NY9608618	**F,36**	**4 mois**	**C2,S2**		A	**ALAT+Bil↑**
PA8851623	M,61	3 ans	C2,S1	(MYOCORIL,C1,S1)	F	ALAT+P.A↑
BX9700024	**F,59**	**4sem.**	**C2,S2**	**LOXEN,C2,S2** **ACUILIX, C2,S2**	A	**ALAT+P.A↑** **+γGT↑**
10010325	M,42	3 sem.	C2,S2	(éthylisme)	A	ALAT+P.A↑
10060020	M,55	3 mois	C2,S1		A	ALAT↑
10060A69	M,?	50 j	C2,S1		A	ALAT↑ (1,5N)
10540L94	F,48	20 mois	C2,S1	MADECASSOL (C1,S1)	A	ALAT + γGT↑
MP9800161	**F,51**	**5 mois**	**C1,S1**	**ESTREVA, C1,S1** **GESTORAL, C1,S1**	A	**ALAT + γGT↑**
10060498	F,50	3 ans	C1,S1		U	γGT↑ dossier succinct
10060038	F,62	> 3 mois	C2,S1		A	γGT↑
120O39	**F,70**	**?**	**C3,S1**	**DIAMICRON** **ICAZ** **HYPERIUM**		γGT↑

Conclusion : Plusieurs cas d' augmentations de transaminases et/ou de γGT ont été rapportés.
La plupart du temps, le MEDIATOR est en association avec d'autres médicaments qui ont la même imputabilité.
Dans quelques cas, le MEDIATOR est le seul médicament pris par le ou la patiente.
Dans la majorité des dossiers, le délai de survenue est de ≅ 3 mois.

Cet effet indésirable n'est pas mentionné dans les RCP

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- BX88003099, patient de 53 ans, éthylique, traité depuis 13 ans par MEDIATOR, ZYLORIC et VISKEN . L'évolution n'est pas connue.

-LY9500598 , femme de 59 ans, hospitalisée pour tentative d'autolyse, traitée par de nombreux médicaments: évolution inconnue, dossier très succinct.

CIRRHOSE						
BX8800309	M,57	13 ans	C1,S1	ZYLORIC,13 ans, C1,S1 VISKEN,13 ans,C1,S1	U	autre étiologie
STEATOSE						
LY9500598	**F,59**			**EQUANIL** **LEVOTHYROX** **LOXAPAC** **ANAFRANIL** **ROHYPNOL**	**U**	**dossier succinct**

II. AUTRES ATTEINTES DIGESTIVES :

Elles concement 14 femmes (âge moyen : 60,6 ans) et 7 hommes (âge moyen : 61,7 ans)

- Dans les 14 cas de diarrhée rapportés, (10 femmes et 4 hommes), le MEDIATOR est utilisé en monothérapie, ou son imputabilité est supérieure aux médicaments associés.

Cet effet indésirable est mentionné dans les RCP.

- 3 cas d'ulcères ont été rapportés par le laboratoire:

- 10060052 : homme de 74 ans, reçoit MEDIATOR, depuis 6 à 8 mois, LIPANTHYL depuis 10 ans , TANAKAN et des AINS. Une fibroscopie montre des ulcères multiples qui nécessitent non seulement l'arrêt des AINS mais de toute thérapeutique.
L'évolution est favorable après prescription d'antiulcéreux. (C1,S1)

- 10540930 : Femme de 64 ans, hospitalisée pour ulcère gastrique, après 3 mois de traitement par MEDIATOR et après 1 an de GLUCOPHAGE RETARD, EUGLUCAN, ZESTRIL, LIPUR.
Le MEDIATOR est arrêté.
L'évolution est favorable après traitement par anti-acide, pansement gastrique et perfusion. (C1,S1)

--10060587 : Femme de 72 ans, avec diabète, HTA, traitée par MODURETIC et ALDOMET depuis plusieurs années et MEDIATOR depuis 3 jours. Apparition de gastralgies intenses après prise de MEDIATOR, avec réadministration positive. (C3,S1)
L'évolution est favorable à l'arrêt du MEDIATOR.
Une fibroscopie ultérieure met en évidence un ulcère duodénal.

- 1 cas de rectocolite hémorragique : (1054P69) chez une femme de 46 ans traitée au long cours par DAONIL, GLUCOPHAGE RETARD, INSULINE, LEVOTHYROX et ELISOR, apparition d'une diarrhée aigue, sanglante et colite inflammatoire ressemblant à une colite hémorragique après 1 cp de MEDIATOR.

L'évolution est favorable après administration de PENTASA. (C2,S1)

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LY8600250	F,70	6 j	C2,S1		A	
MP8600156	M,60	2 mois	C3,S2	MODUCREN, C1,S1	A	
LY8700109	M,71	21 j	C2,S2	DIGOXINE	A	
BX8800223	M,40	3 j	C3,S2		A	
LY8800383	F,72	10 mois	C1,S1		F	
LY8800202	F,58	18 j	C2,S1		A	
MA9000721	F,29	3 j	C2,S2	DININTEL,C1,S2	A	
NC9200041	F,42	3 ans	C2,S2		A	
BR9300084	F,63	1 j	C2,S1	ZOCOR,C1,S1 ZYLORIC, C1,S1 ARMOPHYLLINE, C1,S1 DIAMICRON, C1,S1 BRICANYL, C1,S1	A	
NC9300212	M,75	47 j	C2,S2	DIACTANE, C1,S1	A	
DJ9400277	F,81	7 mois	C1,S2		U	
NC9500365	**F,70**	**2 sem.**	**C2,S2**	**BEFIZAL, C1,S2**	**A**	
CF9700156	**F,62**	**3 sem.**	**C2,S1**		**A**	
540V43	**F,66**	**45 j**	**C2,S1**	**ELISOR** **VEINAMITOL** **TEMESTA, C1,S1**	**A**	**selles molles anorexie dyspepsie**
PANCREATITE						
MA9000382	M,40	6m	C2,S1	ISOMERIDE ,C2,S1	A	
MA9700296	**F,54**	**8j**	**C2,S1**		**A**	**autre étiologiel**
EPIGASTRALGIE						
LY8600060	M,72	13j	C2,S1		A	
ULCERE DUODENAL						
10060587	F,72	3 j	C3,S1	MODURETIC, C1,S1 ALDOMET, C1,S1	A	
ULCERE GASTRIQUE						
10540930	F,64	3 mois	C1,S1	GLUCOPHAGE RETARD, C1,S1 EUGLUCAN, C1,S1 ZESTRIL, C1,S1 LIPUR, C1,S1	A	
ULCERE						
10060052	M,74		C2,S1	AINS, C2,S1 TANAKAN, C2,S1 LIPANTHYL, C1,S1	A	ulcères multiples
RECTOCOLITE HEMORRAGIQUE						
10540P69	F,46	1 j	C1,S1	DAONIL, C1,S1 GLUCOPHAGE RETARD , C1,S1 INSULINE , C1,S1 LEVOTHYROX, C1,S1 ELISOR, C1,S1	F	

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II. A. TABLES HEMATOLOGIQUES

14 observations (8 CRPV, 6 laboratoire) ont été rapportées.

Elles concernent 5 hommes (âge moyen : 62,2 ans) et 9 femmes (âge moyen : 57 ans) .

- Aucun nouveau cas n'a été rapporté depuis la mise au point de Juillet 1995

- L'imputabilité est douteuse dans tous les cas : 11 C1,S1
3 C2,S1

Dans la plupart des observations, il existe un traitement associé, qui peut être responsable de l'effet indésirable

-Dans l'observation 10050F09 : (C2,S1) il s'agit d'1 femme de 70 ans, avec HTA, hyperlipémie, angor et antécédents d'ulcère gastrique, traitée par MEDIATOR depuis 3 semaines:
apparition de purpura et d'hémorragie digestive : plaquettes<5000/mm3 et hémoglobine à 9g/l
La recherche d'anticorps antiplaquettes est positive.
L'évolution est favorable après arrêt du MEDIATOR

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol	
THROMBOPENIE						
LY8500365	M,51	3 mois	C1,S1	RISORDAN, 4 ans, C1,S1 SECTRAL, 4 ans, C1, S1 TILDIEM, 7 mois, C1S1	U	
SE9100183	F,64	2 mois	C1,S1	TENSTATEN, 2m, C1S1 EFFERALGAN, C1S1	U	
PS9400301	F,61	?	C1,S1	GERIMAX, C1,S1 OROCAL, C1,S1 LEVOTHYROX, C1,S1	A	
NC9400153	F,19	2 mois	C2,S1	DOXYCLINE, 5j, C2,S1 ALDACTONE, 2m, C2,S1	A	
LEUCOPENIE						
MA8801234	F,58	2 mois	C1,S1	LIPUR, 2ans, C2,S1	A	
10060617	M,60	4 ans	C1,S1		F	
LYMPHOPENIE						
DJ8800131	F,76	6 j	C1,S1	DIGOXINE, C1,S1 CALCIPARINE, C1,S1 RYTHMODAN, C1,S1	A	somnolence
MA9100793	M,59	8 j	C1,S1		A	hyperthermie
NEUTROPENIE + THROMBOPENIE						
NC8900022	M,72	2 ans	C1,S1	HEMIDAONIL, 6 ans, C1S1	A	
10060073	F,40	+ mois	C1,S1	DIAMICRON, C1,S1 GLUCOPHAGE, C1,S1	F	
10060050	M,69	3 ans	C1,S1	LEGALON	F	
ANEMIE + THROMBOPENIE						
10050F09	F,70	3 sem	C2,S1		A	
HYPERLYMPHOCYTOSE						
10060311	F,56	3-6 mois	C1,S1		U	dossier succinct
HYPEREOSINOPHILIE						
10540640	F,69	3 ans	C2,S1	LOPRIL, C1,S1 FLUDEX, C1,S1	F	

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IV. ATTEINTES RESPIRATOIRES :

20 notifications (10 CRPV et 11 laboratoire) dont 1 doublon ont été rapportées, concernant

- 11 hypertensions pulmonaires:.9 dossiers ont été expertisés par le Professeur WEITZENBLUM , 6 ont été classés en HTA P d'allure primitive lors de l'enquête « anorexigènes et HTAPP», 3 en hypertensions pulmonaires post-embolique(1) et post-capillaire(2).
Elles concernent 9 femmes (âge moyen : 54,8 ans) et 2 hommes (âge moyen : 48 ans)

Le MEDIATOR n'est jamais prescrit seul : il est présent en association à un ou plusieurs anorexigènes (ISOMERIDE : 10 fois, PONDERAL : 2 fois)
Ces cas font partie de l'enquête concernant les anorexigènes

La durée de traitement par MEDIATOR est imprécise dans 5 cas sur 11.
Dans les 6 autres cas, la durée de traitement va de plusieurs mois à 4 ans.

La prise de MEDIATOR et d'anorexigènes est concommitante dans 5 cas, antérieure dans 2 cas, postérieure dans 3 cas, imprécise dans 1 cas.

– 5 cas de toux, après des traitements allant de 8 à 34 mois. L'évolution est inconnue dans 2 cas.

Dans 1 observation (541078), dont l'imputabilité est vraisemblable, chez une femme de 70 ans, traitée par MEDIATOR pour un diabète et AMLOR pour HTA depuis 2 mois, apparition d'une toux sèche qui disparait à l'arrêt du MEDIATOR.
Les dates de prise de MEDIATOR ne sont pas précisées: seul un rechallenge positif est noté. (C3,S1),

- des cas de syndrome hémorragique intra-alvéolaire (MP9500482), tuberculome (SE9400175), pneumopathies interstitielles (LM9800297 et NT9800036) ont tous une imputabilité douteuse: soit une autre étiologie est fortement évoquée, soit l'évolution est inconnue.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION PULMONAIRE						
PP8990081	F,42	1 an	C1,S1	DININTEL, 5ans, C1,S1 Tenuate Dospan,5ans,C1,S1 FRINGANOR, 5ans, C1,S1	U	
NC9300007 = 052454	M,48	4 ans	C1,S1	ISOMERIDE, 3 ans, C1,S1 ZYLORIC, 6 ans, C1,S1 LIPANTHYL	D	
10052455	F,46	25 mois	C1,S1	ISOMERIDE CORGARD BUSPAR VELITEN ALDACTONE	F	
10052733	F,71	60 mois	C1,S1	ISOMERIDE	F	HTAP post-capillaire
10840193	F,47	?	C1,S1	ISOMERIDE COVERSYL LASILIX GLUCOPHAGE	F	
10840255	F,57	?	C1,S1	ISOMERIDE PONDERAL STILNOX XANAX VEINOBIASE	F	

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10840954	F,64			ISOMERIDE STAGID DIAMICRON		HTAP post-capillaire
10840B19	F,51		C1,S1	ISOMERIDE SECTRAL MODURETIC KALEORID LEXOMIL RANIPLEX PREPULSID	F	
10840D01	F,59	4 ans	C1,S1	ISOMERIDE PONDERAL ZOCOR PROGESTOGEL SPIROCTAN	D	
TOUX						
MA9000654	F,60	2 ans	C1,S1	ARTEX, 1 an, C1,S1 GLUCINAN, 2 ans,C1,S1	U	
NC9500265	F,48	10mois	C1,S1	EUTHYRAL, 2mois, C1,S1	A	
MA9600518	F,63	8 mois	C1,S1	MONOTILDIEM, 1 an, C1,S1 KARDEGIC, 1 an, C1,S1 ADANCOR, 1 an, C1,S1	U	
541078	F,70	?	C3,S1	AMLOR, C1,S1	A	
NC9800121	F,71	34 mois	C2,S1	FLUDEX TENORMINE FONZYLANE ROHYPNOL	A	
SYNDROME HEMORRAGIQUE INTRA-ALVEOLAIRE						
MP9500482	F,45	1 mois	C1,S1	PONDERAL, 1 mois, C1,S1	A	
TUBERCULOME						
SE9400175	F,46	2 mois	C1,S1	ISOMERIDE, 2 mois, C1,S1 DININTEL, 2 mois, C1,S1	A	autre étiologie !
PNEUMOPATHIE INTERSTITIELLE						
LM9800297	M,75	?	C1,S1	AMAREL, C1,S1	U	
NT9800036	M,69	10 ans	C1,S1	DETENSIEL, C1,S1 JOSIR, C1,S1 LEXOMIL, C1,S1	F	fibrose interstitielle

V. ATTEINTES CARDIOVASCULAIRES :

18 notifications ont été rapportées : 12 par les CRPV, 6 par le laboratoire

Elles concernent 3 hommes (âge moyen : 51 ans) et 14 femmes (âge moyen : 48,3 ans)

- 3 cas d'hypertension artérielle : dont une observation plausible :

NC9100093 : chez une femme de 51 ans, hypertendue traitée par LOPRESSOR depuis 5 ans, la tension est montée progressivement de 150/90 à 180/110 après introduction de MEDIATOR, malgré l'ajout de RENITEC. La tension a diminué lorsque le MEDIATOR a été arrêté.

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- une fibrillation auriculaire (C2,S2) chez une femme de 25 ans après 9 mois de MEDIATOR, CANOL et TEALINE et 6 mois de MODERATAN. Evolution favorable à l'arrêt de tout le traitement.

- 3 syndromes de Raynaud dont un plausible C2,S2 et 2 douteux (C2,S1 et C1,S1)

- les autres notifications sont isolées et d'imputabilité douteuse

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION ARTERIELLE						
NC9100093	F,51	1an	C2,S2	RENITEC, C1S1 LOPRESSOR, C1S1	A	
CF9300241	F,73	6j	C2,S1		A	
120S330	**F,43**	**15 mois**	**C1,S1**	**SURGESTONE** **PROZAC**	**U**	
HYPOTENSION ARTERIELLE						
10060039	M,52	?	C1,S1		A	R -
SYNCOPE						
PP9010597	F,37	1j	C1,S2	Amfepramone, C1,S2 LUMITENS, C1,S2	A	
MALAISE						
10540A46	F,43	8 mois	C1,S1		A	R -
BRADYCARDIE						
120E93	**M,38**	**1 sem**	**C1,S1**		A	
TACHYCARDIE						
GR9500235	**F,52**	**?**	**C1,S1**	**SOTALEX, C1,S1**	A	
NC8900097	F,60	1j	C2,S2	CERVOXAN, C1,S1 DIGOXINE, C1,S1	A	
FIBRILLATION AURICULAIRE						
LY9700643	**F,25**	**9 m**	**C2,S2**	**MODERATAN ,C2,S2** **CANOL, C2,S2** **TEALINE, C2,S2**	A	**Terrain dépressif**
EXTRASYSTOLES VENTRICULAIRES						
CN9500150	**F,?**		**C2,S1**		A	**dossier succinct**
CN9500151	**F,?**		**C1,S1**		**U**	**dossier succinct**
ACCIDENT VASCULAIRE CEREBRAL						
LL9700372	**F,39**	**3 mois**	**C2,S1**	**SPIRONONE, 3 mois, C2,S1** ***Tabagisme***	A	
PB9800124	**F,72**	**2 ans**	**C1,S1**	**GLIBENESE** **GLUCOR**	F	
SYNDROME DE RAYNAUD						
PC9300059	M,63	3 mois	C1,S1	MINIDIAB, 2ans, C1,S1	F	
PC9700170	**F,30**	**2 sem.**	**C2,S2**		A	
124U10	**F,30**		**C2,S1**	**FONZYLANE**	A	
OEDEMES DES MEMBRES INFERIEURS						
10060561	F,73	1 mois	C2,S1	GLUTRIL, C1,S1 CORDARONE, C1,S1	A	

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13 notifications ont été rapportées : 9 par les CRPV et 4 par le laboratoire

Elles concernent 5 hommes (âge moyen : 66,6 ans) et 8 femmes (âge moyen : 55,2 ans)

-3 cas de dysurie, d'imputation :
C3,S1 : réadministration positive mais durée de traitement inconnu
C2,S2 : apparition après 5 mois de MEDIATOR, évolution favorable à l'arrêt de celui-ci
C2,S1 : apparition après 48 h de traitement par MEDIATOR (cystite concommitante)

- 4 cas de pollakurie :
- en début de traitement 1j,2j et 16j
- ou réadministration positive après 4 mois de traitement

-1 cas de cystalgie (C2,S1) chez une femme de 33 ans après 8 jours de traitement.
L'évolution est favorable à l'arrêt de MEDIATOR

- les autres dossiers ont tous une imputabilité douteuse:
- anurie (MA8900044)
- glomérulonéphrite (LY8700356),
- syndrome néphrotique (BX9700689),
- créatininémie augmentée(10060463)
- soit le dossier est succinct
- soit l'évolution est inconnue ou l'évolution n'est pas favorable à l'arrêt du traitement:
- soit une autre étiologie est possible

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DYSURIE						
BR9100053	F,42	?	C3,S1	VARNOLINE,C1,S1	A	
NC9300208	M,78	5 mois	C2,S2	GLUTRIL, C1,S1 ZYLORIC, C1,S1 PREPULSID, C1,S1	A	
SE9700347	F,?	2 j	C2,S1		A	
POLYURIE						
BX8700115	F,40	7 mois	C2,S1		A	
POLLAKIURIE						
NC8800144	M,62	4 mois	C3,S1		A	
NC9300297	F,67	16 j	C2,S2		A	
10060O44	F,56	1 j	C2,S1		A	
10060O45	M,62	2 j	C2,S1	GLUCOPHAGE RETARD, C1,S1	A	
ANURIE						
MA8900044	M,79	2 mois	C1,S1	ARTEX, 2mois, C1,S1 ZYLORIC, 2 mois, C1,S1 HEMIDAONIL, 2 mois, C1,S1 ALDACTAZINE, 2 mois,C1,S1	N	dossier succinct, non informatif
GLOMERULONEPHRITE						
LY8700356	M,52	5 mois	C1,S1	ZYLORIC, C1,S1 DIAMICRON, C1,S1	U	

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				LASILIX MONOTILDEM, C1,S1 TRINITRINE, C1,S1 GLUCOPHAGE, C1,S1 DAONIL, C1,S1 VOLTARENE, C1,S1 CYTOTEC, C1,S1 AZANTAC, C1,S1		
CREATININEMIE AUGMENTEE						
10060463	F,78	9 mois	C1,S1	ALDOMET, C1,S1 ALDACTAZINE, C1,S1 LIPANTHYL, C1,S1	F	
CYSTALGIES						
10540F68	F,33	8 j	C2,S1		A	

VII. ATTEINTES METABOLIQUES :

21 Notifications ont été rapportées , 18 par le laboratoire, 3 par les CRPV.

Elles concement 11 hommes (âge moyen : 58,7 ans) et 10 femmes (âge moyen : 56,7 ans)

Dans 13 cas, c'est 1 effet lié à aux propriétés pharmacologiques du médicament lui-même:

- hypoglycémie : 6 cas
- malaise hypoglycémique : 1 cas
- hyperglycémie : 2 cas

- hyperlipémie : 2 cas
- augmentation des triglycérides : 2 cas

-3 cas de lactacidémie d'imputabilité douteuse

-dans 1 cas (10060F73), chez un homme de 68 ans, la lactacidémie est à 4.13mmol/l (normale 0.55-2.20) après un traitement de 37 jours par MEDIATOR. Un mois après de MEDIATOR, elle est de 2.27mmol/l.

-2 dossiers succincts: pas de précision sur l'arrêt du MEDIATOR (10060683)
évolution inconnue (10060356)

- 2 cas de goutte chez 2 hommes de 61 et 71 ans (LASILIX est associé dans les 2 cas : C3,S2,B3 et C1,S1,B3)

- 2 cas d 'amaigrissement déclaré par un médecin au laboratoire (10060446 et 10060447) : perte de 5 Kg chez un homme de 36 ans après 1 mois de traitement, perte de 8 Kg chez une femme de 67 ans après 2 mois de traitement pour hypercholestérolémie.

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BX8600168	/55	15j	C1,S1			
HYPERLIPIDEMIE - HYPERCHOLESTEROLEMIE						
10051346	F,47	?	C1,S1	ECAZIDE, C1,S1	A	
TRIGLYCERIDES AUGMENTES						
10051289	M,59	8 mois	C1,S1		U	dossier succinct
10060J12	F,38	2 mois	C1,S1	TARDYFERON CALCIUM DEDROGYL	U	
HYPOTHYROIDIE						
BS9600267	**F,86**	**?**	**C1,S1**	**DAONIL, C1,S1** **SERMION, C1, S1** **LIPANTHYL,C1,S1** **VASTAREL, C1,S1**	A	
GOUTTE						
LY8500568	M,71	8 j	C2,S1	LASILIX, C3,S2	U	
10060F04	M,61	11 j	C2,S1	LASILIX, C1,S1 LOPRIL, C1,S1 ADALATE, C1,S1	A	
LACTACIDEMIE						
10060683	M,41	?	C1,S1	DAONIL ALDACTAZINE VASTAREL	A	dossier succinct
10060356	M,76	6 mois	C1,S1	DIGOXINE ADALATE SERMION AVLOCARDYL	U	
10060F73	M,68	37 j	C2,S1	TILDIEM SERMION	A	
HYPOGLYCEMIE						
10540J00	M,35	5 mois	C1,S1	TENSTATEN, C1,S1 BEFIZAL, C1,S1 ZYLORIC, C1,S1	U	
10060166	F,28	2 mois	C1,S1	GLUCOPHAGE	U	
10060O87	M,63	?	C2,S1	LIPANOR CERVOXAN LURSELLE	A	
10540P03	F,60	15 j	C2,S1	BEFIZAL PROZAC ETIOVEN	A	malaise *DNID*
10060449	F, 60	90 j	C3,S1	ZYLORIC LOPRIL	A	*DNID*
121U61	**F,44**	**110 j**	**C2,S2**	**CIBACENE** **LASILIX** **UTROGESTAN**	**A**	
MALAISE HYPOGLYCEMIQUE						
10060062	M,74	qq j	C2,S1	RENITEC	A	
HYPERGLYCEMIE						
10060488	F,80	6 mois	C1,S1	CATAPRESSAN, C1,S1	F	
10060487	M,62	2 ans	C1,S1	CEBUTID VISKALDIX	A	*DNID*
AMAIGRISSEMENT						
10060446	M,36	1 mois	C2,S1		A	
10060447	F,67	2 mois	C1,S1		A	

VIII. DIVERS : Diminution de l'acuité visuelle

NY9810174	F,67	5 sem	C1,S1		F	

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Annexe 3-9

1 . Allergie, eczema :

Parmi les 27 réactions allergiques, on note:

- 14 cas d'urticaire dont 5 cas d'urticaires géantes ou généralisées
- 4 oedèmes de Quincke ou oedème laryngé
- 6 chocs anaphylactiques
- 3 allergies cutanées

Le délai de survenue est le plus souvent très rapide (1 jour), l'imputation sera donc souvent vraisemblable (15 fois) ou plausible (3 fois).
Elle est douteuse dans les cas où il y a eu un traitement correcteur : 9 fois

Parmi les 6 cas d'eczéma, d'imputabilité douteuse, l'évolution est favorable dans 4 cas.
L'eczéma n'est pas guéri dans 2 cas. (NC9300394 etNY9809751)
Dans l'observation 540W61, le délai d'apparition est long (2 ans) et la crème cosmétique semble être en cause.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
URTICAIRE						
CF8500013	M,50		C1,S2	LEXOMIL, C1,S2	A	
LY8700092	F,69	15 j	C3,S1		A	
TO9100366	M,34	7 j	C2,S2		A	
NC9400046	F,38	1 j	C3,S2		A	
MA9500024	M,45	3 mois	C3,S1	MAXEPA, C3,S1	U	
NY9507878	**M,61**	**2 mois**	**C2,S1**		**A**	
MA9700146	**F,50**	**1 j**	**C2,S2**		**A**	
10060I28	F,54	2 mois	C3,S1		A	
10540989	F,31	4 j	C3,S1	DI-ANTALVIC, FELDENE TRANCOPAL	A	
10540D65	F,48	3 sem	C1,S1		A	urticaire géante
10060H11	F,60	+ mois	C3,S1		A	urticaire géante
SE9800159	**F,32**	**9 j**	**C1,S1**	**PROZAC STRESAM CANOL**	**A**	**urticaire géante**
120T66	**F,59**	**1 j**	**C3,S1**	**ART 50, C1,S1**	**A**	**urticaire généralisée**
121D94	**F,60**	**1 j**	**C3,S1C1,S3**		**A**	**urticaire généralisée + bronchospasme**
OEDEME LARYNGE						
BX9800738	**F,?**	**3 j**	**C1,S1**		**A**	***autre cause!***
OEDEME DE QUINCKE						
PA9200399	F,41	1 j	C2,S1	GLUCINAN, C2,S1	A	
MA9500231	F,56	1 j	C3,S1		A	
10060K99	F,49	3 mois + 9 j	C3,S1		F	
CHOC ANAPHYLACTIQUE						
DJ9200119	F,73	2 j	C3,S2		A	
MA9300967	F,50	8 j	C3,S2		A	
MA9400018	F,?	1 j	C3,S2		A	
MA9700036	**F,60**	**1j**	**C2,S2**		**A**	
123K59	**F,38**	**1 j**	**C1,S1**	**BRONCHOKOD**	**A**	
LY9800499	**M,36**	**1 j**	**C3,S1**		**A**	

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121A605	F,?	20 j	C2,S1	FLOXYFRAL PROTHIADEN NOCTRAN	A	flush
ECZEMA						
NC9300394	F,?	3 ans	C1,S2		F	
MA9500621	F,68	2 ans	C2,S2		A	
NY9809751	M,70	10 mois	C1,S1	MOPRAL, C1,S1 GLUCOR, C1,S1	F	
10840104	M,40	35 j	C1,S1		A	éruption eczématiforme photosensibilité
10060G65	F,64	1 mois	C1,S1	CATAPRESSAN VASTAREL DAFLON FONZYLANE	A	eczéma des membres oed. du visage prurit
540W61	F,67	2 ans	C1,S1	Crème cosmétique	A	éruption eczématiforme
SUDATION EXCESSIVE						
PA9240186	F,79		C1,S2	DIAMICRON, C1,S2 MEDIATENSYL, C1,S2 BRUFEN, C1,S2	A	

2. Eruption, vascularite, purpura

30 notifications ont été rapportées : 20 par les CRPV, 10 par le laboratoire

Elles concernent 18 femmes agées de 47,7 ans et 12 hommes agés de 52,6 ans

Les éruptions cutanées sont variées:

- 16 cas de prurit, d' éruptions érythèmateuse, maculeuse, papuleuse ou maculopapuleuse dont 6 cas d'imputabilité vraisemblable (réadministration positive)

- 3 cas d'érythème polymorphe, avec une évolution favorable à l'arrêt du MEDIATOR, chez 2 hommes agés de 60 et 68 ans. Le délai d'apparition est respectivement de 15 jours et de 6 mois (!).
Dans le 3° cas, (MA9700614) l'évolution est inconnue et le TANAKAN a une imputabilité bibliographique supérieure au MEDIATOR.

- 3 notifications de vascularite aigue leucocytoclasique:
  - dans 1 cas, l'évolution est favorable à l'arrêt du MEDIATOR (RE9420042)
  - dans 1 cas, l'évolution est favorable sans arrêt du MEDIATOR , mais avec un traitement corticoïde (lorsque la corticothérapie est arrêtée, 4 mois plus tard, survient un érythème polymorphe :MA9700957)
  - dans le troisième cas (MP9700134), l'évolution n'est pas complète malgré l'arrêt du MEDIATOR et une corticothérapie.

- 3 cas de purpura:
  - purpura des membres inférieurs avec un oedème apparu une semaine après le début du traitement par MEDIATOR (PP8990384)
  - purpura des membres inférieurs, s'étendant aux membres supérieurs, disparaissant 1 semaine après l'arrêt du traitement (CF9200106)
  - purpura rhumatoïde survenant après 2 semaines de traitement, l' évolution est inconnue (PO9700410)

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DJ9100155	M,31	10j	C3,S2			éruption érythémateuse
MP9300201	F,36	1 mois	C1,S1	DOLIPRANE, 1j,C1,S1 CLARADOL, 1j, C1,S1	A	éruption érythémateuse, prurit
540V73	**F,49**	**1 j**	**C3,S1**	**MEDIATENSYL**	**A**	**éruption + oedème**
PA9333879	F,54	5 sem.	C1,S1	GLUCOPHAGE,3 sem,C1,S1	U	prurit
10060913	F,65	qq j	C2,S1		A	prurit
10060161	M,40	3-4 j	C3,S1	LIPANTHYL	A	prurit
10060F71	F,47	?	C2,S1	TAGAMET, C1,S1 JONCTUM, C1,S1 LEXOMIL, C1,S1	A	prurit + érythème + vertiges
MA9500227	**M,38**	**16j**	**C3,S1**		**A**	**éruption prurigineuse**
10010408	M,72	7 j	C2,S1	ALDACTAZINE CORDITRINE PERSANTINE ZYLORIC	A	éruption prurigineuse
LY9700381	**F,56**	**11 sem.**	**C2,S1**	**LIPANTHYL, 11 SEM, C2S1**	**A**	**éruption**
MA9300723	F,41	1 cp	C2,S1	HEXALYSE,1cp, C2,S1	A	éruption maculopapul.
LY9400078	F,46	1 mois	C2,S1	TOCO 500, C1,S1 CYCLO 3, C1S1 CONFLICTAN, C1,S1 LEXOMIL, C1,S1	A	éruption maculeuse, prurit
1050S90	M,41		C3,S1	amfépramone phénobarbital	A	éruption papuleuse prurit
122X95	**F,32**	**1 mois**	**C3,S1**	**NIDREL FRACTAL AZANTAC**	**A**	**rash maculo-papuleux**
LM9100055	M,56	1 an	C1,S1	DETENSIEL, C1,S2 DIDRONEL, C1,S1	U	prurigo
NC9100505	F,48	1 mois	C2,S2	SOPROL, 1 mois, C2S2	A	éruption pustuleuse
NC9100194	M,60	15 j	C2,S1	EUPRESSYL, C2,S1	A	érythème polymorphe
NY9300951	M,68	6 mois	C2,S1		A	érythème polymorphe
MA9700614	**F,50**	**3 mois**	**C1,S2**	**TANAKAN, C1,S2 MEGAMAG, C1,S2**	**U**	**érythème polymorphe**
MP9700134	**F,58**	**6 j**	**C1,S1**	**SECTRAL BOP LEVOTHYROX**	**F**	**vascularite**
RE9420042	M,41	4 j	C1,S1	SORBITOL	A	vascularite
MA9700957	**F,50**	**8 ans**	**C1,S1**	**STAGID, 8 ANS, C1,S1**	**A**	**vascularite**
PP8990384	F,75	3 sem.	C2,S1	DAONIL, C1,S1 STAGID, C1,S1 TILDIEM, C1,S1 NATIROSE, C1,S1	A	purpura
CF9200106	F,67		C2,S2	VASTAREL, C2,S2 DAFALGAN, C2,S2 ELISOR, C2,S2	A	purpura
PO9700410	**M,47**	**2 sem.**	**C1,S1**	**ATHYMIL,C1,S1**	**F**	**purpura rhumatoide**

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Annexe 3-9

				GLUCOPHAGE, 6 m. C1,S1 ZYLORIC, 33 mois, C1,S1 LOXEN, 33 mois, C1,S1		
NC9400417	F,20	1 mois	C1,S2		F	acné
10540911	F,45	15 j	C2,S1	ASPIRINE	A	pustulose exanthématique
10540F26	F,20	2 mois	C1,S1		F	alopécie
10840616	M,72	7 mois	C2,S1	NIDREL ZYLORIC LASILIX ZOCOR ARTEX	F	colororation noire de la langue

Les effets indésirables cutanés et/ou allergiques ne sont pas mentionnés dans les RCP

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Annexe 3-9

[illegible] ont été rapportées, 50 par les CRPV [illegible]

Elles concernent 23 hommes (Age moyen : 53,9 ans) , 25 femmes (Age moyen : 58,8 ans)

1. Asthénie, Somnolence, Impuissance :

Dans certaines observations:

- soit le délai de survenue semble long : 2ans (LM8600219) ou inconnu (DJ8800131)
- soit le traitement associé peut être responsable de tels effets: PROZAC, GLUCOPHAGE...

Asthénie et somnolence sont mentionnés dans les RCP.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
ASTHENIE						
LM8600219	M,56	2 ans	C2,S2		A	
TO8900326	M,49	1 mois	C1,S1		F	
MA9300480	F,45	6 mois	C2,S1	PRAXINOR, 1 mois, C2,S1 PONDERAL, C1,S1	A	
LY9600435	**F,53**	**8 sem.**	**C2,S1**	**GLUCOPHAGE, 8 sem., C2,S1** **PROZAC**	**A**	
123F40	**M,48**	**1 an**	**C1,S1**	**BEFIZAL**	**U**	
SOMNOLENCE						
DJ8800131	F,76	?	C2,S2		A	+ lymphopénie
TO9200397	F,64	6 j	C3,S2		A	
MA9300577	F,42			ISOMERIDE		
RE9510102	**F,69**	**4 j**	**C2,S1**	**LASILIX, C1,S1** **PREVISCAN, C1,S1** **COVERSYL, C1,S1** **INSULATARD, C1,S1**	**A**	
10060074	F,56	1 mois	C3,S1	FONLIPOL DIGOXINE CORDARONE Antivitamines K	A	
10060150	F,70	4-5 j	C2,S1	GLUCOPHAGE Retard, C1,S1 LIPANTHYL, C1,S1	A	
TROUBLE DE LA VIGILANCE						
10010335	F,72	3 j	C2,S1	TENORMINE SERESTA CYCLOTERIAM	A	
NC9500466	**M,55**	**3 j**	**C3,S2**		**A**	impuissance
10051460	M,45	1 mois	C2,S1	DESATURA DAFLON 500	A	trouble de l'érection

Annexe 3-9

Elles concernent 16 hommes (âge moyen : 53,2 ans) et 14 femmes (âge moyen : 50,4 ans).

Les troubles psychiatriques sont divers : agressivité, nervosité, confusion, délire

La responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue

3 cas sont imputés « vraisemblable » :

- NC9500171 : nervosité et nausées chez une femme de 50 ans, 1 à 2 h après la prise d'1 cp de MEDIATOR

- 10010345 : désorientation et obnubilation, chez une femme de 80 ans. Le traitement a été arrêté après 13 j. Une réadministration ultérieure a été positive. (traitement associé : KERLONE et MOGADON)

- PA97355052 : syndrome de sevrage avec excitation, chez un homme de 27 ans, sportif, qui avait pris 9 cp/j de MEDIATOR, comme « dopant ».

5 cas sont imputés « plausible » :

- NC9700094 : accès d'agitation et agressivité, chez une femme de 74 ans, pendant la prise de MEDIATOR, pendant 6 j. Disparition des symptômes 12 h après l'arrêt du MEDIATOR.

- NC9300347 : irritabilité chez un homme de 39 ans, traité pendant 11 mois par MEDIATOR. L'évolution est favorable à l'arrêt du médicament.

- NC9300349 : dépression, chez un homme de 50 ans, traité pendant 9 mois par MEDIATOR. L'évolution est favorable à l'arrêt du médicament.

- MA9100069 : angoisse et palpitation, chez un homme de 40 ans, 2h après avoir ingéré 4 cp de MEDIATOR.

- CF9000137 : désorientation chez une femme de 79 ans, traitée par MEDIATOR, HALDOL, SERESTA, ZESTRIL, CATAPRESSAN, PRAXILENE, SERMION. L'évolution est favorable à l'arrêt de tous les médicaments.

19 ont été imputés « douteux » : (8 C1,S1, 10 C2,S1, 1 C1,S2)

:

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
TROUBLES PSYCHIATRIQUES						
LY9600963	**M,45**	**1 mois**	**C1,S1**	**LEXOMIL, C2,S1**	**A**	**agressivité**
NC9700094	**F,74**	**6 j**	**C2,S2**		**A**	**agressivité**
541173	**F,45**	**8 j**	**C2,S1**	**CORENITEC, C1,S1**	**A**	**agressivité + hallucination**
MA8900523	F,40		C1,S1	ISOMERIDE, 1j, C2,S1	A	agitation
DJ9800349	**M,74**	**3 mois**	**C2,S1**		**A**	**agitation**
NC9300347	M,39	11 mois	C2,S2		A	irritabilité
NC9500171	F,50	1 cp	C3,S2		A	nervosité
MP9800179	**F,47**	**11 j**	**C2,S1**	**LIPANOR, C1,S1**	**A**	**nervosité**
124G84	**F,35**	**20 j**	**C2,S1**	**MAXEPA LEVOTHYROX HYDROCORTISONE**	**A**	**nervosité + excitation**

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				ASPEGIC BITILDIEM DIAMICRON...		
LY8900392	M,52	20 j	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1	A	cauchemars
10540O46	M,?	qq semaines	C1,S1	ZOCOR, C1,S1 PERSANTINE MAXEPA TILDIEM DAONIL	A	cauchemars
SE9500017	F,41	84 j	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1	A	confusion
10010326	M,61	?	C1,S1	FONZYLANE, C1,S1 SINTROM, C1,S1	A	confusion *autre cause !*
120M85	**M,70**	**11 j**	**C2,S1**	**PREVISCAN, C1,S1 CORDARONE, C1,S1**	**A**	**confusion troubles de la mémoire**
CF9000137	F,79		C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2 SERMION, C2,S2	A	désorientation
10010345	F,80	13 j	C3,S1	MOGADON, C1,S1 KERLONE, C1,S1	A	désorientation obnubilation
10060J96	F,80	?	C1,S1	RENITEC ADALATE HEMIDAONIL TILDIEM	A	désorientation
10060J13	F,82	1 mois	C2,S1	DAONIL	A	désorientation
120M52	**M,60**	**2 j**	**C2,S1**	**LIPANTHYL, C1,S1 ASPEGIC, C1,S1**	**A**	**désorientation sommnolence**
10060560	M,75	plusieurs mois	C2,S1	DAONIL	A	trouble du comportement
RN9500096	**F,59**	**73 j**	**C1,S2**	**LIPANTHYL, C1,S2 PILOSURYL, C1,S2 CANOL, C1,S2 OLIVIASE, C1,S2 Amfépramone, C1,S2**	**A**	**délire**
GR8700216	M,45	16 j	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1	A	délire
10060219	F,65	2 ans	C1,S1		A	bouffées d'angoisse au sevrage
PA9735052	**M,27**	**6 mois**	**C3,S1**	***« 9 cp/j (dopantl) »***	**U**	**excitation au sevrage**

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Annexe 3-9

Elles concernent 5 hommes (âge moyen : 59 ans) et 2 femmes (âge moyen : 39 ans)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
CONVULSION						
PA9223988	M,60	?	C2,S1	TENSIONORME, C2,S1 DIFFU K	A	
10060J47	F,36	2 mois	C1,S1	DAONIL	A	crise comitiale
NEUROPATHIE						
MA8700716	M,73	9 ans	C1,S1	HEMOCLAR TORENTAL	U	autre étiologie!
PARESTHESIE						
BX8800193	M,36	8 j	C1,S1	PRAXINOR, 8j, C1,S1	F	
LM9500090	M,61	4 j	C2,S1		A	
MA9700170	**F,42**	**1 j**	**C2,S2**	**TAMIK, C1,S1**	**U**	
10051683	M,65		C2,S1	DAONIL GLUCOPHAGE LIPANOR ANGIOXINE	A	

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Annexe 3-9

Il s'agit de patients agés, en général, avec une pathologie lourde : diabète, HTA, insuffisance cardiaque pontage coronarien, cirrhose ...

6 cas rapportés par le CRPV de BORDEAUX ont été à l'origine d'une nouvelle mise au point des effets indésirables du MEDIATOR lors du Comité Technique du 30 avril 1998.

- BX9701040 : chez un homme de 74 ans, apparition d'une difficulté à la marche pendant un traitement de 4 semaines par MEDIATOR, les troubles sont apparus au bout de 3 semaines.
ATCD et terrain :HTA, DNID, double pontage coronarien
Traitement associé : PREVISCAN, DAONIL, CAPTOLANE, GLUCOPHAGE
Evolution favorable à l'arrêt de MEDIATOR

- BX9701041 : chez un homme de 78 ans, apparition d'un trouble de l'équilibre pendant un traitement de 10 j par MEDIATOR.
ATCD et terrain : DNID, Infarctus du myocarde,3 pontages coronariens, gastrectomie, anévrisme de l'aorte abdominale, ACFA
Traitement associé : DAONIL, CORDARONE, ASPEGIC, GLUCOR
Evolution favorable à l'arrêt de MEDIATOR

- BX9701023 : chez une femme de 63 ans, apparition de trouble de la marche et perte de l'équilibre, pendant un traitement de 9 semaines par MEDIATOR, les symptômes sont apparus au bout de 8 semaines
ATCD et terrain : DNID, cirrhose hépatique alcoolique, HTA, exérèse basocellulaire, neuropathie diabétique
Traitement associé : AVLOCARDYL, DAFLON, DAONIL, LASILIX, GLUCOR, TRANXENE, IMOVANE
Evolution favorable à l'arrêt de MEDIATOR

- BX 9700381 : chez un homme de 63 ans, apparition de trouble de la marche et perte de l'équilibre, pendant un traitement de 4 semaines par MEDIATOR,
ATCD et terrain : DNID, cirrhose, HTA, neuropathie périphérique avec paresthésie des extrémités
Traitement associé : DAONIL
Evolution favorable à l'arrêt de MEDIATOR

- BX9700301 : chez un homme de 71 ans, apparition de trouble de la marche et perte de l'équilibre, pendant un traitement de 6 semaines par MEDIATOR,
ATCD et terrain : DNID, infarctus du myocarde, pontage coronarien,artérite des membres inférieurs, OAP,
Traitement associé :LOPRIL, CORDARONE, VASTAREL, PRAXILENE, EUGLUCAN
Franche amélioration à l'arrêt de MEDIATOR

- BX9701022 : chez une femme de 74 ans, apparition de trouble de la marche pendant un traitement de 7 mois par MEDIATOR, les symptômes sont apparus au bout de 4 semaines
Traitement associé : DIAMICRON, MOPRAL, TILDIEM, ALDACTAZINE, LYSANXIA
ATCD et terrain : DNID, angor
Evolution favorable à l'arrêt de MEDIATOR

Cet effet indésirable est mentionné dans les RCP

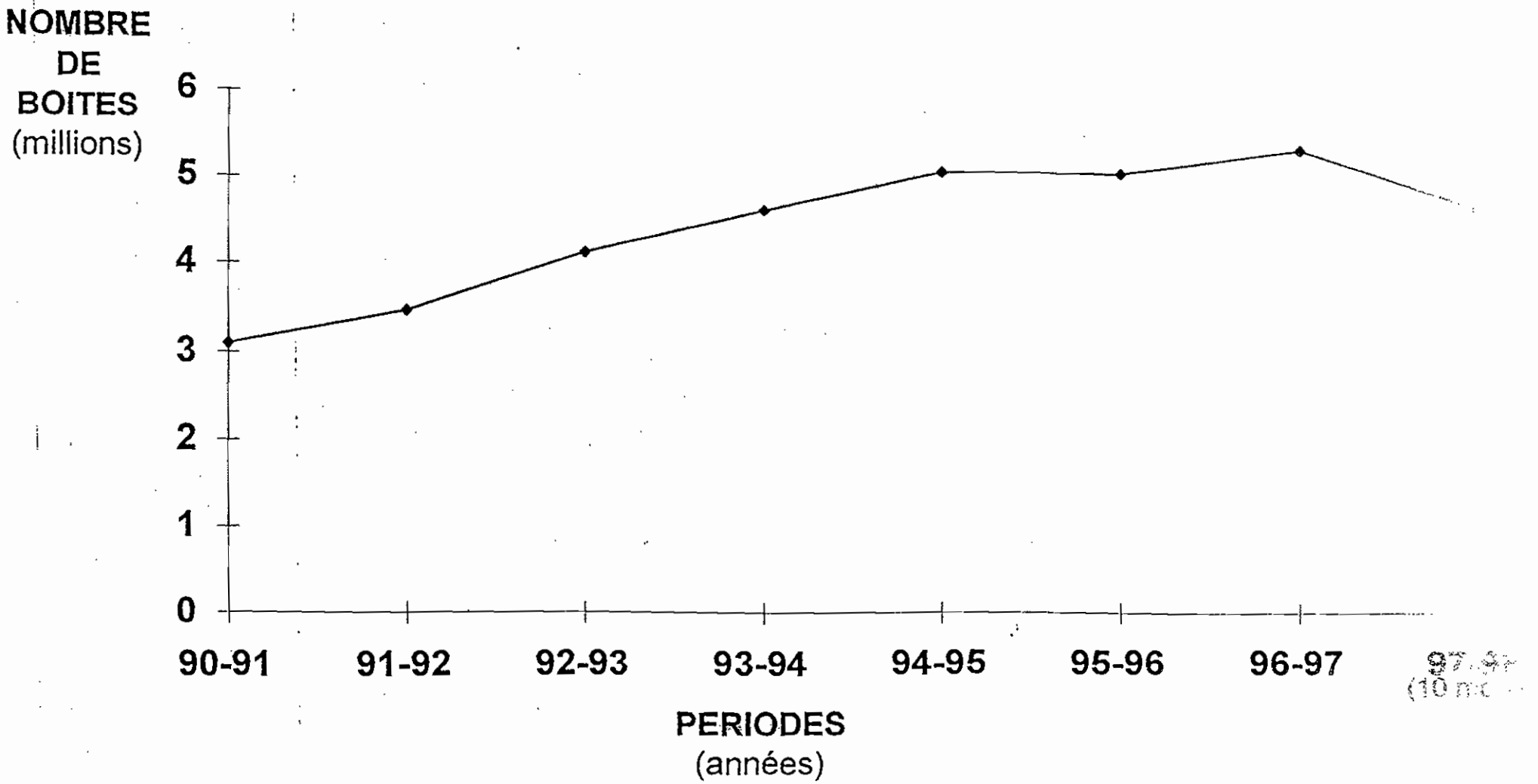
Annexe 3-9

			VERTIGE, TROUBLE			
BX8500092 =060141	M,34	3 mois	C3,S2		A	
MA8800356	F,60	1 j	C2,S2		A	
MA8800929	F,47	1 cp	C2,S2	DAFLON, C1,S1	A	
NC9000297	F,58	15 j	C3,S2		A	
LL9200133	F,63	2 j	C1,S1		U	
NY9306790	F,77	2 j	C1,S2		A	
LM9500091	F,84		C2,S1	SOTALEX, C1,S1 LOXEN, C1,S1 ALDACTONE, C1,S1 CORDIPATCH, C1,S1 PREVISCAN, C1,S1	U	
TS9600227	**F,64**	**4 sem.**	**C3,S1**	**RENITEC, C1,S1** **LIPANTHYL, C1,S1**	**A**	
BX9701040	**M,74**	**4 sem.**	**C2,S1**	**PREVISCAN, C1,S1** **DAONIL, C1,S1** **CAPTOLANE, C1,S1** **GLUCOPHAGE, C1,S1**	**A**	
BX9701041	**M,78**	**10 j**	**C2,S1**	**DAONIL** **CORDARONE** **ASPEGIC** **GLUCOR**	**A**	
NC8900097	F,60	1 cp	C2,S2		A	
MA8700143	F,66	?	C1,S1	FLUVERMAL, C1,S1	F	
BX9701023	**F,63**	**9 sem.**	**C2,S1**	**AVLOCARDYL** **DAFLON** **DAONIL** **LASILIX** **GLUCOR** **TRANXENE** **IMOVANE**	**A**	
BX9700381	**M,63**	**4 sem.**	**C2,S1**	**DAONIL**	**A**	
BX9700301	**M,71**	**6 sem.**	**C2,S1**	**LOPRIL** **CORDARONE** **VASTAREL** **PRAXILENE** **EUGLUCAN**	**A**	
BX971022	**F,74**	**7 mois**	**C2,S1**	**DIAMICRON** **MOPRAL** **TILDIEM** **ALDACTAZINE** **LYSANXIA**	**A**	
10060F71	F,47	?	C2,S1	TAGAMET, C1,S1 JONCTUM, C1,S1 LEXOMIL, C1,S1	A	+ prurit + érythème
10060499	F,40	1 semaine	C3,S1	LEVOTHYROX, C1,S1	A	
10060J48	F,74	2 j	C2,S1	MODURETIC, C1,S1 LOXEN, C1;S1 DETENSIEL, C1,S1	A	
123T12	**F,74**	**?**	**C1,S1**	**GLUCOPHAGE** **DIAMICRON** **TILDIEM** **KERLONE** **RISORDAN** **ALDACTAZINE** **MOPRAL**	**A**	***trouble de la démarche***

ANNEXES

Benfluorex MEDIATOR®

Chiffres de vente
(nombre de boîtes)



1118

Annexe 3-9

REPARTITION DES PRESCRIPTIONS DE MEDIATOR EN FONCTION DES INDICATIONS
Source : DOREMA Médicaments - Printemps - Cumuls 12 mois

INDICATIONS	Juin 94 à Mai 95		Juin 95 à Mai 96			Juin 96 à Mai 97			Juin 97 à Mai 98		
	Prescriptions	Répart. %	Prescriptions	Répart. %	evol. an-1	Prescriptions	Répart. %	evol. an-1	Prescriptions	Répart. %	evol.
Total Prescriptions	893 000	100,0%	821 000	100,0%	-8,1	897 000	100,0%	9,3	948 000	100,0%	
Diabète et apparentés*	389 000	43,6%	407 000	49,6%	4,6	376 000	41,9%	-7,6	420 000	44,3%	
Lipides (Diag. 272)	151 000	16,9%	174 000	21,2%	15,2	248 000	27,6%	42,5	268 000	28,3%	
Obésité (Diag. 278)	212 000	23,7%	124 000	15,1%	-41,5	123 000	13,7%	-0,8	100 000	10,5%	

* Diag. 250-259 + 277 + 790-2

VENTES UNITAIRES DE MEDIATOR

SOURCES	1991	1992		1993		1994		1995		1996		1997		[illegible]
	Unités (000)	Unités (000)	évol. an-1	Unités (000)	évol. an-1	Unités (000)	évol. an-1	Unités (000)	évol. an-1	Unités (000)	évol. an-1	Unités (000)	évol. an-1	[illegible]
IMS - Eisipharm - LMP	3 279	3 767	14,9	4 135	9,8	4 794	15,9	5 157	7,6	5 164	0,1	5 555	7,6	[illegible]
GERS	3 147	3 605	14,6	4 223	17,1	4 792	13,5	5 141	7,3	5 253	2,2	5 531	5,2	[illegible]

Entre 1992 et 1997 : Cumuls 12 mois de janvier à décembre
* Pour 1998 : Cumul 12 mois de août 1997 à juillet 1998 (évolution par rapport au cumul à juillet 1997)

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Annexe 3-9

Annexe 3-10

ANALYSE COMPARATIVE DES PV DES CT de PHARMACOVIGILANCE du 10/09/1998 et 17/12/1998 RELATIF AUX DONNEES DE PHARMACOCINETIQUE ET DU METABOLISME

Le PV du 10/09/1998 (19 lignes) fournit des données incomplètes et n'indique pas en préambule la méthodologie analytique utilisée, ni la dose administrée.
Les paramètres de pharmacocinétiques manquants sont :
- la concentration maximale (Cmax)
- l'aire sous la courbe (AUC)
-et les ½ vies (T1/2)
du médicament et des ses métabolites (pour évaluer leur devenir dans l'organisme).
Concernant le métabolisme, le PV indique bien que la norfenfluramine (métabolite commun au benfluorex et fenfluramine) est retrouvée à un taux plasmatique identique après prise de benfluorex ou après prise de fenfluramine (seule valeur exprimée normalement en ng/ml). Il ne mentionne pas qu'il s'agit du métabolite actif, lipophile du benfluorex dont la pharmacocinétique doit être évaluée avec des méthodes analytiques fiables en terme de sensibilité et de spécificité.
Les concentrations urinaires de norfenfluramine issues du benfluorex sont exprimées en pourcentage sans indication concernant la méthodologie utilisée.
La différence dans les pourcentages de norfenfluramine dans les urines de 24heures après prise de fenfluramine et benfluorex est une incohérence puisque les concentrations plasmatiques à l'équilibre sont les mêmes. Ces résultats n'ont aucun intérêt pour évaluer la pharmacocinétique du produit.
Le PV mentionne de fournir au rapporteur une analyse des aires sous la courbe.

Il aurait été judicieux d'exiger une étude sérieuse de pharmacocinétique avec des méthodes analytiques "HPLC-SM" afin de disposer des dosages précis du médicament et de ses métabolites et notamment une pharmacocinétique de la (d-l) norfenfluramine (qui par ailleurs est le métabolite principal de la fenfluramine).

Le PV du 17/12/1998 (9 lignes) ne présente aucune pertinence par rapport au précédent. Il mentionne cependant la norfenfluramine comme métabolite principal. Il prête à confusion dans la comparaison des taux circulants dans le sang de norfenfluramine puisqu'il indique un taux de 5% par rapport au métabolite principal (dérivé hydrophile) comparativement au taux de 30% de norfenfluramine issue de fenfluramine. Le point principal, soit la concentration sanguine de norfenfluramine n'est pas mentionné dans ce deuxième PV. Les données pharmacocinétiques urinaires sont répétées succinctement. Dans ce PV, aucune concentration du médicament et des métabolites n'est rapportée. Les données en pourcentage ne peuvent être qu'approximative car toutes issues de mesures de radioactivité globales et imprécises.

La conclusion d'ordre pharmacodynamique : "il parait peu probable que le benfluorex induise les mêmes effets que la fenfluramine" est sans lien avec les données de pharmacocinétiques fournies et présentées plus haut.

Docteur JP KANTELIP

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RÉPUBLIQUE FRANÇAISE

Annexe 3-11

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 15 SEP. 1999

COMMISSION NATIONALE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mercredi 7 Juillet 1999)

Etaient présents :

M. RICHE : Président
M. BEGAUD : Vice-président
Mme HARAMBURU (suppléante du Vice-précident), M. BLAYAC (suppléant de Mme ALBENGRES), M. ANDREJAK, Mme ARDOIN, Mme AUTRET-LECA, Mme BALLEREAU, M. BARDIN, Mme LAINE-CESSAC (suppléante de Mme BAVOUX), M. REVEILLAUD (suppléant de M. CARLIER), M. CARON, Mme CHIRON, M. CRETON, Mme ESCHWEGE, M. OLLAGNIER (suppléant de M. IMBS), Mme JOUAN-FLAHAULT, Mme JOUGLARD, Mme KREFT-JAIS, M. LAMBERT, M. LAROUSSE, M. LAVAUD, M. VIAL,
Mme GOUJARD (représentant Monsieur le Directeur Général de l'INSERM),
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
M. ALEXANDRE (représentant Monsieur le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER.

Unité de Pharmacovigilance

Mme CASTOT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle GOEBEL
M. LANG
Mme LEREBOURS
M. MASSET
Mme MESSAN-MURPHY
Melle MAUREL
Mme PARIENTE-KHAYAT
Melle ROMIEE

Assistaient à la réunion (D.E.M.E.B)

Mme BAUMELOU
Mme CALLENS
Mme DURANTEAU
Mme DUMARCET
M. FERNANDEZ
Mme PAVLOVIC
Mme SAINT-RAYMOND
Mme SAINT-SALVI
Mme TCHINOU

Rapporteurs : Mme AUTRET-LECA, M. BENAICHE, Mme CHIFFOLEAU, Mme LAINE-CESSAC, Mme LAPEYRE, M. RICHE, Mme SGRO.

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

Experts : M. BUGAT, Mme COSTAGLIOLA, Mme ELEFANT, M. REVUZ, M. VERNANT.

Etaient excusés :

M. BOULU
M. CHASSANY
M. CRETON
Mme DEGOS
M. GHISLAIN
M. GIROUD
M. MICLEA
M. MUNERA
M. PRUGNEAU
M. ROUGEAU
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux)
M. DUPUIS (représentant de la Commission d'AMM)

LABORATOIRES

ASTA MEDICA	:	Mme CHEVRIER
DAKOTA PHARM	:	Mme GERSBERG Mme LASSALE
EUROPHTA	:	M. GIRARD Mme LECLERC
GLAXOWELLCOME	:	Mme BONS Mme SAINTE-CROIX
PIERRE FABRE MEDICAMENTS	:	Mme COQUET Mme EHKIRCH
PHARMACIA & UPJOHN	:	Mme BRUYNINCKX M. GILLES Mme RICHARD
RPR BELLON	:	Mme BOUDIGNAT M. BERTHOLUM
PRODUITS ROCHE	:	Mme BOULKROUN Mme GEIGER M. GOEHRS Mme SZAFIR M. HASSNER

WYETH LEDERLE : M. CAUGANT
Mme ECSTEIN-FRAISSE
Mme FILLEUL
M. TETELBOUM

La présidence de la séance a été assurée par M. le Pr. RICHE à l'exception de la présentation des dossiers concernant les enquêtes officielles "dobésilate de calcium" et "anthracyclines" pour lesquels il était rapporteur ; celle-ci étant assurée par M. le Pr. BEGAUD.

I - ADOPTION DU PROCÈS-VERBAL DE LA SÉANCE DU 1er Juin 1999

Le procès verbal de la séance du 1er Juin 1999 a été adopté avec les modifications suivantes :

Page 6 : paragraphe "Maladies auto-immunes rapportées entre la date de commercialisation et le 31 mars 1999", 5ème ligne : remplacer "âgés de 15 ou moins" par "âgés de 15 ans au moins"

Page 9 : paragraphe 2. ; 3ème ligne : remplacer "inhibiteurs de l'A.D.N. mitochondrial nécessaire à la réplication" par "inhibiteurs de la γ-polymérase nécessaire à la réplication de l'A.D.N. mitochondrial".

II - EXAMEN DE L'ENQUETE OFFICIELLE SUR LES SYNDROMES HEMORRAGIQUES DES INHIBITEURS SELECTIFS DE LA RECAPTURE DE LA SEROTONINE. PROCEDURES NATIONALES.

Au cours de sa réunion du 10 Février 1999, la Commission Nationale de Pharmacovigilance a pris connaissance des résultats de l'enquête officielle sur les syndromes hémorragiques survenant sous traitement par inhibiteurs de la recapture de la sérotonine (IRS).

Cette enquête concernait 5 spécialités pharmaceutiques :

- **citalopram** (Séropram®),
- **fluoxétine** (Prozac®),
- **fluvoxamine** (Floxyfral®),
- **paroxétine** (Déroxat®),
- **sertraline** (Zoloft®).

Il avait été rappelé qu'une enquête européenne était en cours, pour laquelle la France était co-rapporteur et la Suède rapporteur.

Les membres de la Commission avaient souhaité une harmonisation des RCP des 5 spécialités concernées par l'enquête officielle, en proposant l'ajout dans la section "Effets indésirables" de l'intitulé suivant : "**rares ecchymoses, métrorragies et autres saignements cutanéo-muqueux**" *ainsi qu'être tenus informés de l'évolution de ce dossier.*

Au cours de sa réunion du 7 Juillet 1999, la Commission Nationale a pris connaissance des données actualisées, présentées par le Centre Régional de Pharmacovigilance (CRPV) d'Angers ainsi que des modifications proposées par le Groupe de Travail Européen de Pharmacovigilance les 10 et 11 Juin 1999, à la suite de la communication du rapport suédois.

Les données actualisées ont porté sur les informations suivantes :
- **Les propositions du Groupe de Travail Européen de Pharmacovigilance sont très proches de celles de la Commission Nationale de Pharmacovigilance.**
Seule la mention supplémentaire "hémorragie digestive" semble devoir être ajoutée dans l'intitulé proposé par la Commission Nationale ainsi qu'une information sur le risque hémorragique dans la section "Mises en garde et précautions d'emploi" du RCP.

- **Pour le Groupe de Travail "Thrombose" de l'AFSSAPS, une anomalie fonctionnelle plaquettaire** semble être l'hypothèse à privilégier pour expliquer le mécanisme physiopathologique des syndromes hémorragiques sous IRS;

- **La question du risque péri-opératoire,** soulevée à la suite de la notification au CRPV de Dijon par un chirurgien plasticien de la Côte d'Or, d'observations peu documentées d'hématomes et de petites hémorragies des plaies opératoires de patientes sous paroxétine (Deroxat®) ne semble pas nécessiter de mesures particulières actuellement;

- **La proposition de modifier la section "Interactions médicamenteuses"** à la suite de l'ajout de la mise en garde chez les patients traités par anticoagulants oraux **sera discutée par le Groupe de Travail "Interaction" de l'AFSSAPS puis par le Groupe de Travail Européen de Pharmacovigilance.**

III- EXAMEN DE L'ENQUETE OFFICIELLE SUR DOXIUM® (DOBESILATE DE CALCIUM) ET LA SURVENUE D'AGRANULOCYTOSES. PROCEDURE NATIONALE.

Le CRPV de Brest a présenté les résultats de l'enquête officielle concernant les effets indésirables de Doxium® (dobésilate de calcium). Cette enquête avait été décidée au vu de 6 cas d'agranulocytose mentionnés dans le dossier de demande de modification de l'information du produit.

11 cas d'agranulocytose et 49 cas de fièvre ont été rapportés dans le monde depuis le début de la commercialisation de Doxium®.
Sur les 11 observations d'agranulocytose, il y avait une réadministration positive du produit dans 2 cas. 5 d'entre-elles sont peu informatives (et 7 cas sur les 11 proviennent d'Espagne).
Par ailleurs, une étude cas-témoins[1] réalisée dans la région de Barcelone entre 1980 et 1998 cite 11 cas d'agranulocytose survenus en Espagne avec le dobésilate de calcium. Dans cette étude, l'Odds Ratio d'agranulocytose sous dobésilate de calcium est compris entre 16,7 et 26,3 (IC 95%).
Enfin, 4 nouvelles observations seraient en cours d'évaluation à Barcelone.

Compte tenu de la gravité des effets indésirables et malgré l'existence d'un éventuel biais d'alerte (7 cas espagnols / 11 mondiaux), de l'existence d'autres médicaments asociés à Doxium® dans toutes les observations et de l'absence d'informativité de la plupart de celles-ci, la Commission Nationale de Pharmacovigilance a proposé de modifier le RCP de Doxium® de la façon suivante :

	RCP actuel	RCP proposé
4.4 Mises en garde et précautions d'emploi	Ce produit contient des sulfites qui peuvent éventuellement entraîner ou aggraver des réactions de type anaphylactique.	Ce produit contient des sulfites qui peuvent éventuellement entraîner ou aggraver des réactions de type anaphylactique. Dans le cas de réactions cutanées, de fièvre, de douleurs articulaires ou de modification de la numération formule leucocytaire, le traitement doit être interrompu. Dans le cas de désordres gastro-intestinaux, réduire la posologie ou suspendre temporairement le traitement. Le dobésilate interfère avec le dosage colorimétrique de la créatinine. En conséquence, le taux de créatinine peut être faussement abaissé.

[1] *RISK OF AGRANULOCYTOSIS ASSOCIATED WITH METAMIZOLE. PROGRESS REPORT FOR THE SPANISH MEDICINES AGENCY. MAY 1999.*
L Ibanez, X Vidal, E Bellarin, D Capella, and J-R Laporte
Fundacio Institut Catala de Farmacologia. Universitat Autonoma de Barcelona - Institut Catala de la Salut CSU Vall d'Hebron - 08035 BARCELONA

4.8 Effets indésirables	Gastralgies ou nausées : ces troubles régressent à la diminution de la posologie utilisée et disparaissent totalement à l'arrêt du traitement.	Dans de rares cas, des désordres gastro-intestinaux incluant nausées et diarrhées, de la fièvre, des douleurs articulaires et dans de très rares cas, une agranulocytose ont été rapportés. Ces réactions sont en général spontanément réversibles après l'arrêt du traitement.

Par ailleurs, la Commission Nationale de Pharmacovigilance a estimé que le bénéfice du dobésilate de calcium devait être réévalué rapidement.

Les laboratoires Europhta ont accepté les modifications du RCP proposées en estimant néanmoins que celles-ci ne s'imposaient peut-être pas compte-tenu du caractère hypothétique de la survenue d'agranulocytoses sous Doxium® (ambiguité concernant 2 réadministrations positives).

Les laboratoires Europhta pourraient également proposer un changement de formulation du Doxium® (qui ne contiendrait pas de sulfites).

Enfin, une réévaluation du rapport bénéfice/risque de Doxium® pourrait éventuellement être décidée si les nouveaux cas d'agranulocytose, qui devraient être disponibles d'ici les mois de septembre-octobre 1999, étaient suffisamment informatifs.

IV - INTERVENTION DE M. BENAICHE SUR LES CONFLITS D'INTERETS.

Monsieur Lionel BENAICHE, responsable de la cellule de veille déontologique, a en charge les problèmes de déontologie relatifs aux personnels et aux membres des commissions et experts de l'AFSSAPS.
Le principal objectif de sa mission est de faire des propositions réglementaires et administratives dans le but d'améliorer et de renforcer la transparence des décisions prises par la commission qui est une instance consultative chargée de donner un avis au Directeur Général de l'Agence.

Une déclaration publique d'intérêts a été instituée dès la création de l'Agence du Médicament en 1994. Il s'agit d'un document administratif dans lequel est mentionné la nature précise des liens éventuels des membres des commissions au regard de l'industrie pharmaceutique.

Avant juillet 1998, certaines règles relatives aux déclarations d'intérêts étaient déjà mentionnées dans le Code de la Santé Publique mais aucune règle ne se rapportait à la procédure à suivre en séance.
La loi du 1er juillet 1998 énumère des mesures à suivre en séance et l'administration a l'obligation de les faire respecter. Un membre d'une commission ne peut prendre part au vote ou à la délibération s'il a un lien avec la firme dont le produit est examiné. Il en est de même pour un rapporteur ou un expert qui traite un dossier.

Les décisions rendues par la commission sont succeptibles de recours ou d'annulation en cas de non respect des règles relatives aux conflits d'intérêts.
Il incombe à l'administration de veiller au respect de la procédure en séance en lien étroit avec le président de la commission. Pour cela, des "secrétaires de séance" devront être spécialement formés.

Dans l'avenir, tous les membres des commissions pourront disposer sur table des déclarations publiques d'interêts.
Par ailleurs, un guide de fonctionnement des commissions, rédigé en collaboration avec les présidents de commissions, est en cours de finalisation.

Il s'agit d'un travail progressif qui ne pourra être achevé sans la révision du problème de la valorisation de l'expertise, à savoir le mode de rémunération des experts et leur statut au sein de l'Agence.
Monsieur BENAICHE étudie cet aspect du problème et devrait finaliser un dossier et faire des propositions au directeur général de l'AFSSAPS d'ici la fin de l'année 1999.

A l'issue de l'exposé de Monsieur BENAICHE, les membres de la commission nationale de pharmacovigilance ont posé le problème des relations amicales sans lien financier qui n'entrent pas dans le champ de la déclaration publique d'intérêts.

Par ailleurs, ils ont souhaité rappeler qu'actuellement, tout expert ou membre des commissions de l'Agence doit avancer ses frais de déplacement. Le remboursement de ces frais n'est effectué que plusieurs mois après le déplacement sans aucune vérification possible de la somme remboursée. Il existe donc un réel dysfonctionnement dans la chaîne de remboursement des frais.

Le problème de l'absence de dédommagement du temps passé pour l'expertise a également été soulevé.

V - EXAMEN DE L'ENQUETE OFFICIELLE SUR LES GROSSESSES SURVENUES CHEZ DES FEMMES EXPOSEES AU ROACCUTANE® (ISOTRETINOINE). PROCEDURE NATIONALE.

A la suite des modifications du RCP de Roaccutane® survenues en mars 1997 concernant les modalités de prescription chez les femmes en âge de procréer, le Centre Régional de Pharmacovigilance (CRPV) de Tours a évalué l'incidence des grossesses exposées au Roaccutane® capsule, médicament commercialisé par les laboratoires Produits Roche et l'application des nouvelles modalités de prescription.

A-Résultats de l'enquête:

1. Grossesses exposées au Roaccutane® capsule :

L'analyse porte sur 37 grossesses exposées à l'isotrétinoïne pendant la période de risque tératogène entre mars 1997 et décembre 1998. Ces notifications provenaient des CRPV, des laboratoires Produits Roche et du Centre de Renseignement des Agents tératogènes. La moyenne d'âge des patientes enceintes était de 27 ans.

Dans 11 cas, la prise de Roaccutane® a débuté alors que la patiente était enceinte, 18 grossesses ont débuté alors que les femmes étaient déjà traitées par l'antiacnéique (48%) et 8 grossesses ont débuté moins de 1 mois après l'arrêt du Roaccutane® (22%). Dans 8 cas, la prise de Roaccutane® a été une automédication dont 5 fois chez des femmes déjà enceintes.

Les circonstances connues de survenue des grossesses étaient dans 7 cas un échec de contraception (2 cas de prescription de Diane 35®), 9 cas de contraception mal prise, 4 cas de contraception arrêtée et 5 cas de contraception locale ou absente. Les issues des grossesses ont été les suivantes : 2 bébés nés sans aucune malformation (7%), 24 interruptions de grossesse dont 8 interruptions thérapeutiques (86%) et 2 cas de fausse couches spontanées (7%).

L'estimation de l'incidence des grossesses exposées au Roaccutane® pour la période de mars 1997 à décembre 1998 est de 0,6/1000 femmes en âge de procréer (IC 95% [0,4-0,8]), peu différente de celle estimée avant la modification des modalités de prescription.
La répartition des causes de survenue des grossesses entre les deux périodes étudiées est également similaire : échec de contraception (28% vs 25%), contraception mal prise ou arrêtée (52%vs 60%), contraception absente ou locale (20% vs 15%). Il en est de même pour les issues de grossesse qui restent en majorité des interruptions de grossesses (86% vs 81%).

2. Analyse des modalités de prescriptions de Roaccutane® capsule :

Une enquête auprès de 105 pharmacies réparties sur tout le territoire a été effectuée. 30 CRPV ont participé à l'enquête. Les pharmaciens étaient chargés de vérifier la conformité des prescriptions de Roaccutane® capsule chez les femmes et de les interroger sur leur mode de contraception.

Sur 169 ordonnances analysées, 32% ne comportaient pas toutes les mentions légales de prescription (réalisation d'un test de grossesse avant la prescription et lors des renouvellements, signature d'un formulaire d'accord de soin et de contraception, réalisation de l'évaluation du niveau de compréhension de la patiente).
16% des patientes n'ont pas eu de prescription de contraceptif, et seules 61% des prescriptions de

contraception sont conformes à l'AMM. De plus, 12% des patientes n'ont pas utilisé de méthode contraceptive pendant l'exposition au Roaccutane® capsule.

Bien que l'application des recommandations les plus importantes se soit améliorée depuis le renforcement des modalités de prescription, **seules 18% des patientes ont une ordonnance rédigée correctement avec une contraception conforme à l'AMM, une information correcte et comprise en matière de contraception et de risque tératogène.**

Contrairement à ce qui est demandé dans la notice patient, 94% des pharmaciens n'ont jamais eu de restitution de capsules restantes de Roaccutane®.

Les dermatologues ont été les principaux prescripteurs (84%), les généralistes représentant 11% des prescripteurs. L'évaluation de la conformité des ordonnances aux mentions légales en fonction du prescripteur a montré une conformité dans 80% des premières ordonnances de spécialistes et 69% des renouvellements. Aucune des premières ordonnnances de généralistes n'était conforme aux mentions légales, 42% l'étaient au cours des renouvellements.

B-Présentation des laboratoires Produits Roche

Les laboratoires Produits Roche ont présenté le statut actuel de prescription de Roaccutane® capsule dans d'autres pays européens et aux Etats-Unis :

- Le test de grossesse est nécessaire 15 jours avant le début du traitement dans les autres pays de la communauté européenne et une semaine avant aux USA. Celui-ci est exigé tous les mois pendant le traitement en Europe et aux Etats-Unis, contrairement à la France (tous les 2 mois) mais aucun test de grossesse n'est demandé dans le mois suivant l'arrêt du traitement.
- Une contraception efficace est nécessaire 1 mois avant le début du traitement, pendant le traitement et 1 mois après l'arrêt dans tous les pays européens et aux Etats-Unis.
- Aux Etats-Unis :

-il est recommandé en plus d'associer une 2 ème méthode de contraception (non hormonale);
-le traitement doit être débuté 3 jours après les règles.

Bien que des améliorations des modalités de prescription aient été constatées depuis 1997, des insuffisances subsistent en particulier concernant la prise d'une contraception efficace. Ainsi les laboratoires Produits Roche s'engagent à renforcer l'information des professionnels de santé, en particulier :

- les dermatologues par une information continue (visite médicale et délivrance de "fiches pratiques" d'information sur Roaccutane® et lors des réunions professionnelles régulières);

- les gynécologues lors des congrès sur les méthodes contraceptives sous Roaccutane® capsule et plus particulièrement sur le problème de prescription d'un contraceptif non adapté;

- les médecins généralistes et les pharmaciens à partir de septembre 1999 par une visite médicale d'information et de remise de documents relatifs à la délivrance de ce médicament.

Conclusion :

Après discussion et interrogation de ses membres, la Commission Nationale de Pharmacovigilance a rejeté la proposition de restreindre la prescription de Roaccutane® capsule aux dermatologues considérant qu'un médecin généraliste bien informé devrait être en mesure de prescrire ce médicament aussi bien qu'un dermatologue.
Concernant l'information des patientes, les membres de la Commission Nationale ont clairement admis que l'on ne pourra jamais obtenir une sécurité absolue en terme de survenue de grossesse sous Roaccutane® puisqu'il y aura toujours un pourcentage de femmes qui ne respecteront pas le contrat de soin et de contraception mais il convient de tout mettre en oeuvre pour minimiser ce pourcentage.

Les propositions retenues par la Commission Nationale de Pharmacovigilance sont :

1. Modification de la rubrique "Mises en garde et précaution d'emploi" du RCP de Roaccutane® en demandant que figure sur l'ordonnance la mention "test de grossesse négatif" au lieu de "réalisation récente du test de grossesse".

2. Renouvellement de l'information des médecins prescripteurs (spécialistes ou généralistes) sur le respect des modalités de prescriptions, en particulier sur la nécessité de prescrire une contraception efficace dans le cadre de l'AMM. Il a été rappelé que la contraception ne faisait pas partie des indications de Diane 35® (indice de Pearl non disponible).

3. Renforcement de l'information des pharmaciens sur les modalités de délivrance (vérification de la conformité de l'ordonnance en matière de contraception et refus de délivrance si ordonnance non conforme à l'AMM).

VI - EXAMEN DE L'ENQUETE OFFICIELLE SUR LES EFFETS INDESIRABLES DU LAMICTAL® (LAMOTRIGINE). PROCEDURE NATIONALE.

Le centre régional de pharmacovigilance de Nantes a présenté les résultats de l'enquête officielle sur les effets indésirables du Lamictal® (lamotrigine) médicament commercialisé par les laboratoires GlaxoWellcome et indiqué dans le traitement des épilepsies. Cette enquête fait le point sur l'ensemble des effets indésirables notifiés depuis 1995, date d'octroi de l'AMM, jusqu'au 23 septembre 1998.
Par ailleurs, le CRPV de Nantes a présenté ses conclusions sur la demande de modification du Résumé des Caractéristiques du Produit déposée le 10 février 1999 par les laboratoires GlaxoWellcome.

I/ L'enquête

Le CRPV de Nantes a analysé, outre les données internationales communiquées, 169 observations imputables au Lamictal® survenues en France, dont 69 effets graves :
3 notifications concernaient des enfants de moins de 2 ans, 24 notifications des enfants de 2 à 12 ans, 134 patients de 12 à 70 ans et 3 patients de plus de 70 ans.

- **Les effets dermatologiques et allergologiques** (69 notifications) :
20 cas graves sont rapportés parmi lesquels l'analyse de la prescription fait apparaitre 8 fois une posologie non respectée, soit dans la dose administrée, soit dans la chronologie de l'ascension des doses. Parmi ces cas graves, on retrouve 2 syndromes de Lyell, 2 syndromes de Stevens Johnson, 1 toxidermie bulleuse et 5 cas d'hypersensibilité.
Le Lamictal® est le plus souvent associé à d'autres antiépileptiques, principalement l'acide valproïque.

- **Les effets neurologiques** (51 notifications) :
24 cas graves sont rapportés dont 6 aggravations des crises/état de mal, 7 syndromes vertigineux, 5 réactions de confusion, de trouble mnésique et 3 agitations ou réaction d'agressivité.
Le Lamictal® est le plus souvent associé à d'autres antiépileptiques.

- **Les effets hématologiques** (18 notifications) :
8 cas graves lesquels concernent des femmes, toutefois aucune de ces notifications n'est suffisamment documentée pour établir une relation de causalité.

- **Les effets ophtalmologiques** (10 notifications non graves), **hépatologiques** (6 notifications) **gastro-entérologiques** (6 notifications), **néphrologiques** (2 notifications graves) :
1 cas grave d'augmentation des enzymes hépatiques, ainsi que 2 cas graves de pancréatite ont été analysés.

- **les autres effets** (19 notifications graves) sont variés tels un syndrome pseudo-grippal, une sueur profuse, un épisode d'hypoglycémie avec perte de poids.

Conclusion :

La majorité des effets indésirables est correctement signalé dans le RCP actuel et les indications sont respectées. Le risque de l'association avec l'acide valproïque apparaît confirmé, notamment le risque de survenue d'effets dermatologiques graves ou non (rash, éruption, syndrome de Lyell, hypersensibilité) et d'effets neurologiques, qui restent les plus fréquents.

La fréquence des effets indésirables a été difficile à évaluer en raison de l'adaptation progressive de la posologie et d'une durée de traitement variable. L'exposition est estimée à environ 14000 patients-années, sur la base des données de vente GERS fournies par le laboratoire, sur la base d'une posologie moyenne de 196 mg/j et d'une durée de traitement moyenne d'un an.
La fréquence des effets indésirables, tous effets confondus est de 1,45 effets pour 100 patients-années. Pour les effets dermatologiques et neurologiques, cette fréquence est respectivement de 0,49 et de 0,36 pour 100 patients-années.

Les résultats de l'enquête ne modifient pas le profil de tolérance du médicament et confirment les données dont les laboratoires GlaxoWellcome font état dans le RCP proposé.
Une sous-rubrique "effets neurologiques" pourrait être individualisée dans le RCP afin d'améliorer la lisibilité de la rubrique "Effets indésirables".

II/ Demande de modification de l'information

Les demandes de modification portent sur plusieurs rubriques du RCP qui sont les suivantes :

- Rubrique "Pharmacocinétique" : elles ont été évaluées par un expert pharmacocinéticien lors de la réunion du Groupe de Travail Thérapeutique de l'AFSSAPS le 18 février 1999. Un avis favorable a été donné à la modification des rubriques "pharmacocinétique" ainsi que sur l'utilisation chez le sujet âgé et l'insuffisant hépatique. Cependant, la mention chez les sujets âgés de plus de 65 ans *"aucune adaptation posologique n'est nécessaire"* a reçu un avis défavorable.

- Rubrique "Posologie et mode d'administration" : la Commission Nationale de Pharmacovigilance a émis un avis favorable.

- Rubrique "Contre-indications" : avis défavorable de la Commission Nationale de Pharmacovigilance sur la suppression de la contre-indication de l'allaitement (Cf rubrique "Grossesse et allaitement").

- Rubrique "Mises en garde et précautions particulières d'emploi" : avis favorable de la Commission Nationale de Pharmacovigilance sauf en ce qui concerne le risque d'éruption cutanée grave de 1 pour 1000 chez l'adulte. L'ajout "rapporté comme étant un syndrome de Stevens Johnson" est tendancieuse et ne se justifie donc pas .

- Rubrique "Interactions médicamenteuses" : la Commission Nationale de Pharmacovigilance a émis un avis favorable.

- Rubrique "Grossesse et allaitement" : les laboratoires GlaxoWellcome désiraient ne pas contre-indiquer l'allaitement mais mettre en avant le rapport bénéfice/risque de l'allaitement. La Commission Nationale de Pharmacovigilance souhaite laisser la contre-indication compte-tenu du passage important du médicament dans le lait et des risques conséquents.

- Rubrique "Effets indésirables" : la Commission Nationale de Pharmacovigilance a émis un avis favorable aux propositions des laboratoires GlaxoWellcome et propose en supplément le regroupement des effets neurologiques dans une sous-rubrique "Troubles neurologiques".

- Rubrique "Surdosage" : la Commission Nationale de Pharmacovigilance a émis un avis favorable.

VII - EXAMEN DE L'ENQUETE OFFICIELLE SUR LES LEUCEMIES SECONDAIRES LIEES A L'ADMINISTRATION DES ANTHRACYCLINES. PROCEDURES NATIONALES ET PROCEDURE EUROPEENNE CENTRALISEE.

Un bref rappel sur le risque leucémogène de la NOVANTRONE® a tout d'abord été fait par Monsieur le Professeur B. Bégaud (Cf Procès-verbal de la Commision Nationale de pharmacovigilance du 1er juin 1999)

La Commission Nationale de Pharmacovigilance a pris connaissance des résultats de l'enquête officielle de pharmacovigilance présentée par les CRPV de Brest et Toulouse portant sur le risque leucémogène des anthracyclines indiquées dans le traitement du cancer du sein.

Les spécialités concernées sont les suivantes :

- **épirubicine :** FARMORUBICINE® : laboratoires Pharmacia-Upjohn.

- **doxorubicine :** ADRIBLASTINE® : laboratoires Pharmacia-Upjohn.
  DOXORUBICINE PIERRE FABRE® : laboratoires Pierre Fabre.
  DOXORUBICINE DAKOTA PHARM® : laboratoires Dakota Pharm.
  CHLORHYDRATE DE DOXORUBICINE ASTA MEDICA® : laboratoires Asta Médica.

- **pirarubicine :** THEPRUBICINE® : laboratoires Rhône-Poulenc Rorer Bellon.

L'idarubicine, la daunorubicine et la zorubicine n'ont pas l'indication dans le cancer du sein.

Les données analysées proviennent des trois sources suivantes :
1/ Notifications individuelles (spontanées, sollicitées par les CRPV, cas de la Fédération Nationale des Centres de Lutte Contre le Cancer : FNCLCC)
2/ Données des registres de Côte d'Or.
3/ Epirubicin Secondary Leukemia Monitoring Plan.

I/ Notifications individuelles.

a/ Notifications françaises : 55 observations d'hémopathies malignes après traitement d'un cancer du sein par anthracyclines ont été recensées. Pour 5 observations, l'anthracycline n'était pas associée à un agent alkylant. On dénombre 34 cas avec l'épirubicine, 20 cas avec la doxorubicine et un cas avec la pirarubicine. Les hémopathies les plus fréquemment observées sont les leucémies aiguës myéloïdes (LAM) classées M4, M5, et M2 selon la classification FAB. Les myélodysplasies et les phases pré-leucémiques sont rares. La moyenne du délai d'apparition est de 3,6 ans pour l'épirubicine et de 5,6 ans pour la doxorubicine.

b/ Notifications internationales : 29 observations ont été communiquées par les laboratoires Pharmacia-Upjohn. Les spécialités concernées sont l'épirubicine et la doxorubicine. 8 cas de myélodysplasies ont été observés (4 sous épirubicine et 4 sous doxorubicine). Les leucémies les plus fréquemment rencontrées sont les LAM de type M4, M5 et M2. Le délai d'apparition des atteintes hématologiques est plus court par rapport aux notifications françaises (2 à 2,5 ans) et se rapproche plus du délai d'apparition moyen observé pour les leucémies secondaires après traitement par inhibiteurs des topoisomérases II.
Mais l'ensemble de ces observations est très hétérogène.

2/ Données des registres de Côte d'Or.

Le risque leucémogène a été estimé à partir des 351 femmes ayant eu une exposition aux anthracyclines sur la période de 1982-1996. Un seul cas de LAM a été rapporté.

3/ Epirubicin Secondary Leukemia Monitoring Plan.

L'Epirubicin Secondary Leukemia Monitoring Plan est une étude de surveillance qui a permis d'estimer le risque leucémogène sur une cohorte de 10687 patients inclus dans 27 essais cliniques randomisés.
19 cas de leucémies secondaires ont été notés : 16 cas de LAM (leucémie aiguë myéloïde) et 3 cas de LAL (leucémie aiguë lymphoïde).
Le risque de leucémie aiguë myéloïde pour toute la population de patientes traitées pour cancer du sein a été estimé a 0,058 pour 1000 patientes-mois, soit 16 cas pour 8725 patientes.
Le risque de leucémie aiguë myéloïde pour la population de patientes traitées par épirubicine pour cancer du sein a été estimé a 0,080 pour 1000 patientes-mois, soit 15 cas pour 6086 patientes.

Dans le cadre des traitements adjuvants de cancer du sein par épirubicine, au sein de cette cohorte:
- Chez des patientes ayant reçu un traitement adjuvant par épirubicine pour cancer du sein, le risque relatif de développer une leucémie aiguë myéloïde est d'environ 0,2% à 3 ans et de 0,8% à 5 ans.
- Le risque relatif sous épirubicine seule par rapport aux protocoles FEC/EC n'apparaît pas significativement différent.
- Le risque relatif de développer une leucémie aiguë myéloïde apparaît augmenté pour les protocoles épirubicine à "haute dose" (>25mg/m^2/semaine) versus épirubicine à dose standard (<ou =25mg/m^2/semaine) avec un risque relatif de 6,13 (p=0,0003).
- Le risque relatif de développer une leucémie aiguë myéloïde apparaît augmenté pour les protocoles épirubicine administrée de façon "intensifiée" dans les protocoles FEC ou EC (épirubicine >90mg/m^2/cycle) versus épirubicine administrée dans les protocoles FEC ou EC à dose standard (<ou =90mg/m^2/cycle) avec un risque relatif de 9,3 (p=0,0001).

L'ensemble des données suggère l'existence d'un risque de leucémie secondaire après exposition aux anthracyclines. Les caractéristiques de ces leucémies secondaires sont compatibles avec l'effet leucémogène des inhibiteurs des topoisomérases II : court délai d'apparition, translocations chromosomiques équilibrées, pronostic relativement favorable.

En conclusion :

a/ Compte-tenu de l'ensemble de ces données, la Commission Nationale de Pharmacovigilance propose que le risque leucémogène de la mitoxantrone, de l'épirubicine et de la doxorubicine soit mentionné à la rubrique "Effets indésirables" du RCP de chaque spécialité.
Un libellé identique est proposé pour les 3 spécialités.

"La survenue de leucémies aiguës myéloïdes secondaires, avec ou sans phase préleucémique, a été rapportée chez des patients traités par une association de (DCI du médicament) *et d'agents anticancéreux altérant l'ADN.*
Comme avec les agents radio-mimétiques, les autres inhibiteurs de la topoisomérase II et les intercalants, des syndromes myélodysplasiques et des leucémies aiguës myéloïdes ont été observés. Ils sont de mauvais pronostic car peu sensibles à la chimiothérapie.
Par ailleurs, a été rapporté un nombre plus élevé qu'attendu de leucémies secondaires se présentant comme des leucémies de novo LAM2, LAM3, LAM4. De telles formes peuvent présenter une courte

période de latence (de 1 à 3 ans). Ces formes sont de meilleur pronostic et justifient d'un diagnostic précoce et d'un traitement adapté à visée curative."

b/ Par ailleurs, le risque de leucémie aiguë myéloïde justifiant un diagnostic précoce, il est proposé de mentionner un libellé identique à la rubrique "Mises en garde et précautions particulières d'emploi" du RCP pour ces trois spécialités :

"Certaines leucémies secondaires aux agents anticancéreux (cf rubrique "Effets indésirables") peuvent être curables à condition d'une prise en charge précoce et adaptée. En conséquence, tout patient traité par (DCI du médicament) ***doit être surveillé et exploré en cas d'anomalies hématologiques"***

Autant le risque de leucémie secondaire peut être accepté au cours de cancers évolués chez des patientes lourdement pré-traitées, autant ce risque pèse dans le choix d'un agent anticancéreux et dans ses modalités d'administration chez des sujets jeunes, en cas de cancers curables et de traitements adjuvants.
C'est pourquoi, en cas de traitement adjuvant, le risque de leucémie secondaire doit être comparé au bénéfice attendu en survie.
Par conséquent, une réévaluation du rapport bénéfice/risque de l'épirubicine, de la doxorubicine et de la mitoxantrone dans le traitement adjuvant du cancer du sein a été demandée.
L'enquête reste ouverte concernant l'évaluation du bénéfice/risque dans les autres indications thérapeutiques de ces spécialités.

VIII - QUESTIONS DIVERSES.

- Le Dr Anne CASTOT, chef de l'Unité de pharmacovigilance de l'AFSSAPS a annoncé son prochain départ de l'Unité pour prendre en charge à partir du mois d'août 1999, au sein de la Direction de l'Evaluation des Médicaments et des Produits Biologiques (DEMEB), la coordination des vigilances. Le futur responsable de l'Unité de pharmacovigilance sera le Dr Carmen KREFT-JAÏS.

- Cisapride (PREPULSID®) :

Un point sur la demande de modification d'information de la spécialité Prépulsid® déposée le 2 juin 1999 par les laboratoires Janssen-Cilag, titulaire de l'A.M.M., a été présenté par le Dr J. Caron.

Prépulsid® (cisapride) est autorisé en France selon une procédure nationale depuis 1988 dans l'indication du traitement du reflux gastro-oesophagien, de l'oesophagite par reflux gastro-oesophagien et des troubles liés à un retard de l'évacuation gastrique (gastroparésie).

En juin 1998 : compte-tenu des effets arythmogènes du cisapride, la Food and Drug Administration (F.D.A.) a pris la décision de réserver l'utilisation du cisapride au traitement de 2ème intention du reflux gastro-oesophagien, en renforçant considérablement les rubriques "Contre-indications", "Mises en garde et précautions d'emploi" du Résumé des Caractéristiques du Produit (R.C.P.).

Parallèlement, les laboratoires Janssen-Cilag ont déposé *fin juin 1998* une demande de modification d'information dans tous les pays de l'Union européenne. Ce sujet a été abordé au Comité des Spécialités Pharmaceutiques (CSP) de l'Agence Européenne pour l'Evaluation des Médicaments (EMEA) réuni les *21 et 23 juillet 1998*. Ce dernier a exprimé la nécessité d'une réévaluation du rapport bénéfice/risque et d'une harmonisation du RCP au niveau européen.

En septembre 1998 : la France a soumis aux états membres de l'Union européenne un rapport d'évaluation relatif au risque et *en mars 1999* un rapport d'évaluation relatif à l'efficacité.

En février 1999 : les laboratoires Janssen-Cilag ont soumis les résultats d'une expertise clinique menée par des cardiologues américains sur tous les effets indésirables cardiaques rapportés depuis la mise sur le marché de Prépulsid®.

En mai 1999 : les laboratoires Janssen-Cilag ont soumis les résultats d'une étude d'interaction chez le volontaire sain qui met en évidence une augmentation de 50% de la biodisponibilité du cisapride lors de l'administration de 200 ml de jus de pamplemousse .

Le 5 mai 1999 : les laboratoires Janssen-Cilag ont informé l'AFSSAPS que le libellé du cisapride était en cours de révision au niveau de la F.D.A. afin d'introduire de nouvelles mises en garde et contre-indications notamment chez les patients ayant des antécédents familiaux connus de prolongation du QT et les patients ayant une bradycardie cliniquement significative ainsi que l'interaction avec le jus de pamplemousse. L'Unité de Pharmacovigilance de l'AFSSAPS a communiqué cette information le 26 mai 1999 à l'ensemble des états membres de l'Union européenne. Ces modifications ont donné lieu aux Etats-Unis à une lettre d'information des prescripteurs (*parue le 1er juin 1999* sur le site internet des laboratoires Janssen-Cilag/Etats-Unis et *le 10 juin 1999* sur le site de la F.D.A.).

Le *25 mai 1999*, un groupe d'experts a été réuni à l'AFSSAPS afin de réévaluer le rapport bénéfice/risque du cisapride chez l'adulte et l'enfant. Il a été proposé de renforcer les mises en garde

et précautions d'emploi et de restreindre les indications.

Le *2 juin 1999*, les laboratoires Janssen-Cilag ont déposé auprès de l'AFSSAPS et dans tous les états membres de l'Union européenne une demande de modification de l'information médicale.

Cette demande concerne les rubriques "Posologie et mode d'administration" ("ajout" du jus de pamplemousse), "Contre-indications" (renforcement de la rubrique en cas d'association avec des médicaments susceptibles d'allonger le QT, hypokaliémie, hypomagnésémie, bradycardie cliniquement significative, QT long congénital et antécédents familiaux de QT long congénital), "Mises en garde" (renforcement de la rubrique), "Interactions" (renforcement de la rubrique), "Effets indésirables", "Surdosage", "Propriétés pharmacodynamiques" et" Données de sécurité préclinique". Ce dossier a été présenté lors du Groupe de Travail Européen de Pharmacovigilance réuni les *10 et 11 juin 1999* à Londres. Le Groupe de travail a approuvé les modifications du R.C.P. proposées par les laboratoires Janssen-Cilag.

Selon le rapporteur la demande de modification de l'information médicale est acceptable sous réserve de quelques amendements. Le libellé proposé par le rapporteur a été distribué en séance. Une lettre d'information des prescripteurs devra être envoyée par les laboratoires Janssen-Cilag.

- **Métamizole / agranulocytose :**

A la demande du CSP de l'Agence Européenne pour l'Evaluation des Médicaments et à la suite de l'évaluation par la Suède du risque de survenue d'agranulocytoses, la France est chargée de réévaluer le rapport bénéfice/risque du métamizole pour la réunion du CSP prévue à la fin septembre 1999. A cet effet, un groupe *ad-hoc* de la Commission d'Autorisation de Mise sur le Marché est prévu le jeudi 9 septembre 1999 à 14h00. Ce groupe sera composé de membres de la Commission d'AMM et de membres de la Commission Nationale de Pharmacovigilance.

Une télécopie sera prochainement adressée à tous les membres de la Commission Nationale de Pharmacovigilance afin de savoir qui souhaite participer à ce groupe de travail.

Benfluorex (MEDIATOR®)

En France, le benfluorex a fait l'objet d'une enquête officieuse dès 1995 en raison de sa parentée structurale avec les anorexigènes amphétaminiques. Cette enquête est devenue officielle en mai 1998.

Depuis septembre 1998, à la demande des autorités sanitaires italiennes, le benfluorex fait également l'objet d'une évaluation au niveau du Groupe de Travail Européen de Pharmacovigilance (l'Italie et la France sont rapporteurs sur ce dossier). L'un des motifs de cette enquête est la métabolisation du benfluorex en 9 métabolites dont l'un des 3 principaux est la norfenfluramine qui est également le métabolite des spécialités pharmaceutiques appartenant à la classe des "fenfluramines".

Les données disponibles issues de l'enquête officielle de pharmacovigilance ne permettent pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex. Cependant, des doutes persistent concernant notamment le devenir de la norfenfluramine. La réalisation par les laboratoires SERVIER d'une étude de pharmacocinétique du benfluorex et de ses métabolites pourrait permettre de lever ces doutes.

Au courant du mois de juin 1999, un cas d'Hypertension Artérielle Pulmonaire (HTAP) d'allure primitive a été rapporté chez une femme de 51 ans traitée par benfluorex depuis 4 à 5 ans. Il s'agit du premier cas d'HTAP rapporté avec le benfluorex utilisé sans association de médicament anorexigène. 11 cas avaient auparavant été rapportés lors d'un traitement associant le benfluorex à de la dexfenfluramine dans 10 cas et à de l'amfépramone et du clobenzorex dans 1 cas.

Cette observation est en cours de documentation et le service de Pneumologie de l'hôpital Antoine Béclère entreprend une interrogation de tous les patients ayant une HTAP à la recherche d'une prise antérieure de MEDIATOR®.

Ce dossier devrait être discuté à la prochaine réunion du Groupe de Travail Européen de Pharmacovigilance les 12 et 13 juillet 1999.

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FACSIMILE MESSAGE TO: Dr. Edith La Mache - Pharmacovigilance - EMEA

NO: 0044.171/4188551 DATE: September 25, 1998

FROM: Prof. Silvio Garattini

TOTAL PAGES BEING TRANSMITTED (INCLUDING THIS COVER LETTER): 03

Copied to: **Prof. G. Vicari** **Fax: 06/49387115**
Dr. N. Martini **Fax: 06/59943456**

****

RE: Article 15 a referral

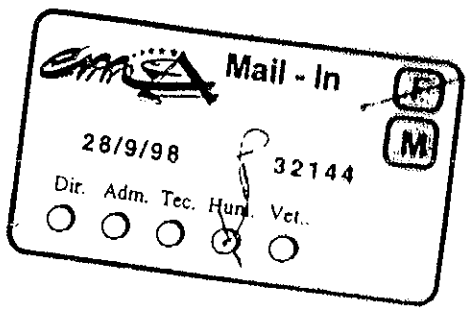
Dear Dr. La Mache,

with regards to the ongoing procedures on fenfluramine and anorectict we would like to call your attention on a medicinal product that could be included in the list of fenfluramine-containing drugs. It is MEDIAXAL by Servier, which containes Benfluorex. In Italy MEDIAXAL is intended for the treatment of obesity. This indication is based on its anti-hyperlipoproteinemic properties, not on some anorexic effect.
However, as shown in the two attachments the chemical structure of Benfluorex is strictly related to that of fenfluramine, which might be generated *in vivo* by metabolic degradation of Benfluorex. Therefore, we are wondering whether Benfluorex can be regarded as a fenfluramine-containing medicinal product.
Please, note that while MEDIAXAL is the only medicinal product containing Benfluorex on the market in Italy, other such products listed in the attachment may still be on the market in other countries.

Thank you for your kind attention.

Best regards,

Prof. Silvio Garattini



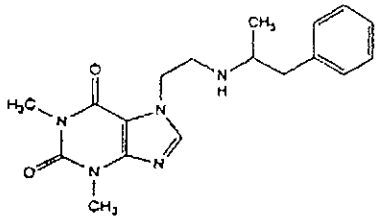
20157 MILANO, Italy - Via Eritrea, 62 - *Tel.* (02) 39014.1 - *Telefax* (02) 3546277 - (02) 39001918
Cable address: NEGRINST MILANO - *E. Mail:* MNEGRI @ IRFMN.MNEGRI.IT - *WWW Home Page:* WWW.IRFMN.MNEGRI.IT

Fenetylline (Rec.INN)

Psychostimulant

CAS-Nr.: 3736-08-1 $C_{18}H_{23}N_5O_2$

1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-7-[2-[(1-methyl-2-phenylethyl)amino]ethyl]-



OS: *Fenethylline BAN*
OS: *Fénétylline DCF*
IS: *Fenetylinum*
Fitton® (Teva, Israel)

DERIV.
hydrochloride:
OS: *Fenethylline Hydrochloride USAN*
Biocapton® (Farmakhim, Bulgaria)
Captagon® (ASTA Medica, Germany)
Captagon® (Promedica, France)

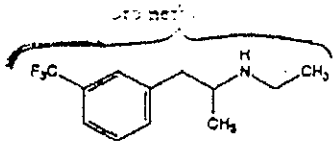
Fénétylline — Fenetylline

Fenfluramine (Rec.INN)

Anorexic

CAS-Nr.: 458-24-2 $C_{12}H_{16}F_3N$

Benzeneethanamine, N-ethyl-α-methyl-3-



OS: *Fenfluramine BAN, DCF*
IS: *S 768*
Obetrol® (Mulda, Turkey)
Ponderax® (Mason, Hong Kong)

DERIV.
hydrochloride:
OS: *Fenfluramine Hydrochloride BANM, USAN*
IS: *AHR 3002*
IS: *Ganal*
IS: *S 5019*
PH: *Fenfluramine (chlorhydrate de) Ph. Franç. X*
PH: *Fenfluramine Hydrochloride BP 1993*
Acino® (Ima, Argentina)
Adipomin® (Streuli, Switzerland)
Dexbasan® (Leiras, Finland)
Dima-Fen® (Stroder, Italy)
Fenurate® (Hermes, S. Africa)
Ketalina® (Katwijk, Netherlands)
Megrefor® (Mulda, Turkey)
Minifage® (Servier, France)
Minifage AP® (Servier, France)
Moderex AP® (Aché, Brazil)
Obesfen® (Bera, Argentina)
Obetrol® (Yurtoglu, Turkey)
Pesus® (Valeas, Italy)
Ponderal® (Benzon, Denmark)
Ponderal® (Biopharma, France)
Ponderal® (Servier, Canada)
Ponderal® (Servier, Italy)
Ponderax® (Abic, Israel)
Ponderax® (Bender, Austria)
Ponderax® (Ittherapia, Germany)
Ponderax® (Servier, France)
Ponderax Pacaps® (Servier, Great Britain)
Pondimin® (Robins, USA)
Pondimin® (Wyeth-Ayerst, Canada)
Ponflural® (Servier, France)
Ponflural® (Servier, Switzerland)
Rotondin® (Cassaco, Argentina)
Slendol® (Farmos Group, Finland)
Slimerax® (Biddle Sawyer, India)

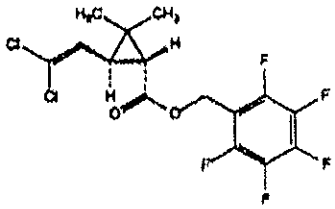
Fenfluramine (chlorhydrate de) — Fenfluramine, hydrochloride

Fenfluthrin (Rec.INN)

Insecticide

CAS-Nr.: 75867-00-4 $C_{15}H_{11}Cl_2F_5O_2$

Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (pentafluorophenyl)methyl ester, (1R-trans)-



OS: *Fenfluthrin BAN*
IS: *Bay Vn 6528*
Baynac® (Bayer)

Fenfluthrin — Fenfluthrin

Fenibutazan® — Phenylbutazone

Feniburol® — Phenylbutazone

Fenicol® — Chloramphenicol

Fenicomycin® — Chloramphenicol

Fenicort® — Prednisolone, 21-(sodium tetrahydrophthalate)

Fenigidin® — Nifedipine

Fenilbutazone — Phenylbutazone

Fenilbutina® — Phenylbutazone, diethylaminoethanol

Fenilcal® — Phenobarbital, calcium salt

Fenilefrina cloridrato — Phenylephrine, hydrochloride

Fenilfar® — Phenylephrine, hydrochloride

Fenilor® — Broxyquinoline

Feninf® — Thioctic Acid, ethylenediamine

Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral)

From:
Sender:
Date: 24/11/1998

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

At their meeting in October 1998, the CPMP considered a letter from Prof. Garattini concerning benfluorex which is an active substance used in the treatment of obesity because of its anti-hyperlipoproteinemic effect. It could possibly be metabolised to fenfluramine which is subject to an ongoing Article 15a Referral because of heart valve disorders. The CPMP agreed that the PhVWP should investigate if there is a safety issue with this active substance. Benfluorex containing products are authorised in France, Greece, Italy and Spain. A French investigation has not provided any evidence for a safety concern. In Italy, a problem of misuse might exist. The PhVWP agreed that Italy as Rapporteur will request data on metabolism and a safety update from the marketing authorisation holder. Italy will then prepare an Assessment Report for further discussion in February 1999. If necessary, a new Article 12 procedure could be initiated because benfluorex was not included in any of the previously initiated referral procedures.

Proposed Issues for Discussion

Annexe 3-14

Ministero della Sanità

F3006 F6 1397 14 DIC. 1998

TO: DR. A. CASTOT
HEAD OF PHARMACOVIGILANCE UNIT
AGENCE DU MEDICAMENT
FAX 0033 1 55 87 35 32

FROM: ITALIAN MINISTRY OF HEALTH
DRUG EVALUATION AND PHARMACOVIGILANCE DEPARTMENT
V.LE DELLA CIVILTA' ROMANA, 7
ROMA
FAX + 39 6 5994 3554

SUBJECT: ASSESSMENT REPORT FOR BENFLUOREX.

Dear dr. Castot,
I would be very grateful if you could send me a copy of the assessment report on the pharmacokinetics and metabolism of benfluorex that you performed in France. It should be very useful to carry out the Italian assessment on the possible inclusion of benfluorex in the anorectics group.
Thank you in advance for your kind accordance.

HEAD OF UNIT
DR. GIUSEPPE PLUCHINO

RBM

TOTALE P.01

Annexe 3-15

I. R. I. S.

Direction de la Recherche et du Développement

6, place des Pléiades - 92415 Courbevoie Cedex (France) - Tél. : 01 55 72 60 00 - Télécopie : 01 55 72 60 11 - Télex : 610 959 F

(International) Phone : 33 1 55 72 60 00 - Fax : 33 1 55 72 60 11

Division Pharmacovigilance
Dr F. WAGNIART
☎ 01 55 72 70 70
Fax 0155 72 65 88

Courbevoie
12 Janvier 1999

Dr Carole FOSSET
Unité Pharmacovigilance
Agence du Médicament
143-145 boulevard A. France
93200 SAINT DENIS

Cher Confrère,

Vous trouverez ci-joint pour votre information une copie des documents transmis le 23 décembre 1998 au Ministère de la Santé Italien (Dipartimento per la Valutazione dei Medicinali e la farmacovigilanza) en réponse à leur demande urgente concernant le Benfluorex :

- PSUR relatif à la période 1 Jan 92 - 31 Dec 96
- Addendum couvrant la période 1 Jan 97 - 15 Dec 98
- Résumé de la cinétique et du métabolisme

Veuillez croire, Cher Confrère, à l'assurance de mes sentiments les meilleurs.

F. WAGNIART

Annexe 3-15

1450
SERVIER

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER
I. R. I. S.

Direction de la Recherche et du Développement

6, place des Pléiades - 92415 Courbevoie Cedex (France) - Tél. : 01 46 41 60 00 - Télécopie : 01 46 41 60 11 - Télex : 610 959 F

(International) Phone : 33 1 46 41 60 00 - Fax : 33 1 46 41 60 11

Division Pharmacovigilance

Confidentiel

BENFLUOREX

MEDIATOR ®

RAPPORT PERIODIQUE DE PHARMACOVIGILANCE

Période 1er Janvier 1992 - 31 Décembre 1996

28 février 1997

F. WAGNIART

Annexe 3-15

Benfluorex

MEDIATOR ®

Rapport périodique de pharmacovigilance

Période 1er Janvier 1992 - 31 Décembre 1996

SOMMAIRE

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2 - Autorisations de mise sur le marché dans le monde 6

3 - Actions engagées par la Compagnie ou par les Autorités de Santé pour des motifs de sécurité 8

4 - Données de prescription 9

5 - Observations de pharmacovigilance 10

6 - Etudes 11

7 - Evaluation globale de la sécurité 12

8 - Informations importantes récentes ..... Néant

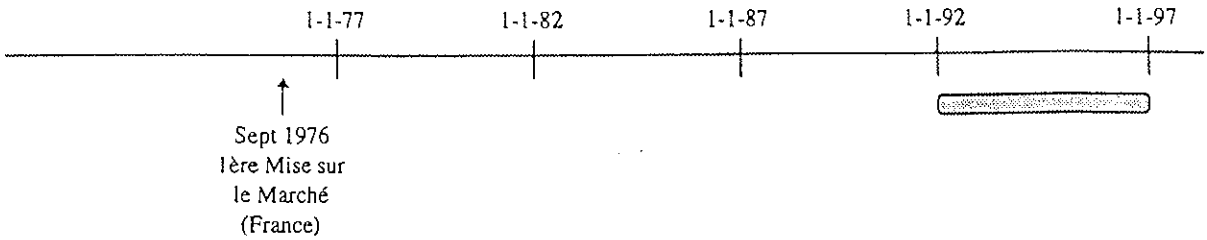
Annexe A : Résumé des Caractéristiques du Produit, MEDIATOR®, France 21 Avril 1992 (renouvellement).

Annexe B : Observations de pharmacovigilance (Spontaneous Reports of Suspected Adverse Drug Reactions - Period 1 January 1992 - 31 December 1996).

Annexe 3-15

1. Introduction

Ce rapport périodique de pharmacovigilance est le premier d'une série de rapports quinquennaux établi conformément aux nouvelles directives de l'union européenne et aux recommandations ICH (International Conference on Harmonization). Il fait la synthèse des données de sécurité collectées par la Division Pharmacovigilance de l'Institut de Recherches Internationales Servier entre le 1er janvier 1992 et le 31 décembre 1996. Cette période se situe 16 à 20 ans après la 1ère mise sur le marché du Benfluorex.



Le Benfluorex est une molécule de synthèse [Chlorhydrate N-(2-benzoyloxyéthyl) N-(2-(3-trifluorométhylphényl) isopropyl) amine] possédant une double activité hypolipémiante et anti-hyperglycémiante, indiquée comme traitement adjuvant du régime dans les hypertriglycéridémies et en association au régime dans le diabète de type 2.
La posologie recommandée est de 3 comprimés, soit 450mg.

Annexe 3-15

2. Autorisations de Mise sur le Marché dans le Monde

a) EU Countries

Approval Date	Country	Launch Date	Trade Name
Jul 1974	France	Sep 1976	MEDIATOR
Oct 1976	Luxemburg	Mar 1977	MEDIATOR
Oct 1977	Portugal	Apr 1979	MEDIATOR
			PALAMEDA
			PROPLATONE
Jun 1978	Spain	Jan 1980	MODULATOR
Oct 1978	Greece	Oct 1982	LIPOPHORAL
Dec 1980	Italy	Mar 1981	MEDIAXAL

b) Non-Eu Countries

Approval Date	Country	Launch Date	Trade Name
Nov 1976	Madagascar		MEDIATOR
Dec 1976	Benin		MEDIATOR
Jan 1977	Ivory Coast		MEDIATOR
Jun 1977	Cameroun		MEDIATOR
Jan 1978	Senegal		MEDIATOR
Jul 1978	Mali		MEDIATOR
Dec 1979	Switzerland	Dec 1981	MEDIAXAL
Aug 1980	Mexico	-	LIPASCOR
Sep 1980	Guatemala	May 1986	LIPASCOR
Oct 1980	Honduras	May 1986	LIPASCOR
Oct 1980	Nicaragua	May 1986	LIPASCOR
Oct 1980	Philippines	-	MEDIAXAL
Dec 1980	Salvador	May 1986	LIPASCOR
May 1981	Panama	May 1986	LIPASCOR
Jul 1981	Venezuela	Sep 1984	LIPASCOR
Oct 1981	Dominic Rep	May 1986	LIPASCOR
Feb 1982	Thailand	-	MEDIAXAL
Mar 1982	Hong-Kong	May 1985	MEDIAXAL
Apr 1982	Bahrein	-	MEDIAXAL
Jun 1982	Cyprus	-	LIPOPHORAL
Feb 1983	Trinidad & Tobago	Sep 1985	MEDIAXAL
Mar 1983	Curacao	Aug 1985	MEDIAXAL
Nov 1983	Syria	-	MEDIAXAL
May 1985	Korea	-	MEDIAXAL
Jul 1985	Kuwait	Oct 1986	MEDIAXAL
Aug 1985	Jamaica	Jan 1989	MEDIAXAL
Feb 1986	Costa Rica	Jun 1986	LIPASCOR
< Jun 1986	Mauritius	Jun 1986	MEDIATOR
Oct 1986	Ecuador	Nov 1988	LIPASCOR
Feb 1987	Malaysia	Oct 1985	MEDIAXAL
Apr 1987	Chile	Aug 1988	LIPASCOR
Jul 1987	Argentina	Dec 1987	LIPASCOR
Mar 1988	Bolivia	Jun 1989	LIPASCOR

Annexe 3-15

b) Non-Eu Countries (Cont'd)

Approval Date	Country	Launch Date	Trade Name
Mar 1989	Uruguay	Nov 1989	LIPASCOR
Apr 1989	Congo		
Apr 1990	Peru	-	LIPASCOR
May 1990	Colombia	-	LIPASCOR
Jul 1990	Singapore	Dec 1985	MEDIAXAL
Sep 1990	Morocco	-	MEDIATOR
Nov 1991	Vietnam	-	
Feb 1992	Togo	-	MEDIATOR
Jul 1992	Gabon	-	MEDIATOR
Jan 1993	Aruba	Aug 1985	MEDIAXAL
Feb 1994	Pakistan		MEDIAXAL
May 1994	Guinea		
Aug 1994	Ghana		
Dec 1995	Cambodia		
Jun 1996	Turkey		

Annexe 3-15

3. Actions engagées par la Compagnie ou par les Autorités de Santé pour des motifs de sécurité

Aucune action n'a été engagée au cours de la période de référence de ce rapport.

A noter cependant, en France, l'Arrêté Ministériel du 25 octobre 1995 portant interdiction d'exécution et de délivrance de certaines préparations magistrales incluant le Benfluorex ; mesure de principe destinée à bannir toutes les préparations magistrales à visée amaigrissante, suite à la présentation des résultats d'une étude prospective cas-témoins ayant démontré une association entre la prise de substances amaigrissantes en général et la survenue d'une hypertension pulmonaire primitive, et bien qu'à ce jour aucune observation n'ait été rapportée à l'utilisation du Benfluorex seul, c'est-à-dire non associé à un médicament anti-obésité.

Annexe 3-15

4. Données de prescription

Période Octobre 1991 - Septembre 1996

Estimation basée sur une posologie quotidienne moyenne à 2,4 comprimés ; mois de 30,4 jours

a) Pays de l'Union Européenne

Country	Launching Date	No of Patient-Months	
		Since launching	oct 91 - Sep 96
France	Sep 1976	20,487,173	9,338,345
Luxemburg	Mar 1977	27,944	9,227
Portugal	Apr 1979	280,840	70,043
Greece	Oct 1982	167,461	15,165
Italy	Nov 1982	3,074,644	932,267
Spain	Jan 1990	313,664	34,655
Total		24,351,726	10,399,702

b) Pays hors Union Européenne

Country	Launching Date	No of Patient-Months	
		Since launching	oct 91 - Sep 96
Venezuela	Mar 1984	188,068	72,782
Malaisia	Dec 1985	126,785	88,713
Argentina	Nov 1987	97,752	65,236
Other countries		835,074	503,825
Total		1,247,679	730,556

c) Tous Pays

Total		25,599,405	11,130,258

Annexe 3-15

5. Observations de pharmacovigilance

Toutes les notifications spontanées d'effets indésirables reçues par la Division Pharmacovigilance de l'Institut de Recherches Internationales Servier, quel que soit le pays d'origine, entre le 1er janvier 1992 et le 31 décembre 1996 sont présentées en Annexe B. Les cas sont ordonnés par appareil ou système d'organe.

Au total, 35 observations ont été documentées au cours de la période de référence de ce rapport ; 34 sont d'origine française, 1 d'origine italienne.

Observations attendues, observations inattendues

Ces observations se répartissent, en fonction de leur caractère attendu ou inattendu, de la manière suivante :

Expected Reactions

Reactions	Total No of Reports	No of Serious Reports
Digestive system		
Dyspepsia, anorexia	1	-
Nervous system		
Somnolence	1	-

Unexpected Reactions

Reactions	Total No of Reports	No of Serious Reports
Body as a whole		
Lipothymia	1	-
Pain feet	1	-
Photosensitivity	1	-
Cardiovascular system		
Bradycardia	1	-
Palpitations	1	1
Schock, ventricular tachycardia	1	1
Syncope	1	1
Digestive system		
Gastric ulcer	1	1
Hemorrhagic rectocolitis	1	-
Hepatopathy	2	1
Sub-occlusive episode	1	-
Tongue coloration	1	-
Hemic and lymphatic system		
Agranulocytosis	1	1
Metabolic and Nutritional disorders		
Gamma GT increased	1	-
Hypoglycemia	2	-
Lithemia decreased	1	-
Musculoskeletal system		
Myopathy (SGOT/SGPT increased)	1	1

Annexe 3-15

Reactions	Total No of Reports	No of Serious Reports
Nervous system		
Confusion / delirium / hallucination	3	2
Nightmares	1	-
Personality disorder	1	-
Polyneuropathy	1	1
Respiratory system		
Cough	2	-
Respiratory failure	1	1
Sneezing	1	-
Skin and Appendages		
Alopecia	1	-
Eczema	1	-
Erythema/Rash	2	-
Face edema	1	-
Pruritus	2	-
Urticaria	3	-
Urogenital system		
Bladder pain	1	-

Intoxication aiguë

Une observation de surdosage accidentel a été rapporté chez un enfant de 2 ans et demi, sans aucune conséquence (Ref. No 540O22).

Imputabilité

L'imputabilité est douteuse dans 30 cas et plausible ou vraisemblable dans 5 cas de réactions cutanées (Ref. No 540989, 540S90, 540V73), augmentation des gamma GT (Ref No 120O39), toux (Ref No 541078).

Gravité

10 patients ont été hospitalisés

- Ref. No 540W55 : Palpitations sous Sotalol et Benfluorex (observation peu documentée, médicaments maintenus)
- Ref No 540V17 : Confusion mentale sous Amfépramone et Benfluorex
- Ref No 540O22 : Intoxication accidentelle chez un enfant de 2ans et demi, sans aucune conséquence médicale
- Ref No 541083 : Torsade de pointes sous Dextropropoxyphène, Benfluorex et Piroxicam (aucun facteur prédisposant apparent)
- Ref No 540930 : Ulcère gastrique sous Benfluorex, Metformine, Gemfibrozil, Lisinopril, Glibenclamide.
- Ref No 120i53 : Hépatopathie (augmentation modérée de la bilirubine et des transaminases), stéatose hépatique probable.
- Ref No 541259 : Agranulocytose sous Sulfasalazine, Fluoxetine, Benfluorex et Benazepril.
- Ref No 541175 : Augmentation des enzymes musculaires et des SGOT /SGPT sous Fenofibrate et Benfluorex.
- Ref No 120M85 : Malaises amnésiques et confusion chez un homme polyartériel (sténose carotidienne et anévrisme de l'aorte descendante opérés récemment).
- Ref No 541183 : Poussée d'insuffisance respiratoire aiguë chez une patiente atteinte de COPD et de cardiopathie hypertensive.

Dans tous ces cas, l'imputabilité du Benfluorex est douteuse.

Annexe 3-15

6. Etudes

Aucune étude nouvelle relative à la sécurité du Benfluorex n'a été analysée ou publiée au cours de la période de référence de ce rapport.

5 études cliniques ou de pharmacologie clinique ont cependant été réalisées dont les données d'acceptabilité peuvent être résumées de la façon suivante.

Ces études de 3 mois contrôlées contre placebo en parallèle ont comporté un total de 173 patients inclus dans les groupes benfluorex (n = 87) et placebo (n = 86).

- 4 patients du groupe placebo (4.7%) et 6 patients du groupe benfluorex (6,9%) ont arrêté l'étude pour événements indésirables (tableau).

Les effets indésirables rapportés sous benfluorex sont des diarrhées et des douleurs abdominales persistantes, et plus rarement, hypoglycémie, hyperglycémie, oedème palpébral avec prurit modéré.

Sous placebo, les patients se plaignaient d'asthénie et d'hypoglycémie, ainsi que de sécheresse buccale.

Evènements indésirables (incidence et symptômes) ayant entraîné l'arrêt du traitement (benfluorex/placebo) dans 5 études contrôlées (rapports internes Servier)

Etudes	Nombre d'inclus		Nombre d'arrêts de traitement		Evènements indésirables	
	PL	BF	PL	BF	Placebo	Benfluorex
Velussi, 1994	15	15	2	0	-sécheresse buccale -hospitalisation pour poussée arthritique	
Erkelens, 1994	10	10	0	0		
Pontiroli, 1994	14	16	0	0		
Louvet, 1995	13	12	0	1		-diarrhée et douleurs abdominales persistantes
Tomasi, 1996	34	34	2	5	-hypoglycémie -asthénie modérées	-hypoglycémie modérée -hyperglycémie sévère -diarrhée sévère -oedème palpébral avec prurit modéré -troubles digestifs modérés
	86	87	4 (4,7%)	6 (6,9%)		

Annexe 3-15

Les effets indésirables n'ayant pas entraîné d'arrêt de traitement sont rapportés dans le tableau ci-dessous. Aucune différence n'est observée entre les pourcentages d'effets indésirables sous placebo et sous Benfluorex (16%). Sous benfluorex, les effets indésirables le plus souvent rapportés sont toujours les troubles digestifs (diarrhées, gastrites, nausées, douleurs abdominales) et plus rarement des sensations vertigineuses, de la fatigue, un prurit modéré, une tendance oedémateuse, des bouffées de chaleur, une hypoglycémie.

Evènements indésirables (incidence et symptômes) n'ayant pas entraîné l'arrêt du traitement dans 5 études contrôlées (rapports internes Servier)

Etudes	Nombre d'inclus		Nombre d'arrêts de traitement		Evènements indésirables	
	PL	BF	PL	BF	Placebo	Benfluorex
Velussi, 1994	15	15	2	2	-sécheresse buccale -douleurs abdominales	- diarrhées - gastrites/diarrhées
Erkelens, 1994	10	10	3	6	-nausées (2) -sensations vertigineuses (1)	- nausées -diarrhées -sensations vertigineuses -fatigue -prurit modéré -tendance oedémateuse
Pontiroli, 1994	14	16	1	1	-céphalées	-hypotension quelques heures (hospitalisation)
Louvet, 1995	13	12	6 (T90)	4 (T90)	le plus souvent : douleurs abdominales et autres troubles digestifs, asthénie, bouffées de chaleur	
Tomasi, 1996	34	34	2	1	-vomissements -pharyngites	-hypoglycémie
	86	87	14 (16,3%)	14 (16%)		

Aucune relation causale entre évènement indésirable et benfluorex n'a été montrée, sauf pour le patient présentant des nausées dans l'étude d'Erkelens. Dans l'étude Louvet, une patiente est décédée d'un cancer vésiculaire métastasé un mois après l'arrêt de traitement sous placebo.

Aucune modification de pression artérielle et de fréquence cardiaque n'est observée sauf dans l'étude de Tomasi (la fréquence cardiaque couchée augmente significativement entre TO et T90 sous benfluorex). Dans l'étude d'Erkelens, un léger oedème des membres inférieurs, et des crépitants minimes des bases pulmonaires, respectivement chez deux patients sous placebo ont été rapportés.

Chez ces patients, l'observance a été bonne : Velussi (>80%), Erkelens (>90%), Pontiroli (proche de 100%), Louvet (benfluorex : 89,4% ; placebo : 94,7%), Tomasi (≥90%).

Références

ERKELENS DW.
Evaluation of the effects of benfluorex (450mg/day, per os) in combination with insulin in 20 obese type 2 diabetic with secondary failure. Rapport interne 1994.

LOUVET JP.
Etude en double aveugle randomisée versus placebo des effets du benfluorex sur le statut métabolique de diabétiques non-insulinodépendants traités par sulfonylurées. Rapport interne 1995.

Annexe 3-15

PONTIROLI A.
Association du benfluorex (450mg/jour per os) à l'insulinothérapie chez 30 patients diabétiques de type 2 mal contrôlés par le traitement insulinique seul. Rapport interne 1994.

TOMASI F.
Effets de l'administration de benfluorex (450mg/jour pendant 3 mois) sur le contrôle métabolique, chez 60 patients diabétiques de type 2 traités par sulfonylurées. Etude en double aveugle versus placebo. Rapport interne 1996.

VELUSSI M.
Effets de l'administration du benfluorex (450mg/jour per os pendant 3 mois) sur l'insulinémie et sur le métabolisme glucidique chez 30 patients diabétiques de type 2, hyperinsulinémiques et en surpoids. Etude contrôlée versus placebo. Rapport interne 1994.

7. Evaluation globale de la sécurité

Aucun élément nouveau n'a été enregistré en matière de sécurité au cours de la période de référence de ce rapport.

Annexe A

Résumé des Caractéristiques du Produit

MEDIATOR ®

France, 21 avril 1992

Annexe 3-15

Résumé des Caractéristiques du Produit

I - DENOMINATION

MEDIATOR

II - COMPOSITION QUALITATIVE ET QUANTITATIVE

	p. comp.	p. boîte
Benfluorex (DCI) chlorhydrate	150mg	4,5g

Excipient : amidon de maïs, carboxyméthylcellulose sodique, cire d'abeille blanche, éthylcellulose, stéarate de magnésium, oléate de glycérol, polysorbate 80, polyvidone, silice colloïdale, saccharose, bicarbonate de sodium, talc, dioxyde de titane.

III- FORME PHARMACEUTIQUE

Comprimé enrobé (blanc) : Boîte de 30.

IV- DONNEES CLINIQUES

IV.1. Indications thérapeutiques

- Adjuvant du régime adapté dans les hypertriglycéridémies . La poursuite du régime est toujours indispensable.
- Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

IV.2. Posologie et mode d'administration

3 comprimés par jour.

Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

- 1 comprimé la première semaine au dîner,
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner,
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois 1 comprimé par jour, en fonction des résultats biologiques.

En association avec le régime, Médiator constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

IV.3. Contre-indications

- Pancréatites chroniques avérées.

Annexe 3-15

Mises en garde

Les troubles métaboliques relevant d'un traitement par Médiator sont essentiellement observés chez l'adulte.

La prescription de Médiator n'est donc pas justifiée chez l'enfant.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

Précautions d'emploi :

Si, après une période d'administration de quelques mois (3 à 6 mois), une réduction satisfaisante des concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

IV.5. Interactions

IV.6. Grossesse et Allaitement

GROSSESSE : Les résultats des études réalisées chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence de données dans l'espèce humaine, ces résultats expérimentaux ne permettent pas de préjuger un effet malformatif. Cependant par mesure de prudence, ne pas prescrire pendant la grossesse.

ALLAITEMENT : en l'absence de données sur le passage dans le lait maternel, l'allaitement est déconseillé pendant la durée du traitement.

IV.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

IV.8. Effets indésirables

Les effets secondaires suivants ont été observés : digestifs (nausées, vomissements, gastralgies, diarrhées), asthénie, somnolence ou état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.

IV.9. Surdosage

Conduite à tenir en cas d'absorption massive : le traitement sera purement symptomatique : lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience, des fonctions respiratoire et cardiaque.

V - PROPRIETES

V.1. Propriétés pharmacodynamiques :

Hypolipémiant :

Il agit sur plusieurs facteurs liés au risque athérogène.

- *Actions de Médiator sur le métabolisme lipidique* :
- Médiator diminue l'absorption intestinale des triglycérides (rat). Cet effet, confirmé chez l'homme en pharmacologie clinique, repose sur la diminution d'activité de la lipase pancréatique.

Annexe 3-15

- Il réduit la synthèse hépatique des triglycérides et du cholestérol in vitro et in vivo (rat).
- Il diminue la stéatose hépatique induite par des régimes riches en lipides, en glucides chez le rat obèse et au cours du diabète expérimental (rat).
- Il limite l'incorporation du cholestérol dans la paroi artérielle (lapin).

Ce mode d'action est susceptible d'expliquer la diminution du cholestérol et des triglycérides chez l'homme.

- *Actions de Médiator sur le métabolisme glucidique* :
- Il facilite la pénétration et l'utilisation cellulaires du glucose (rat).
- Il diminue l'hyperglycémie du rat diabétique (insulinoprive ou non) et l'aire d'H.P.O chez le lapin.
- Dans le diabète asymptomatique chez les patients obèses, il entraîne une baisse de la glycémie post-prandiale et une amélioration de la courbe d'H.P.O. supérieure à celle qu'on obtient avec un régime identique associé à un placebo.

Médiator, n'ayant pas d'action sur l'insulino-sécrétion, ne peut pas provoquer d'hypoglycémie.

- *Effet complémentaire de Médiator* :

Chez des patients obèses hyperuricémiques traités par Médiator et régime, une baisse de l'uricémie d'environ 14% a été observée.

Aucune interférence indésirable de Médiator avec les traitements associés au cours des études n'a été constatée.

Médiator :

- ne potentialise pas les anticoagulants,
- ne provoque pas d'hypoglycémie,
- n'interfère pas avec la fonction thyroïdienne.

V.2. Propriétés pharmacocinétiques

- Absorption gastro-intestinale rapide et totale avec un pic maximal survenant entre 1 et 2 heures après l'administration.
- Elimination rapide et totale par voie urinaire : en 8 heures, une excrétion moyenne d'environ 74 % de la dose administrée est constatée.

L'élimination se fait en 2 phases :

- une première phase rapide (60% en 3 ou 4 heures),
- une deuxième phase lente, se terminant en 36 heures environ.

VI- DONNEES PHARMACEUTIQUES

VI.1. Incompatibilités

VI.2. Durée de conservation : 4 ans

VI.3. Précautions particulières de conservation

VI.4. Nature et contenance du récipient

VI.5. Mode d'emploi, instruction

Annexe 3-15

VII- PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE

317.557.9 : 30 comprimés
317.559.1 : 100 comprimés

VIII- CLASSIFICATION EN MATIERE DE DELIVRANCE

LISTE I

IX - TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

Les Laboratoires Servier
22, rue Garnier
92200 Neuilly sur Seine

X - DATE D'APPROBATION / REVISION

16-7-1974, avec validation partielle le 22-04-1987 (validation endocrinologie en attente), renouvellement le 21-04-1992.

-:-:-:-

Annexe B

Observations de Pharmacovigilance

Benfluorex

1 janvier 1992 - 31 Décembre 1996

APPENDIX B

BENFLUOREX - Spontaneous Reports of Suspected Adverse Drug Reaction - Period : 1 January 1992 - 31 December 1996

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description (* Serious reaction)	Outcome	Comments
Body as a whole									
840104	France	HP	40	M	300mg	1.5m	Photosensibility reaction	Recovery	
540A46	France	HP	43	F	300mg	>8m	Lipothymia	Recovery	Negative rechallenge . Drug maintained
540F84	France	HP	53	F	450mg	u	Pain feet	Persistency	
540O22	France	HP	2	M	450mg	1d	Accidental overdose *	Recovery	No signs/symptoms
Cardiovascular System									
540W55	France	CRPV	52	F	u	u	Palpitation *	Recovery	Sotalol associated .Drugs maintained
541083	France	CRPV	59	F	150mg	5m	Torsade de pointes *	Recovery	Several drugs associated
120E93	France	HP	38	M	450mg	1w	Bradycardia	Recovery	
Digestive System									
840616	France	HP	72	M	300mg	14m	Tongue coloration	Improvement	
540D08	France	HP	61	F	450mg	days	Sub-occlusive episod	Recovery	Intestinal polyposis associated
540L94	France	HP	48	F	450mg	20m	Hepatopathy	Improvement	
540P69	France	HP	46	F	150mg	u	Hemorrhage rectocolitis	Improvement	
540V43	France	HP	66	F	450mg	45d	Dyspepsia , anorexia	Recovery	
540930	France	HP	64	F	300mg	3m	Ulcer stomach *	Recovery	
120I53	France	CRPV	36	F	450mg	4m	Hepatopathy *	Recovery	Likely liver steatosis .
Hemic and Lymphatic System									
541259	France	CRPV	73	F	150mg	u	Agranulocytosis *	Recovery	Several drugs associated
Metabolic and Nutritional disorders									
540H49	France	HP	56	F	450mg	>2y	Lithemia decrease	Unknown	Drug maintained . Interaction with [illegible]
540J00	France	HP	35	M	150mg	months	Hypoglycemia	Unknown	
540P03	France	HP	60	F	450mg	15d	Malaise (hypoglycemic)	Recovery	
120O39	France	HP	70	F	150mg	u	GGT increased	Recovery	Positive rechallenge .
Musculoskeletal System									
541175	France	CRPV	66	F	150mg	2m	Myopathy (Increased SGOT & SGPT)*	Recovery	Fenofibrate associated .

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Annexe 3-15

Benfluorex - Spontaneous Report of Suspected Adverse Drug Reaction : Period 1 January 1992 - 31 December 1996

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description (* Serious reaction)	Outcome	Comments
Nervous System									
540J08	France	HP	68	M	450mg	1m	Polyneuropathy*	Recovery	
540O46	France	HP	u	M	450mg	u	Nightmares	Recovery	Drug maintained with reduced dosage
540V17	France	CRPV	59	F	450mg	2m	Delirium , agitation , disorientation *	Recovery	Amfepramone associated .
541173	France	HP	45	F	300mg	8d	Hallucination , aggressivity	Recovery	
120M52	France	HP	60	M	150mg	2d	Somnolence , personality disorder	Recovery	
120M85	France	HP	70	M	300mg	11d	Amnesia , confusion (malaise) *	Improvement	Cerebrovascular insufficiency
Respiratory System									
541078	France	HP	70	F	450mg	u	Coughing , sneezing	Recovery	Positive rechallenge .
541183	Italy	HP	56	F	450mg	#2m	Respiratory insufficiency (syncope)*	Recovery	COPD and hypertensive cardiopathy cases
Skin and Appendages									
540D65	France	HP	48	F	150-450mg	days	Giant urticaria	Recovery	History of allergies .
540F26	France	HP	20	F	450mg	>2m	Alopecia	Persistency	Drug maintained .
540S90	France	HP	41	M	300mg	days	Papulous erythema , pruritus	Recovery	Positive rechallenge .
540U37	France	HP	51	M	300mg	9d	Pruritus , rash	Recovery	
540V73	France	HP	49	F	150mg	1d	Urticaria , edema , fever	Recovery	Positive rechallenge .
540W61	France	HP	67	F	150mg	2y	Eczema , face edema (coughing)	Recovery	Possibly cosmetics-induced
540989	France	HP	31	F	450mg	3d	Urticaria	Recovery	Positive rechallenge .
Urogenital System									
540F68	France	HP	33	F	450mg	8d	Bladder pain	Recovery	

1170

Annexe 3-15

Legend

HP	*Health Professional*
CRPV	*Regional Pharmacovigilance Center*
u	*Unknown*

LABORATOIRE : SERVIER

Envoi le : _____

Réception le : _____

Accusé le : _____

ou le 12/05/97.

BENFLUOREX . Médiator (12).

Conforme OUI NON

Si NON
2-pas de synthèse
3-pas de chiffres
4-pas d'imprimés
8-pas gravité Europe
9-pas de données internationales
10-pas de données françaises

DÉCLARATION OBLIGATOIRE ☐

PSUR ☒

1/01/92 → 31/12/96.

N°1678

Quinquénal ☒ Annuelle ☐ Semestrielle ☐ Autre ☐

	FRANCE		INTERNATIONAL (FRANCE + HORS FRANCE)	
Variété unitaire	Nbre Effets	Nbre d'E.I (gravité Europe)	Nbre d'Effets	Nbre d'E.I graves
	~~35~~	~~30~~	36	11 ~~36~~

1171

Annexe 3-15

Annexe 3-16

AGENCE DU MEDICAMENT
Direction de l'Evaluation
Unité de Pharmacovigilance

FAX

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
Agence du Médicament

DATE : 21 JAN. 1999

Pages (incl. cover) : 38

TO : **Fax N° :**

Italy . Dr Giuseppe PLUCHINO 39-6-5994.3554
..... 39-6-5994.3456
..... 39-6-5994.3365

SUBJECT / OBJET : Benfluorex

Dear colleague,

Further to your request, please find enclosed the french assessment report on the pharmacokinetics, metabolism and safety of benfluorex.

I apologize for the delay of my response.
Don't hesitate to contact us if you need more information.

Best regards.

Le Chef de l'unité de Pharmacovigilance

Dr Anne CASTOT

Annexe 3-16

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Jean Minjoz 25030 BESANCON Cedex

MEDIATOR (benfluorex)

ENQUETE OFFICIELLE

Comité Technique du 17 Décembre 1998

Confidentiel

M.DAVID-LAROCHE
P.BECHTEL

Annexe 3-16

Le MEDIATOR (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par le laboratoire BIOPHARMA, sous forme de comprimés, dosés à 150 mgL
La posologie recommandée est de 3 comprimés par jour.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène.
(Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Une enquête officieuse a été ouverte, suite à la première mise au point des effets indésirables du benfluorex, présentée lors du Comité Technique du 11 juillet 1995.
Deux mises au point ont été faites :
-le 30 Avril 1998 sur les effets indésiirables du benfluorex, rapportés aux CRPV
-le 10 Septembre 1998 sur le métabolisme et les chiffres de vente du benfluorex.

<u>Les effets indésirables rapportés dans les RCP sont :</u>

- effets digestifs : nausées, vomissements, gastralgies, diarrhée
- asthénie
- somnolence
- état vertigineux

Annexe 3-16

DONNEES PHARMACOCINETIQUES ET METABOLIQUES CHLORHYDRATE DE BENFLUOREX

I- Pharmacocinétique.

L'absorption gastro-intestinale du chlorhydrate de benfluforex est complète et rapide, le Tmax est compris entre 1h et 2h.
Le volume de distribution est de 0.37+/- 0.03l/kg chez l'homme.
Chez le rat il est de 1.4l/kg.
Chez le chien de 1.6l/kg.
Chez le singe de 0.36l/kg.
Chez le babouin de 0.31l/kg

On notera que le volume de distribution est identique chez les primates et chez l'homme.

II. Métabolisme.

Le benfluorex est rapidement métabolisé au niveau du foie. Il produit au moins 9 métabolites. (Fig 1). Des données récentes utilisant notamment des méthodes de détection spécifiques et sensibles ont permis de montrer qu'il existait deux métabolites principaux (fig 2) :

- le 1-(3 trifluorométhylphényl)-2N-2-(carboxymethyl)amino propane (S1475)
- la norfenfluramine (S 585)

Une étude réalisée chez 6 volontaires sains qui ont reçu pendant 14 jours une dose quotidienne de 3fois 150mg de benfluorex, a montré que :

- l'état stationnaire était atteint en 4 à 5 jours
- au bout des 14 jours la concentration plasmatique de benfluorex était très faible, autour de 10ng/ml, la concentration plasmatique du métabolite S1475 était très importante, aux alentours de 200ng/ml, la concentration plasmatique du norfenfluramine ne dépassait pas 30ng/ml (fig 3).

Il est très intéressant de comparer les métabolites produits par la biotransformation de benfluorex à ceux produits par la biotransformation de la fenfluramine (fig 4). La norfenfluramine représente la voie principale du métabolisme de la fenfluramine avec des concentrations urinaires de 7,4% de la dose pour la forme libre et de 50,7% pour la forme conjuguée à l'acide glucuronique.

Sans qu'il y ait d'explications à partir de la fenfluramine il semble que la norfenfluramine produite ne subit aucune biotransformation supplémentaire, alors que la norfenfluramine produite à partir de benfluorex est transformée en 3-trifluorométhylphényl-1-hydroxypropanone-2. Ce qui explique qu'on ne trouve pas plus de 2% de norfenfluramine dans l'urine.

Dans une étude où pendant 15 jours un groupe de 8 volontaires a reçu une dose journalière de trois fois 20mg de fenfluramine, la concentration sanguine de fenfluramine au bout de cette période était d'environ 120 ng/ml et celle de norfenfluramine d'environ 50ng/ml (fig 5).

En comparant les deux études :

- après fenfluramine le taux circulant de norfenfluramine représente 30% du taux circulant de fenfluramine

- après benfluorex la norfenfluramine représente 5% du taux circulant du métabolite principal S1475.

Il est impossible d'exclure la possibilité de passage de la barrière hémato-cérébrale de la norfenfluramine produite par le métabolisme de benfluorex.
Il faut toutefois noter qu'après administration de fenfluramine la quantité circulante de norfenfluramine vient s'additionner à celle de la fenfluramine et donc renforcer son action centrale anorexigène.

Nous rappelerons que malgré la production de norfenfluramine, la propriété pharmacodynamique d'anorexigène n'a jamais été attribuée à benfluorex.

SCHEMA DU METABOLISME

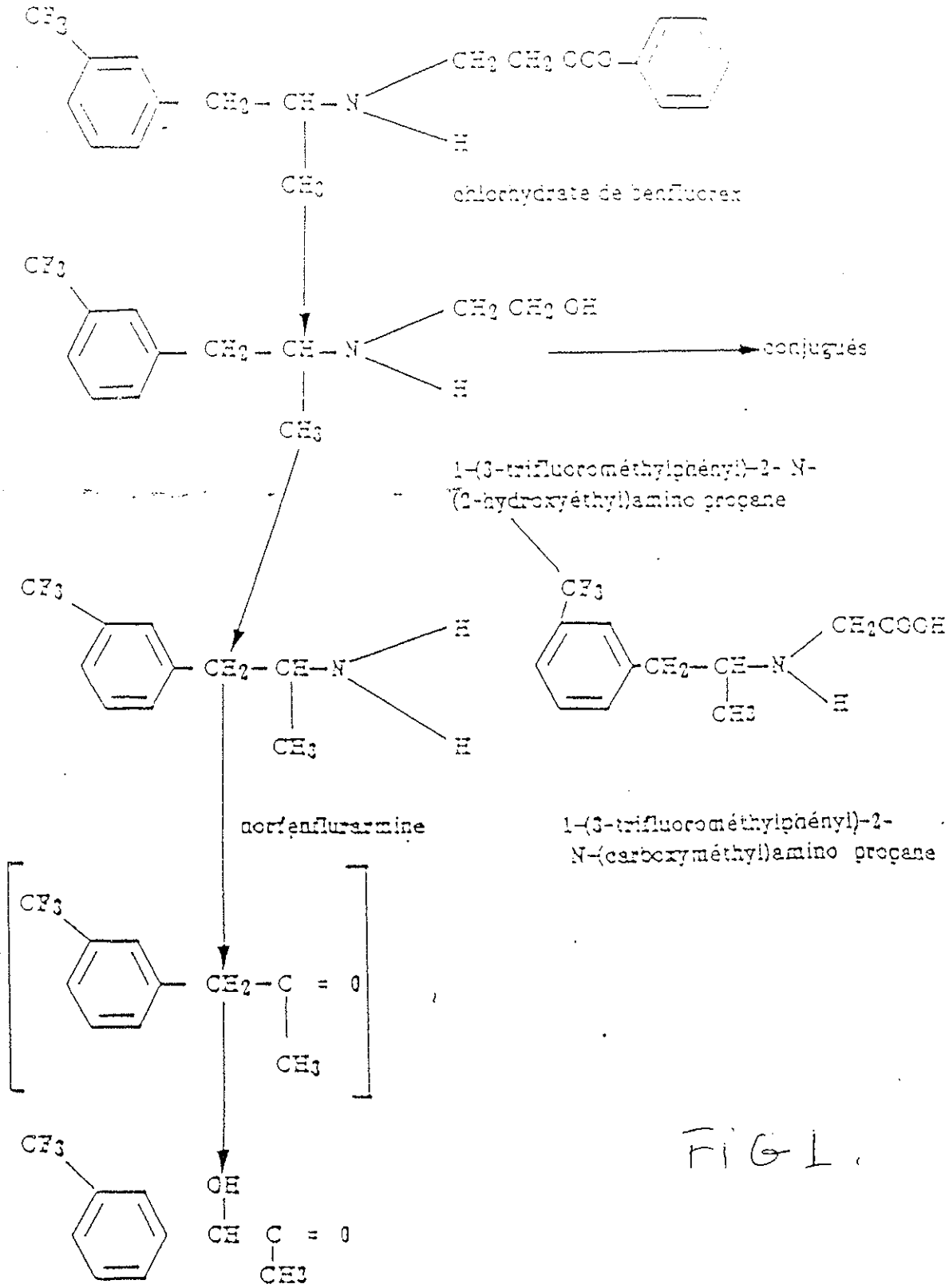
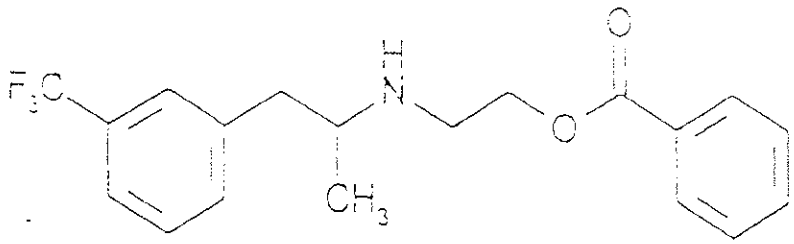


FIG 1.

Annexe 3-16

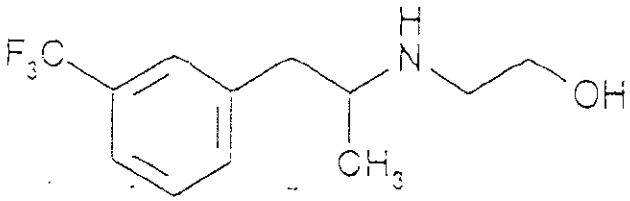
BENFLUOREX

EXCRETION URINAIRE



chlorhydrate de benfluorex

ND



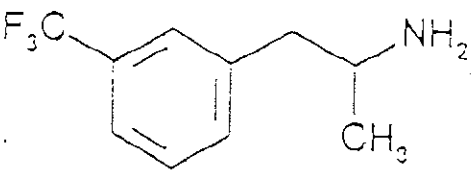
1-(3-trifluorométhylphényl)-2N-(2-hydroxyéthyl)amino propane

12

+ Acide benzoique

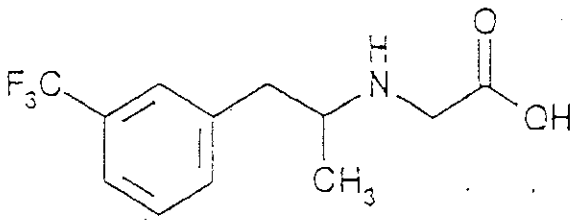
conj. gluc.

14



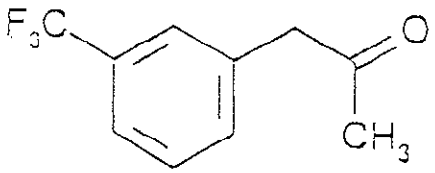
2

norfenfluramine



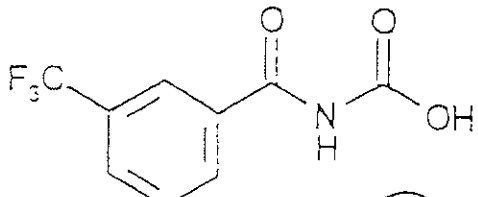
63

1-(3-trifluorométhylphényl)-2N–2-(carboxyméthyl)amino propane



3

FIG 2



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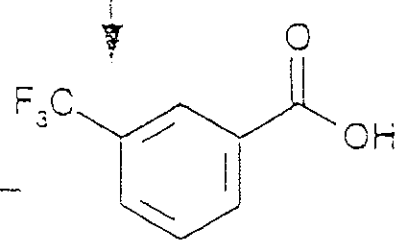
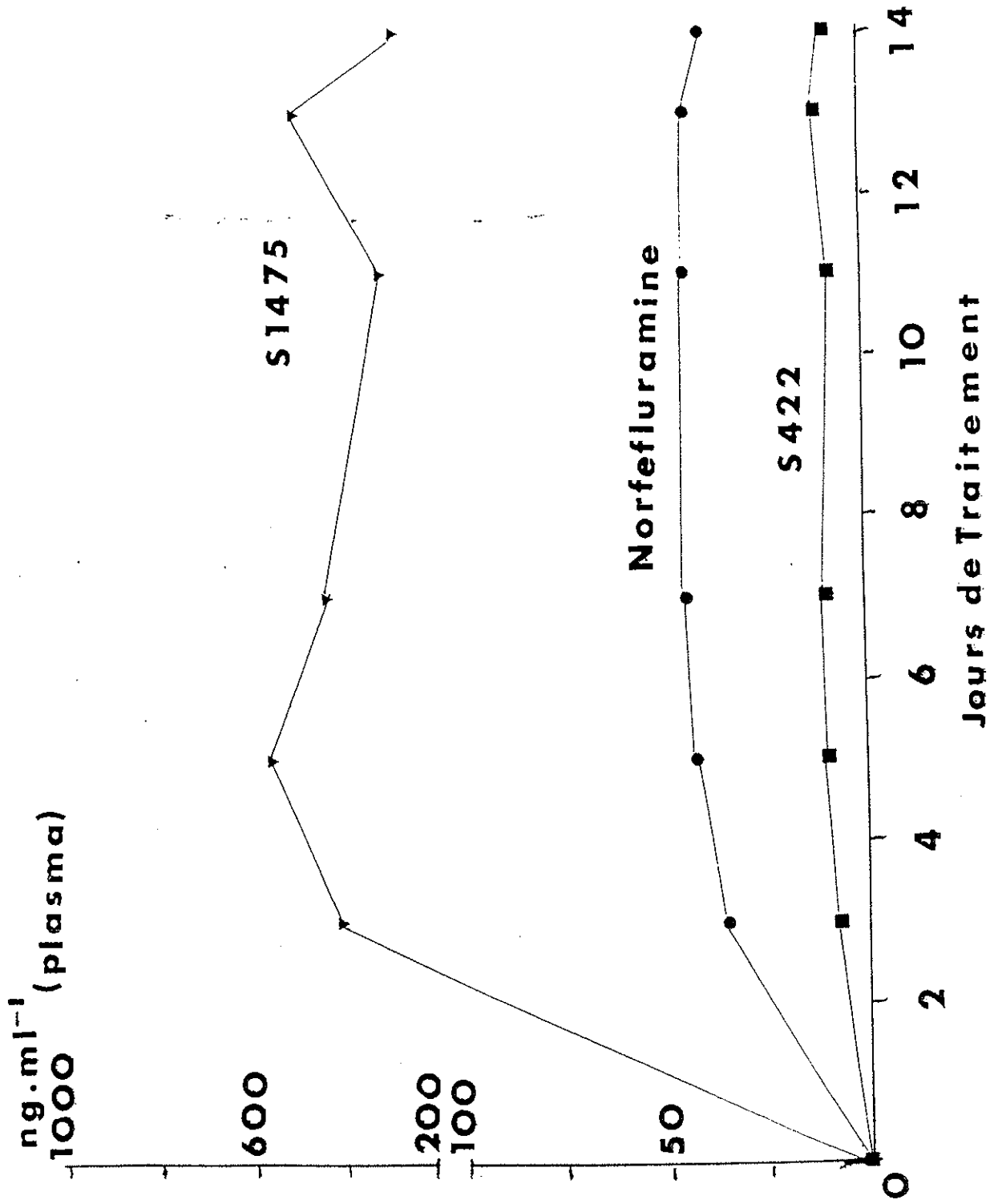


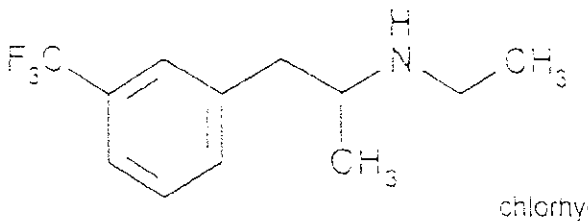


Métabolites du BENFLUOREX

Annexe 3-16

FENFLURAMINE

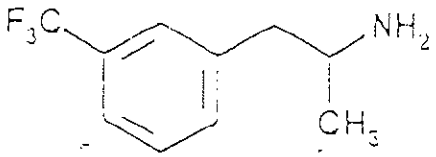
% EXCRETION URINAIRE



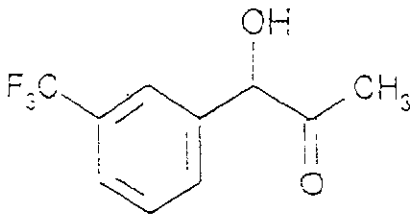
chlorhydrate de fenfluramine

11

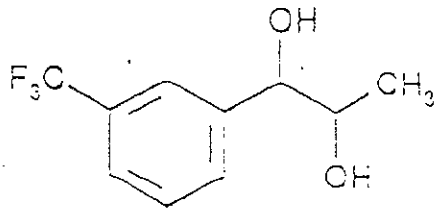
norfenfluramine



7.4



ND



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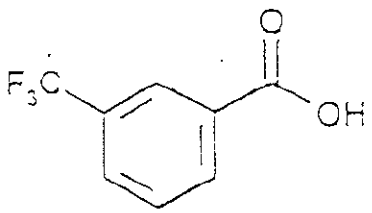
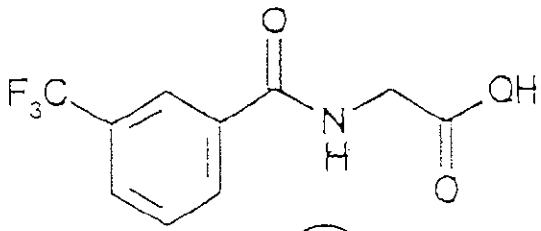


ND

gluc. conj.

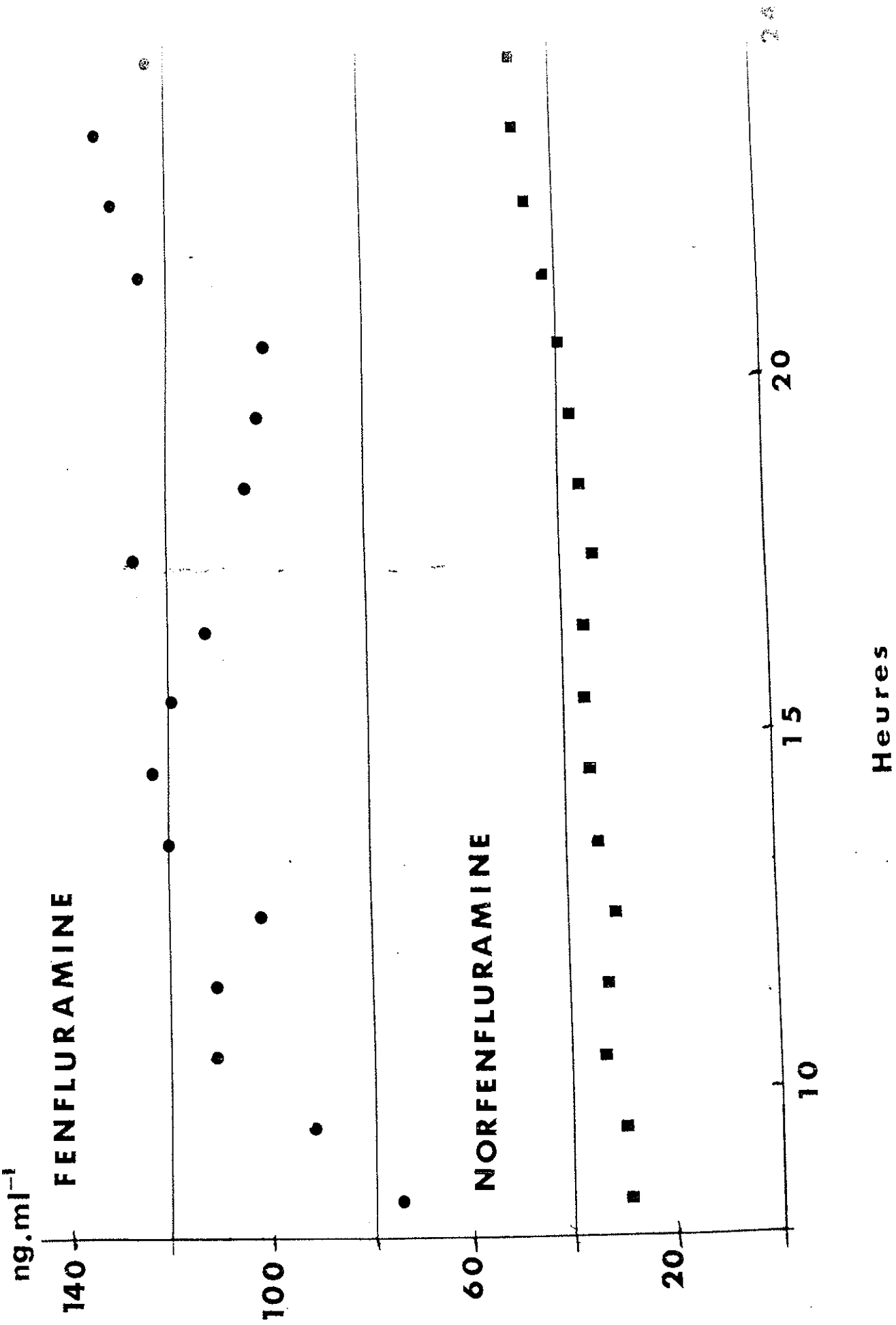
50.7



8.4

Fig 4

Annexe 3-16


ng.ml⁻¹
FENFLURAMINE
NORFENFLURAMINE
140
100
60
20
10
15
20
Heures

Annexe 3-16

A. BILAN GLOBAL

265 notifications validées ont été rapportées :

163 aux Centres Régionaux de Pharmacovigilance, 105 au laboratoire.(dont 3 doublons)

Elles concernent 93 hommes et 171 femmes (1 sexe non précisé), dont l'age moyen est de :

- 56,9 ans pour les hommes
- 55,9 ans pour les femmes

Répartition par classe-organe des effets indésirables notifiés :

APPAREIL	Nombre de Notifications CRPV	Nombre de Notifications Laboratoire	TOTAL	Nombre de doublons
FOIE	17	9	25	1
APP. DIGESTIF (sauf foie)	16	5	21	-
HEMATOLOGIE	8	6	14	-
APPAREIL RESPIRATOIRE	10	11	20	1
CARDIO-VASCULAIRE	12	6	18	-
APPAREIL URINAIRE	9	4	13	-
PEAU - ALLERGIE	41	23	64	-
NEURO-PSYCHIATRIE	30	18	48	-
VERTIGES	16	5	20	1
METABOLISME	3	18	21	-
APPAREIL SENSORIEL	1	-	-	-
TOTAL	163	105	265	3

N.B : les nouvelles notifications par rapport à la mise au point de Juillet 1995, sont imprimées **«en gras »** dans les tableaux suivants.
Dans la colonne, « traitement associé », le médicament est souligné, lorsque l'imputabilité bibliographique est supérieure au MEDIATOR.

Annexe 3-16

23 cas d'hépatites ou de perturbations de la biologie hépatique ont été notifiés : (le benfluorex est le seul suspect ou d'imputabilité égale ou supérieure aux médicaments associés)

-15 aux CRPV, 9 au laboratoire (dont 1 doublon) .

Elles concernent 15 femmes (âge moyen : 55,1 ans) et 8 hommes (âge moyen (58,6 ans)

Dans 7 cas le benfluorex a une imputation plausible:

DJ9300271 : Femme de 50 ans , traité pendant 2 semaines par MEDIATOR, une préparation d'aubépine, 200mg, et amfépramone 35 mg ,citrarginine, Veinobiase et depuis 1 mois et demi par AXONYL.
ALAT = 625 UI/L, ASAT : 303 UI/L, γGT: 656 UI/L, Ph.Alc. : 198 UI/L.
Evolution favorable 2 semaines après l'arrêt du traitement ,sauf les γGT qui sont encore à 171 UI/L

NY8804047=060K94 (doublon) : homme de 47 ans, traité par MEDIATOR, pendant 6 mois, puis 3 mois (après un arrêt de 3 mois)
ALAT : 375 UI/L , ASAT : 105 UI/L, γGT : 182 UI/L
L'évolution est lentement favorable dans un délai de 2 mois.

DJ9100164 : homme de 61 ans, éthylique chronique, traité depuis 4 ans par RENITEC, DOGMATIL, LASILIX, depuis 1 an par RYTHMODAN et depuis 3 ans par MEDIATOR.
ALAT : 1350 UI/L, ASAT : 410 UI/L, γGT : 280 UI/L
La régression de l'hépatite est partielle à l'arrêt de toutes les thérapeutiques, chez ce patient éthylique.

NC9600020 :Femme de 39 ans, traité par MEDIATOR depuis 8 mois.
ALAT: 205 UI/L (4N), ASAT : 89 UI/L (2N), γGT: 134 UI/L
L'évolution est favorable à l'arrêt du MEDIATOR.

NY9608618 : Femme de 36 ans, traité par MEDIATOR, pour cure d'amaigrissement pendant 4 mois.
ALAT : 126 UI/L, ASAT : 41UI/L, γGT : 110 UI/L
L'évolution est favorable à l'arrêt du MEDIATOR.

BX9700024 : Femme de 59 ans, apparition d'un ictère avec prurit, après 4 semaines de traitement par MEDIATOR. (LOXEN et ACUILIX sont pris au long cours)
ALAT: 1017 UI/L (30N), ASAT : 391 UI/L (10N), γGT : 1042 UI/L, Ph. alc. : 907 UI/L (4N)

10010325 : Homme de 42 ans présentant une cytolyse modére et une cholestase discrète 3 semaines après le début d'un traitement par MEDIATOR, pour hypertriglycéridémie et diabète modéré.
L'évolution est favorable à l'arrêt du MEDIATOR.

Dans 1 cas, l'imputation est vraisemblable :

Observation 120O39 : observation très succinte du laboratoire, concernant une augmentation des γGT (169 UI/L) , chez une femme de 70 ans, qui était traitée par ailleurs par Diamicron, Icaz et Hypérium. La réintroduction a été positive.

Dans 15 cas, l'imputation est douteuse : dont 10 C2,S1, 5 C1,S1

Annexe 3-16

N°	S / Age	Durée TTT	Impli MEDIATOR	TT associé / Imputabilité		
Hépatite mixte						
RE8660098	M,82	1 mois	C2,S1	CORVASAL, DIAMICRON TADENAN	A	
DJ9300271	F,50	2 sem.	C2,S2	Amfépramone, C2,S2	A	γGT↑
10060607	M,61	15 j	C2,S1	GLUCOPHAGE RETARD, C1,S1 DIAMICRON, C1,S1 SECTRAL, C1,S1 RISORDAN, C1,S1	A	
Hépatite cytolytique						
NY8804047 = 060K94	M,47	3 mois	C2,S2		A	γGT↑
DJ9100164	M,61	3 ans	C2,S2	RENITEC, C2,S2 DOGMATIL	A	γGT↑
Hépatite cholostatique						
NC9200360	F,85	3 mois	C2,S1	TENSTATEN, C2,S1	A	
Biologie hépatique perturbée						
NC9600020	**F,39**	**8 mois**	**C2,S2**		**A**	**ALAT↑**
MA9700402	**F,47**	**12 sem.**	**C2,S1**		**A**	**ALAT↑**
MA9400451	F,57	3 mois	C1,S1	Amfépramone, C1,S1	U	ALAT↑
BX9700611	**F,51**	**6 j**	**C2,S1**	**LUTERAN, C2,S1** **LEVOTHYROX , C2,S1** **TENORMINE, C2,S1**	**F**	**ALAT↑**
PA9803765	**F,66**	**3 mois**	**C1,S1**	**LAROXYL** **GLUCOR** **TEATROIS** **TEALINE...**	**U**	**ALAT↑** **Prep.Magistr.**
PB9300028	M,60	15 j	C1,S1	Prep. magistrale: 15 j Yohimbine Dexfenfluramine Metformine, 2 ans ANAFRANIL, 2 ans	A	ALAT↑
NY9608618	**F,36**	**4 mois**	**C2,S2**		**A**	**ALAT+Bil↑**
PA8851623	M,61	3 ans	C2,S1	(MYOCORIL,C1,S1)	F	ALAT+P.A↑
BX9700024	**F,59**	**4sem.**	**C2,S2**	**LOXEN,C2,S2** **ACUILIX, C2,S2**	**A**	**ALAT+P.A↑** **+γGT↑**
10010325	M,42	3 sem.	C2,S2	(éthylisme)	A	ALAT+P.A↑
10060020	M,55	3 mois	C2,S1		A	ALAT ↑
10060A69	M,?	50 j	C2,S1		A	ALAT ↑ (1,5N)
10540L94	F,48	20 mois	C2,S1	MADECASSOL (C1,S1)	A	ALAT + γGT↑
MP9800161	**F,51**	**5 mois**	**C1,S1**	**ESTREVA, C1,S1** **GESTORAL, C1,S1**	**A**	**ALAT + γGT↑**
10060498	F,50	3 ans	C1,S1		U	γGT↑ dossier succinct
10060038	F,62	> 3 mois	C2,S1		A	γGT↑
120O39	**F,70**	**?**	**C3,S1**	**DIAMICRON** **ICAZ** **HYPERIUM**		γGT↑

Conclusion : Plusieurs cas d' augmentations de transaminases et/ou de γGT ont été rapportés.
La plupart du temps, le MEDIATOR est en association avec d'autres médicaments qui ont la même imputabilité.
Dans quelques cas, le MEDIATOR est le seul médicament pris par le ou la patiente.
Dans la majorité des dossiers, le délai de survenue est de ≅ 3 mois.

Cet effet indésirable n'est pas mentionné dans les RCP

Annexe 3-16

- AUTRES ATTEINTES HEPATIQUES

2 observations d'imputabilité douteuse ont été rapportées:

- BX88003099, patient de 53 ans, éthylique, traité depuis 13 ans par MEDIATOR, ZYLORIC et VISKEN . L'évolution n'est pas connue.

-LY9500598 , femme de 59 ans, hospitalisée pour tentative d'autolyse, traitée par de nombreux médicaments: évolution inconnue, dossier très succinct.

CIRRHOSE						
BX8800309	M,57	13 ans	C1,S1	ZYLORIC,13 ans, C1,S1 VISKEN,13 ans,C1,S1	U	autre étiologie
STEATOSE						
LY9500598	**F,59**			**EQUANIL** **LEVOTHYROX** **LOXAPAC** **ANAFRANIL** **ROHYPNOL**	**U**	**dossier succinct**

II. AUTRES ATTEINTES DIGESTIVES :

Elles concernent 14 femmes (âge moyen : 60,6 ans) et 7 hommes (âge moyen : 61,7 ans)

- Dans les 14 cas de diarrhée rapportés, (10 femmes et 4 hommes), le MEDIATOR est utilisé en monothérapie, ou son imputabilité est supérieure aux médicaments associés.

Cet effet indésirable est mentionné dans les RCP.

- 3 cas d'ulcères ont été rapportés par le laboratoire:

- 10060052 : homme de 74 ans, reçoit MEDIATOR, depuis 6 à 8 mois, LIPANTHYL depuis 10 ans , TANAKAN et des AINS. Une fibroscopie montre des ulcères multiples qui nécessitent non seulement l'arrêt des AINS mais de toute thérapeutique.
L'évolution est favorable après prescription d'antiulcéreux. (C1,S1)

- 10540930 : Femme de 64 ans, hospitalisée pour ulcère gastrique, après 3 mois de traitement par MEDIATOR et après 1 an de GLUCOPHAGE RETARD, EUGLUCAN, ZESTRIL, LIPUR.
Le MEDIATOR est arrêté.
L'évolution est favorable après traitement par anti-acide, pansement gastrique et perfusion. (C1,S1)

-10060587 : Femme de 72 ans, avec diabète, HTA, traitée par MODURETIC et ALDOMET depuis plusieurs années et MEDIATOR depuis 3 jours. Apparition de gastralgies intenses après prise de MEDIATOR, avec réadministration positive. (C3,S1)
L'évolution est favorable à l'arrêt du MEDIATOR.
Une fibroscopie ultérieure met en évidence un ulcère duodénal.

- 1 cas de rectocolite hémorragique : (1054P69) chez une femme de 46 ans traitée au long cours par DAONIL, GLUCOPHAGE RETARD, INSULINE, LEVOTHYROX et ELISOR, apparition d'une diarrhée aigue, sanglante et colite inflammatoire ressemblant à une colite hémorragique après 1 cp de MEDIATOR.

L'évolution est favorable après administration de PENTASA. (C2,S1)

Annexe 3-16

N	S / Age	Durée TTT	Imput. MEDIATOR	TTT associés / Imputabilité	E.20	
DIARRHEE						
LY8600250	F,70	6 j	C2,S1		A	
MP8600156	M,60	2 mois	C3,S2	MODUCREN, C1,S1	A	
LY8700109	M,71	21 j	C2,S2	DIGOXINE	A	
BX8800223	M,40	3 j	C3,S2		A	
LY8800383	F,72	10 mois	C1,S1		F	
LY8800202	F,58	18 j	C2,S1		A	
MA9000721	F,29	3 j	C2,S2	DININTEL,C1,S2	A	
NC9200041	F,42	3 ans	C2,S2		A	
BR9300084	F,63	1 j	C2,S1	ZOCOR,C1,S1 ZYLORIC, C1,S1 ARMOPHYLLINE, C1,S1 DIAMICRON, C1,S1 BRICANYL, C1,S1	A	
NC9300212	M,75	47 j	C2,S2	DIACTANE, C1,S1	A	
DJ9400277	F,81	7 mois	C1,S2		U	
NC9500365	**F,70**	**2 sem.**	**C2,S2**	**BEFIZAL, C1,S2**	**A**	
CF9700156	**F,62**	**3 sem.**	**C2,S1**		**A**	
540V43	**F,66**	**45 j**	**C2,S1**	**ELISOR** **VEINAMITOL** **TEMESTA, C1,S1**	**A**	**selles molles anorexie dyspepsie**
PANCREATITE						
MA9000382	M,40	6m	C2,S1	ISOMERIDE ,C2,S1	A	
MA9700296	**F,54**	**8j**	**C2,S1**		**A**	**autre étiologie!**
EPIGASTRALGIE						
LY8600060	M,72	13j	C2,S1		A	
ULCERE DUODENAL						
10060587	F,72	3 j	C3,S1	MODURETIC, C1,S1 ALDOMET, C1,S1	A	
ULCERE GASTRIQUE						
10540930	F,64	3 mois	C1,S1	GLUCOPHAGE RETARD, C1,S1 EUGLUCAN, C1,S1 ZESTRIL, C1,S1 LIPUR, C1,S1	A	
ULCERE						
10060052	M,74		C2,S1	AINS, C2,S1 TANAKAN, C2,S1 LIPANTHYL, C1,S1	A	ulcères multiples
RECTOCOLITE HEMORRAGIQUE						
10540P69	F,46	1 j	C1,S1	DAONIL, C1,S1 GLUCOPHAGE RETARD , C1,S1 INSULINE , C1,S1 LEVOTHYROX, C1,S1 ELISOR, C1,S1	F	

Annexe 3-16

II - A - TROUBLES HEMATOLOGIQUES

14 observations (8 CRPV, 6 laboratoire) ont été rapportées.

Elles concernent 5 hommes (âge moyen : 62,2 ans) et 9 femmes (âge moyen : 57 ans) .

- Aucun nouveau cas n'a été rapporté depuis la mise au point de Juillet 1995

- L'imputabilité est douteuse dans tous les cas : 11 C1,S1
3 C2,S1

Dans la plupart des observations, il existe un traitement associé, qui peut être responsable de l'effet indésirable

-Dans l'observation 10050F09 : (C2,S1) il s'agit d'1 femme de 70 ans, avec HTA, hyperlipémie, angor et antécédents d'ulcère gastrique, traitée par MEDIATOR depuis 3 semaines:
apparition de purpura et d'hémorragie digestive : plaquettes<5000/mm3 et hémoglobine à 9g/l
La recherche d'anticorps antiplaquettes est positive.
L'évolution est favorable après arrêt du MEDIATOR

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol	
THROMBOPENIE						
LY8500365	M,51	3 mois	C1,S1	RISORDAN, 4 ans, C1,S1 SECTRAL, 4 ans, C1, S1 TILDIEM, 7 mois, C1S1	U	
SE9100183	F,64	2 mois	C1,S1	TENSTATEN, 2m, C1S1 EFFERALGAN, C1S1	U	
PS9400301	F,61	?	C1,S1	GERIMAX, C1,S1 OROCAL, C1,S1 LEVOTHYROX, C1,S1	A	
NC9400153	F,19	2 mois	C2,S1	DOXYCLINE, 5j, C2,S1 ALDACTONE, 2m, C2,S1	A	
LEUCOPENIE						
MA8801234	F,58	2 mois	C1,S1	LIPUR, 2ans, C2,S1	A	
10060617	M,60	4 ans	C1,S1		F	
LYMPHOPENIE						
DJ8800131	F,76	6 j	C1,S1	DIGOXINE, C1,S1 CALCIPARINE, C1,S1 RYTHMODAN, C1,S1	A	somnolence
MA9100793	M,59	8 j	C1,S1		A	hyperthermie
NEUTROPENIE + THROMBOPENIE						
NC8900022	M,72	2 ans	C1,S1	HEMIDAONIL, 6 ans, C1S1	A	
10060073	F,40	+ mois	C1,S1	DIAMICRON, C1,S1 GLUCOPHAGE, C1,S1	F	
10060050	M,69	3 ans	C1,S1	LEGALON	F	
ANEMIE + THROMBOPENIE						
10050F09	F,70	3 sem	C2,S1		A	
HYPERLYMPHOCYTOSE						
10060311	F,56	3-6 mois	C1,S1		U	dossier succinct
HYPEREOSINOPHILIE						
10540640	F,69	3 ans	C2,S1	LOPRIL, C1,S1 FLUDEX, C1,S1	F	

Annexe 3-16

IV. ATTEINTES RESPIRATOIRES :

20 notifications (10 CRPV et 11 laboratoire) dont 1 doublon ont été rapportées, concernant

- 11 hypertensions pulmonaires: 9 dossiers ont été expertisés par le Professeur WEITZENBLUM , 6 ont été classés en HTA P d'allure primitive lors de l'enquête « anorexigènes et HTAPP», 3 en hypertensions pulmonaires post-embolique(1) et post-capillaire(2).
Elles concernent 9 femmes (âge moyen : 54,8 ans) et 2 hommes (âge moyen : 48 ans)

Le MEDIATOR n'est jamais prescrit seul : il est présent en association à un ou plusieurs anorexigènes (ISOMERIDE : 10 fois, PONDERAL : 2 fois)
Ces cas font partie de l'enquête concernant les anorexigènes

La durée de traitement par MEDIATOR est imprécise dans 5 cas sur 11.
Dans les 6 autres cas, la durée de traitement va de plusieurs mois à 4 ans.

La prise de MEDIATOR et d'anorexigènes est concommitante dans 5 cas, antérieure dans 2 cas, postérieure dans 3 cas, imprécise dans 1 cas.

– 5 cas de toux, après des traitements allant de 8 à 34 mois. L'évolution est inconnue dans 2 cas.

Dans 1 observation (541078), dont l'imputabilité est vraisemblable, chez une femme de 70 ans, traitée par MEDIATOR pour un diabète et AMLOR pour HTA depuis 2 mois, apparition d'une toux sèche qui disparait à l'arrêt du MEDIATOR.
Les dates de prise de MEDIATOR ne sont pas précisées: seul un rechallenge positif est noté. (C3,S1),

- des cas de syndrome hémorragique intra-alvéolaire (MP9500482), tuberculome (SE9400175), pneumopathies interstitielles (LM9800297 et NT9800036) ont tous une imputabilité douteuse: soit une autre étiologie est fortement évoquée, soit l'évolution est inconnue.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION PULMONAIRE						
PP8990081	F,42	1 an	C1,S1	DININTEL, 5ans, C1,S1 Tenuate Dospan,5ans,C1,S1 FRINGANOR, 5ans, C1,S1	U	
NC9300007 = 052454	M,48	4 ans	C1,S1	ISOMERIDE, 3 ans, C1,S1 ZYLORIC, 6 ans, C1,S1 LIPANTHYL	D	
10052455	F,46	25 mois	C1,S1	ISOMERIDE CORGARD BUSPAR VELITEN ALDACTONE	F	
10052733	F,71	60 mois	C1,S1	ISOMERIDE	F	HTAP post-capillaire
10840193	F,47	?	C1,S1	ISOMERIDE COVERSYL LASILIX GLUCOPHAGE	F	
10840255	F,57	?	C1,S1	ISOMERIDE PONDERAL STILNOX XANAX VEINOBIASE	F	

Annexe 3-16

				FLUDEX		
10840770	F,66		C1,S1	ISOMERIDE FENPROPOREX	F	HTAP post-embolique
10840954	F,54		C1,S1	ISOMERIDE STAGID DIAMICRON	A	HTAP post-capillaire
10840B19	**F,51**		**C1,S1**	**ISOMERIDE SECTRAL MODURETIC KALEORID LEXOMIL RANIPLEX PREPULSID**	**F**	
10840D01	**F,59**	**4 ans**	**C1,S1**	**ISOMERIDE PONDERAL ZOCOR PROGESTOGEL SPIROCTAN**	**D**	
				TOUX		
MA9000654	F,60	2 ans	C1,S1	ARTEX, 1 an, C1,S1 GLUCINAN, 2 ans,C1,S1	U	
NC9500265	**F,48**	**10mois**	**C1,S1**	**EUTHYRAL, 2mois, C1,S1**	**A**	
MA9600518	**F,63**	**8 mois**	**C1,S1**	**MONOTILDIEM, 1 an, C1,S1 KARDEGIC, 1 an, C1,S1 ADANCOR, 1 an, C1,S1**	**U**	
541078	**F,70**	**?**	**C3,S1**	**AMLOR, C1,S1**	**A**	
NC9800121	**F,71**	**34 mois**	**C2,S1**	**FLUDEX TENORMINE FONZYLANE ROHYPNOL**	**A**	
				SYNDROME HEMORRAGIQUE INTRA-ALVEOLAIRE		
MP9500482	**F,45**	**1 mois**	**C1,S1**	**PONDERAL, 1 mois, C1,S1**	**A**	
				TUBERCULOME		
SE9400175	F,46	2 mois	C1,S1	ISOMERIDE, 2 mois, C1,S1 DININTEL, 2 mois, C1,S1	A	autre étiologie !
				PNEUMOPATHIE INTERSTITIELLE		
LM9800297	**M,75**	**?**	**C1,S1**	**AMAREL, C1,S1**	**U**	
NT9800036	**M,69**	**10 ans**	**C1,S1**	**DETENSIEL, C1,S1 JOSIR, C1,S1 LEXOMIL, C1,S1**	**F**	**fibrose interstitielle**

V. ATTEINTES CARDIOVASCULAIRES :

18 notifications ont été rapportées : 12 par les CRPV, 6 par le laboratoire

Elles concernent 3 hommes (âge moyen : 51 ans) et 14 femmes (âge moyen : 48,3 ans)

- 3 cas d'hypertension artérielle : dont une observation plausible :

NC9100093 : chez une femme de 51 ans, hypertendue traitée par LOPRESSOR depuis 5 ans, la tension est montée progressivement de 150/90 à 180/110 après introduction de MEDIATOR, malgré l'ajout de RENITEC. La tension a diminué lorsque le MEDIATOR a été arrêté.

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NC8900097 : chez une patiente de 60 ans, qui a pris 3 comprimés de MEDIATOR, le soir. Apparition 3 heures plus tard de vertiges, puis d'angoisse, tachycardie et prurit généralisé. L'évolution est favorable.

- une fibrillation auriculaire (C2,S2) chez une femme de 25 ans après 9 mois de MEDIATOR, CANOL et TEALINE et 6 mois de MODERATAN. Evolution favorable à l'arrêt de tout le traitement.

- 3 syndromes de Raynaud dont un plausible C2,S2 et 2 douteux (C2,S1 et C1,S1)

- les autres notifications sont isolées et d'imputabilité douteuse

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION ARTERIELLE						
NC9100093	F,51	1an	C2,S2	RENITEC, C1S1 LOPRESSOR, C1S1	A	
CF9300241	F,73	6j	C2,S1		A	
120S330	**F,43**	**15 mois**	**C1,S1**	**SURGESTONE** **PROZAC**	**U**	
HYPOTENSION ARTERIELLE						
10060039	M,52	?	C1,S1		A	R -
SYNCOPE						
PP9010597	F,37	1j	C1,S2	Amfepramone, C1,S2 LUMITENS, C1,S2	A	
MALAISE						
10540A46	F,43	8 mois	C1,S1		A	R -
BRADYCARDIE						
120E93	**M,38**	**1 sem**	**C1,S1**		**A**	
TACHYCARDIE						
GR9500235	**F,52**	**?**	**C1,S1**	**SOTALEX, C1,S1**	**A**	
NC8900097	F,60	1j	C2,S2	CERVOXAN, C1,S1 DIGOXINE, C1,S1	A	
FIBRILLATION AURICULAIRE						
LY9700643	**F,25**	**9 m**	**C2,S2**	**MODERATAN ,C2,S2** **CANOL, C2,S2** **TEALINE, C2,S2**	**A**	**Terrain dépressif**
EXTRASYSTOLES VENTRICULAIRES						
CN9500150	**F,?**		**C2,S1**		**A**	**dossier succinct**
CN9500151	**F,?**		**C1,S1**		**U**	**dossier succinct**
ACCIDENT VASCULAIRE CEREBRAL						
LL9700372	**F,39**	**3 mois**	**C2,S1**	**SPIRONONE, 3 mois, C2,S1** ***Tabagisme***	**A**	
PB9800124	**F,72**	**2 ans**	**C1,S1**	**GLIBENESE** **GLUCOR**	**F**	
SYNDROME DE RAYNAUD						
PC9300059	M,63	3 mois	C1,S1	MINIDIAB, 2ans, C1,S1	F	
PC9700170	**F,30**	**2 sem.**	**C2,S2**		**A**	
124U10	**F,30**		**C2,S1**	**FONZYLANE**	**A**	
OEDEMES DES MEMBRES INFERIEURS						
10060561	F,73	1 mois	C2,S1	GLUTRIL, C1,S1 CORDARONE, C1,S1	A	

Annexe 3-16

ATTEINTES RENALES

13 notifications ont été rapportées , 9 par les CRPV et 4 par le laboratoire

Elles concernent 5 hommes (âge moyen : 66,6 ans) et 8 femmes (âge moyen : 55,2 ans)

-3 cas de dysurie, d'imputation :
C3,S1 : réadministration positive mais durée de traitement inconnu
C2,S2 : apparition après 5 mois de MEDIATOR, évolution favorable à l'arrêt de celui-ci
C2,S1 : apparition après 48 h de traitement par MEDIATOR (cystite concommitante)

- 4 cas de pollakurie :
- en début de traitement 1j,2j et 16j
- ou réadministration positive après 4 mois de traitement

-1 cas de cystalgie (C2,S1) chez une femme de 33 ans après 8 jours de traitement.
L'évolution est favorable à l'arrêt de MEDIATOR

- les autres dossiers ont tous une imputabilité douteuse:
- anurie (MA8900044)
- glomérulonéphrite (LY8700356),
- syndrome néphrotique (BX9700689),
- créatininémie augmentée(10060463)
- soit le dossier est succinct
- soit l'évolution est inconnue ou l'évolution n'est pas favorable à l'arrêt du traitement:
- soit une autre étiologie est possible

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DYSURIE						
BR9100053	F,42	?	C3,S1	VARNOLINE,C1,S1	A	
NC9300208	M,78	5 mois	C2,S2	GLUTRIL, C1,S1 ZYLORIC, C1,S1 PREPULSID, C1,S1	A	
SE9700347	**F,?**	**2 j**	**C2,S1**		A	
POLYURIE						
BX8700115	F,40	7 mois	C2,S1		A	
POLLAKIURIE						
NC8800144	M,62	4 mois	C3,S1		A	
NC9300297	F,67	16 j	C2,S2		A	
10060O44	F,56	1 j	C2,S1		A	
10060O45	M,62	2 j	C2,S1	GLUCOPHAGE RETARD, C1,S1	A	
ANURIE						
MA8900044	M,79	2 mois	C1,S1	ARTEX, 2mois, C1,S1 ZYLORIC, 2 mois, C1,S1 HEMIDAONIL, 2 mois, C1,S1 ALDACTAZINE, 2 mois,C1,S1	N	dossier succinct, non informatif
GLOMERULONEPHRITE						
LY8700356	M,52	5 mois	C1,S1	ZYLORIC, C1,S1 DIAMICRON, C1,S1	U	

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BX 9700689	F,71	?	C1,S1	TROLOVOL, C1,S1 LASILIX,C1,S1 MONOTILDIEM, C1,S1 TRINITRINE, C1,S1 GLUCOPHAGE, C1,S1 DAONIL, C1,S1 VOLTARENE, C1,S1 CYTOTEC, C1,S1 AZANTAC, C1,S1	F	
CREATININEMIE AUGMENTEE						
10060463	F,78	9 mois	C1,S1	ALDOMET, C1,S1 ALDACTAZINE, C1,S1 LIPANTHYL, C1,S1	F	
CYSTALGIES						
10540F68	F,33	8 j	C2,S1		A	

VII. ATTEINTES METABOLIQUES :

21 Notifications ont été rapportées , 18 par le laboratoire, 3 par les CRPV.

Elles concernent 11 hommes (âge moyen : 58,7 ans) et 10 femmes (âge moyen : 56,7 ans)

Dans 13 cas, c'est 1 effet lié à aux propriétés pharmacologiques du médicament lui-même:

- hypoglycémie : 6 cas
- malaise hypoglycémique : 1 cas
- hyperglycémie : 2 cas

- hyperlipémie : 2 cas
- augmentation des triglycérides : 2 cas

-3 cas de lactacidémie d'imputabilité douteuse

-dans 1 cas (10060F73), chez un homme de 68 ans, la lactacidémie est à 4.13mmol/l (normale 0.55-2.20) après un traitement de 37 jours par MEDIATOR. Un mois après de MEDIATOR, elle est de 2.27mmol/l.

-2 dossiers succincts: pas de précision sur l'arrêt du MEDIATOR (10060683)
évolution inconnue (10060356)

- 2 cas de goutte chez 2 hommes de 61 et 71 ans (LASILIX est associé dans les 2 cas : C3,S2,B3 et C1,S1,B3)

- 2 cas d 'amaigrissement déclaré par un médecin au laboratoire (10060446 et 10060447) : perte de 5 Kg chez un homme de 36 ans après 1 mois de traitement, perte de 8 Kg chez une femme de 67 ans après 2 mois de traitement pour hypercholestérolémie.

Annexe 3-16

IX. ATTEINTES CUTANEES et REACTIONS ALLERGIQUES

Elles concernent 20 hommes (Age moyen = 51,5 ans) et 44 femmes (Age moyen = 51,4 ans)

1 . Allergie, eczema :

Parmi les 27 réactions allergiques, on note:

- 14 cas d'urticaire dont 5 cas d'urticaires géantes ou généralisées
- 4 oedèmes de Quincke ou oedème laryngé
- 6 chocs anaphylactiques
- 3 allergies cutanées

Le délai de survenue est le plus souvent très rapide (1 jour), l'imputation sera donc souvent vraisemblable (15 fois) ou plausible (3 fois).
Elle est douteuse dans les cas où il y a eu un traitement correcteur : 9 fois

Parmi les 6 cas d'eczéma, d'imputabilité douteuse, l'évolution est favorable dans 4 cas.
L'eczéma n'est pas guéri dans 2 cas. (NC9300394 etNY9809751)
Dans l'observation 540W61, le délai d'apparition est long (2 ans) et la crème cosmétique semble être en cause.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
URTICAIRE						
CF8500013	M,50		C1,S2	LEXOMIL, C1,S2	A	
LY8700092	F,69	15 j	C3,S1		A	
TO9100366	M,34	7 j	C2,S2		A	
NC9400046	F,38	1 j	C3,S2		A	
MA9500024	M,45	3 mois	C3,S1	MAXEPA, C3,S1	U	
NY9507878	**M,61**	**2 mois**	**C2,S1**		**A**	
MA9700146	**F,50**	**1 j**	**C2,S2**		**A**	
10060I28	F,54	2 mois	C3,S1		A	
10540989	F,31	4 j	C3,S1	DI-ANTALVIC, FELDENE TRANCOPAL	A	
10540D65	F,48	3 sem	C1,S1		A	urticaire géante
10060H11	F,60	+ mois	C3,S1		A	urticaire géante
SE9800159	**F,32**	**9 j**	**C1,S1**	**PROZAC STRESAM CANOL**	**A**	**urticaire géante**
120T66	**F,59**	**1 j**	**C3,S1**	**ART 50, C1,S1**	**A**	**urticaire généralisée**
121D94	**F,60**	**1 j**	**C3,S1C1,S3**		**A**	**urticaire généralisée + bronchospasme**
OEDEME LARYNGE						
BX9800738	**F,?**	**3 j**	**C1,S1**		**A**	***autre cause!***
OEDEME DE QUINCKE						
PA9200399	F,41	1 j	C2,S1	GLUCINAN, C2,S1	A	
MA9500231	F,56	1 j	C3,S1		A	
10060K99	F,49	3 mois + 9 j	C3,S1		F	
CHOC ANAPHYLACTIQUE						
DJ9200119	F,73	2 j	C3,S2		A	
MA9300967	F,50	8 j	C3,S2		A	
MA9400018	F,?	1 j	C3,S2		A	
MA9700036	**F,60**	**1j**	**C2,S2**		**A**	
123K59	**F,38**	**1 j**	**C1,S1**	**BRONCHOKOD**	**A**	
LY9800499	**M,36**	**1 j**	**C3,S1**		**A**	

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10060G60	F,?	3 j	C1,S1		A	oedème face et lèvres
121A605	F,?	20 j	C2,S1	FLOXYFRAL PROTHIADEN NOCTRAN	A	flush
ECZEMA						
NC9300394	F,?	3 ans	C1,S2		F	
MA9500621	F,68	2 ans	C2,S2		A	
NY9809751	M,70	10 mois	C1,S1	MOPRAL, C1,S1 GLUCOR, C1,S1	F	
10840104	M,40	35 j	C1,S1		A	éruption eczématiforme photosensibilité
10060G65	F,64	1 mois	C1,S1	CATAPRESSAN VASTAREL DAFLON FONZYLANE	A	eczéma des membres oed. du visage prurit
540W61	**F,67**	**2 ans**	**C1,S1**	**Crème cosmétique**	A	éruption eczématiforme
SUDATION EXCESSIVE						
PA9240186	F,79		C1,S2	DIAMICRON, C1,S2 MEDIATENSYL, C1,S2 BRUFEN, C1,S2	A	

2. Eruption, vascularite, purpura

30 notifications ont été rapportées : 20 par les CRPV, 10 par le laboratoire

Elles concernent 18 femmes agées de 47,7 ans et 12 hommes agés de 52,6 ans

Les éruptions cutanées sont variées:

- 16 cas de prurit, d' éruptions érythèmateuse, maculeuse, papuleuse ou maculopapuleuse dont 6 cas d'imputabilité vraisemblable (réadministration positive)

- 3 cas d'érythème polymorphe, avec une évolution favorable à l'arrêt du MEDIATOR, chez 2 hommes agés de 60 et 68 ans. Le délai d'apparition est respectivement de 15 jours et de 6 mois (!).
Dans le 3° cas, (MA9700614) l'évolution est inconnue et le TANAKAN a une imputabilité bibliographique supérieure au MEDIATOR.

- 3 notifications de vascularite aigue leucocytoclasique:
  - dans 1 cas, l'évolution est favorable à l'arrêt du MEDIATOR (RE9420042)
  - dans 1 cas, l'évolution est favorable sans arrêt du MEDIATOR , mais avec un traitement corticoïde (lorsque la corticothérapie est arrêtée, 4 mois plus tard, survient un érythème polymorphe :MA9700957)
  - dans le troisième cas (MP9700134), l'évolution n'est pas complète malgré l'arrêt du MEDIATOR et une corticothérapie.

- 3 cas de purpura:
  - purpura des membres inférieurs avec un oedème apparu une semaine après le début du traitement par MEDIATOR (PP8990384)
  - purpura des membres inférieurs, s'étendant aux membres supérieurs, disparaissant 1 semaine après l'arrêt du traitement (CF9200106)
  - purpura rhumatoïde survenant après 2 semaines de traitement, l' évolution est inconnue (PO9700410)

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ÉRUPTION

DJ9100155	M,31	10j	C3,S2		A	éruption érythémateuse
MP9300201	F,36	1 mois	C1,S1	DOLIPRANE, 1j,C1,S1 CLARADOL, 1j, C1,S1	A	éruption érythémateuse, prurit
540V73	**F,49**	**1 j**	**C3,S1**	**MEDIATENSYL**	**A**	**éruption + oedème**
PA9333879	F,54	5 sem.	C1,S1	GLUCOPHAGE,3 sem,C1,S1	U	prurit
10060913	F,65	qq j	C2,S1		A	prurit
10060161	M,40	3-4 j	C3,S1	LIPANTHYL	A	prurit
10060F71	F,47	?	C2,S1	TAGAMET, C1,S1 JONCTUM, C1,S1 LEXOMIL, C1,S1	A	prurit + érythème + vertiges
MA9500227	**M,38**	**16j**	**C3,S1**		**A**	**éruption prurigineuse**
10010408	M,72	7 j	C2,S1	ALDACTAZINE CORDITRINE PERSANTINE ZYLORIC	A	éruption prurigineuse
LY9700381	**F,56**	**11 sem.**	**C2,S1**	**LIPANTHYL, 11 SEM, C2S1**	**A**	**éruption**
MA9300723	F,41	1 cp	C2,S1	HEXALYSE,1cp, C2,S1	A	éruption maculopapul.
LY9400078	F,46	1 mois	C2,S1	TOCO 500, C1,S1 CYCLO 3, C1S1 CONFLICTAN, C1,S1 LEXOMIL, C1,S1	A	éruption maculeuse, prurit
1050S90	M,41		C3,S1	amfépramone phénobarbital	A	éruption papuleuse prurit
122X95	**F,32**	**1 mois**	**C3,S1**	**NIDREL FRACTAL AZANTAC**	A	**rash maculo-papuleux**
LM9100055	M,56	1 an	C1,S1	DETENSIEL, C1,S2 DIDRONEL, C1,S1	U	prurigo
NC9100505	F,48	1 mois	C2,S2	SOPROL, 1 mois, C2S2	A	éruption pustuleuse
NC9100194	M,60	15 j	C2,S1	EUPRESSYL, C2,S1	A	érythème polymorphe
NY9300951	M,68	6 mois	C2,S1		A	érythème polymorphe
MA9700614	**F,50**	**3 mois**	**C1,S2**	**TANAKAN, C1,S2 MEGAMAG, C1,S2**	**U**	**érythème polymorphe**
MP9700134	**F,58**	**6 j**	**C1,S1**	**SECTRAL BOP LEVOTHYROX**	**F**	**vascularite**
RE9420042	M,41	4 j	C1,S1	SORBITOL	A	vascularite
MA9700957	**F,50**	**8 ans**	**C1,S1**	**STAGID, 8 ANS, C1,S1**	**A**	**vascularite**
PP8990384	F,75	3 sem.	C2,S1	DAONIL, C1,S1 STAGID, C1,S1 TILDIEM, C1,S1 NATIROSE, C1,S1	A	purpura
CF9200106	F,67		C2,S2	VASTAREL, C2,S2 DAFALGAN, C2,S2 ELISOR, C2,S2	A	purpura
PO9700410	**M,47**	**2 sem.**	**C1,S1**	**ATHYMIL,C1,S1**	**F**	**purpura rhumatoide**

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PA9739366	M,61	3 mois	C1,S1	COZAAR, 3 j, C1,S1 DAONIL, 8 mois, C1,S1 GLUCOPHAGE, 8 m., C1,S1 ZYLORIC, 33 mois, C1,S1 LOXEN, 33 mois, C1,S1		
NC9400417	F,20	1 mois	C1,S2		F	acné
10540911	F,45	15 j	C2,S1	ASPIRINE	A	pustulose exanthématique
10540F26	F,20	2 mois	C1,S1		F	alopécie
10840616	M,72	7 mois	C2,S1	NIDREL ZYLORIC LASILIX ZOCOR ARTEX	F	colororation noire de la langue

Les effets indésirables cutanés et/ou allergiques ne sont pas mentionnés dans les RCP

Annexe 3-16

48 notifications ont été rapportées, 30 par les CRPV, 18 par le laboratoire :

Elles concernent 23 hommes (Age moyen : 53,9 ans) , 25 femmes (Age moyen : 58,8 ans)

1. Asthénie, Somnolence, Impuissance :

Dans certaines observations:
- soit le délai de survenue semble long : 2ans (LM8600219) ou inconnu (DJ8800131)
- soit le traitement associé peut être responsable de tels effets: PROZAC, GLUCOPHAGE...

Asthénie et somnolence sont mentionnés dans les RCP.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
ASTHENIE						
LM8600219	M,56	2 ans	C2,S2		A	
TO8900326	M,49	1 mois	C1,S1		F	
MA9300480	F,45	6 mois	C2,S1	PRAXINOR, 1 mois, C2,S1 PONDERAL, C1,S1	A	
LY9600435	**F,53**	**8 sem.**	**C2,S1**	**GLUCOPHAGE, 8 sem., C2,S1** **PROZAC**	A	
123F40	**M,48**	**1 an**	**C1,S1**	**BEFIZAL**	U	
SOMNOLENCE						
DJ8800131	F,76	?	C2,S2		A	+ lymphopénie
TO9200397	F,64	6 j	C3,S2		A	
MA9300577	F,42			ISOMERIDE		
RE9510102	**F,69**	**4 j**	**C2,S1**	**LASILIX, C1,S1** **PREVISCAN, C1,S1** **COVERSYL, C1,S1** **INSULATARD, C1,S1**	A	
10060074	F,56	1 mois	C3,S1	FONLIPOL DIGOXINE CORDARONE Antivitamines K	A	
10060150	F,70	4-5 j	C2,S1	GLUCOPHAGE Retard, C1,S1 LIPANTHYL, C1,S1	A	
TROUBLE DE LA VIGILANCE						
10010335	F,72	3 j	C2,S1	TENORMINE SERESTA CYCLOTERIAM	A	
NC9500466	**M,55**	**3 j**	**C3,S2**		**A**	impuissance
10051460	M,45	1 mois	C2,S1	DESATURA DAFLON 500	A	trouble de l'érection

Annexe 3-16

Elles concernent 13 hommes (âge moyen :53,2 ans) et 14 femmes (âge moyen : 60,4 ans)

Les troubles psychiatriques sont divers : agressivité, nervosité, confusion, délire

La responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue

3 cas sont imputés « vraisemblable » :

- NC9500171 : nervosité et nausées chez une femme de 50 ans, 1 à 2 h après la prise d'1 cp de MEDIATOR

- 10010345 : désorientation et obnubilation, chez une femme de 80 ans. Le traitement a été arrêté après 13 j. Une réadministration ultérieure a été positive. (traitement associé : KERLONE et MOGADON)

- PA97355052 : syndrome de sevrage avec excitation, chez un homme de 27 ans, sportif, qui avait pris 9 cp/j de MEDIATOR, comme « dopant ».

5 cas sont imputés « plausible » :

- NC9700094 : accès d'agitation et agressivité, chez une femme de 74 ans, pendant la prise de MEDIATOR, pendant 6 j. Disparition des symptômes 12 h après l'arrêt du MEDIATOR.

- NC9300347 : irritabilité chez un homme de 39 ans, traité pendant 11 mois par MEDIATOR. L'évolution est favorable à l'arrêt du médicament.

- NC9300349 : dépression, chez un homme de 50 ans, traité pendant 9 mois par MEDIATOR. L'évolution est favorable à l'arrêt du médicament.

- MA9100069 : angoisse et palpitation, chez un homme de 40 ans, 2h après avoir ingéré 4 cp de MEDIATOR.

- CF9000137 : désorientation chez une femme de 79 ans, traitée par MEDIATOR, HALDOL, SERESTA, ZESTRIL, CATAPRESSAN, PRAXILENE, SERMION. L'évolution est favorable à l'arrêt de tous les médicaments.

19 ont été imputés « douteux » : (8 C1,S1, 10 C2,S1, 1 C1,S2)

:

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
TROUBLES PSYCHIATRIQUES						
LY9600963	**M,45**	**1 mois**	**C1,S1**	**LEXOMIL, C2,S1**	**A**	**agressivité**
NC9700094	**F,74**	**6 j**	**C2,S2**		**A**	**agressivité**
541173	**F,45**	**8 j**	**C2,S1**	**CORENITEC, C1,S1**	**A**	**agressivité + hallucination**
MA8900523	F,40		C1,S1	ISOMERIDE, 1j, C2,S1	A	agitation
DJ9800349	**M,74**	**3 mois**	**C2,S1**		**A**	**agitation**
NC9300347	M,39	11 mois	C2,S2		A	irritabilité
NC9500171	F,50	1 cp	C3,S2		A	nervosité
MP9800179	**F,47**	**11 j**	**C2,S1**	**LIPANOR, C1,S1**	**A**	**nervosité**
124G84	**F,35**	**20 j**	**C2,S1**	**MAXEPA LEVOTHYROX HYDROCORTISONE**	**A**	**nervosité + excitation**

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TS9500338	F,69	?	C2,S1	DAONIL, C1,S1 ALPRESS BITILDIEM DIAMICRON...	A	[illegible]
LY8900392	M,52	20 j	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1	A	cauchemars
10540O46	M,?	qq semaines	C1,S1	ZOCOR, C1,S1 PERSANTINE MAXEPA TILDIEM DAONIL	A	cauchemars
SE9500017	F,41	84 j	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1	A	confusion
10010326	M,61	?	C1,S1	FONZYLANE, C1,S1 SINTROM, C1,S1	A	confusion *autre cause !*
120M85	**M,70**	**11 j**	**C2,S1**	**PREVISCAN, C1,S1** **CORDARONE, C1,S1**	**A**	**confusion troubles de la mémoire**
CF9000137	F,79		C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2 SERMION, C2,S2	A	désorientation
10010345	F,80	13 j	C3,S1	MOGADON, C1,S1 KERLONE, C1,S1	A	désorientation obnubilation
10060J96	F,80	?	C1,S1	RENITEC ADALATE HEMIDAONIL TILDIEM	A	désorientation
10060J13	F,82	1 mois	C2,S1	DAONIL	A	désorientation
120M52	**M,60**	**2 j**	**C2,S1**	**LIPANTHYL, C1,S1** **ASPEGIC, C1,S1**	**A**	**désorientation sommnolence**
10060560	M,75	plusieurs mois	C2,S1	DAONIL	A	trouble du comportement
RN9500096	**F,59**	**73 j**	**C1,S2**	**LIPANTHYL, C1,S2** **PILOSURYL, C1,S2** **CANOL, C1,S2** **OLIVIASE, C1,S2** **Amfépramone, C1,S2**	**A**	**délire**
GR8700216	M,45	16 j	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1	A	délire
10060219	F,65	2 ans	C1,S1		A	bouffées d'angoisse au sevrage
PA9735052	**M,27**	**6 mois**	**C3,S1**	***« 9 cp/j (dopant!) »***	**U**	**excitation au sevrage**

28

Annexe 3-16

7 notifications d'imputabilité douteuse ont été rapportées (5 CRPV, 2 laboratoire)

Elles concernent 5 hommes (âge moyen : 59 ans) et 2 femmes (âge moyen : 39 ans)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
CONVULSION						
PA9223988	M,60	?	C2,S1	TENSIONORME, C2,S1 DIFFU K	A	
10060J47	F,36	2 mois	C1,S1	DAONIL	A	crise comitiale
NEUROPATHIE						
MA8700716	M,73	9 ans	C1,S1	HEMOCLAR TORENTAL	U	autre étiologie!
PARESTHESIE						
BX8800193	M,36	8 j	C1,S1	PRAXINOR, 8j, C1,S1	F	
LM9500090	M,61	4 j	C2,S1		A	
MA9700170	**F,42**	**1 j**	**C2,S2**	**TAMIK, C1,S1**	**U**	
10051683	M,65		C2,S1	DAONIL GLUCOPHAGE LIPANOR ANGIOXINE	A	

Annexe 3-16

MEDIATOR

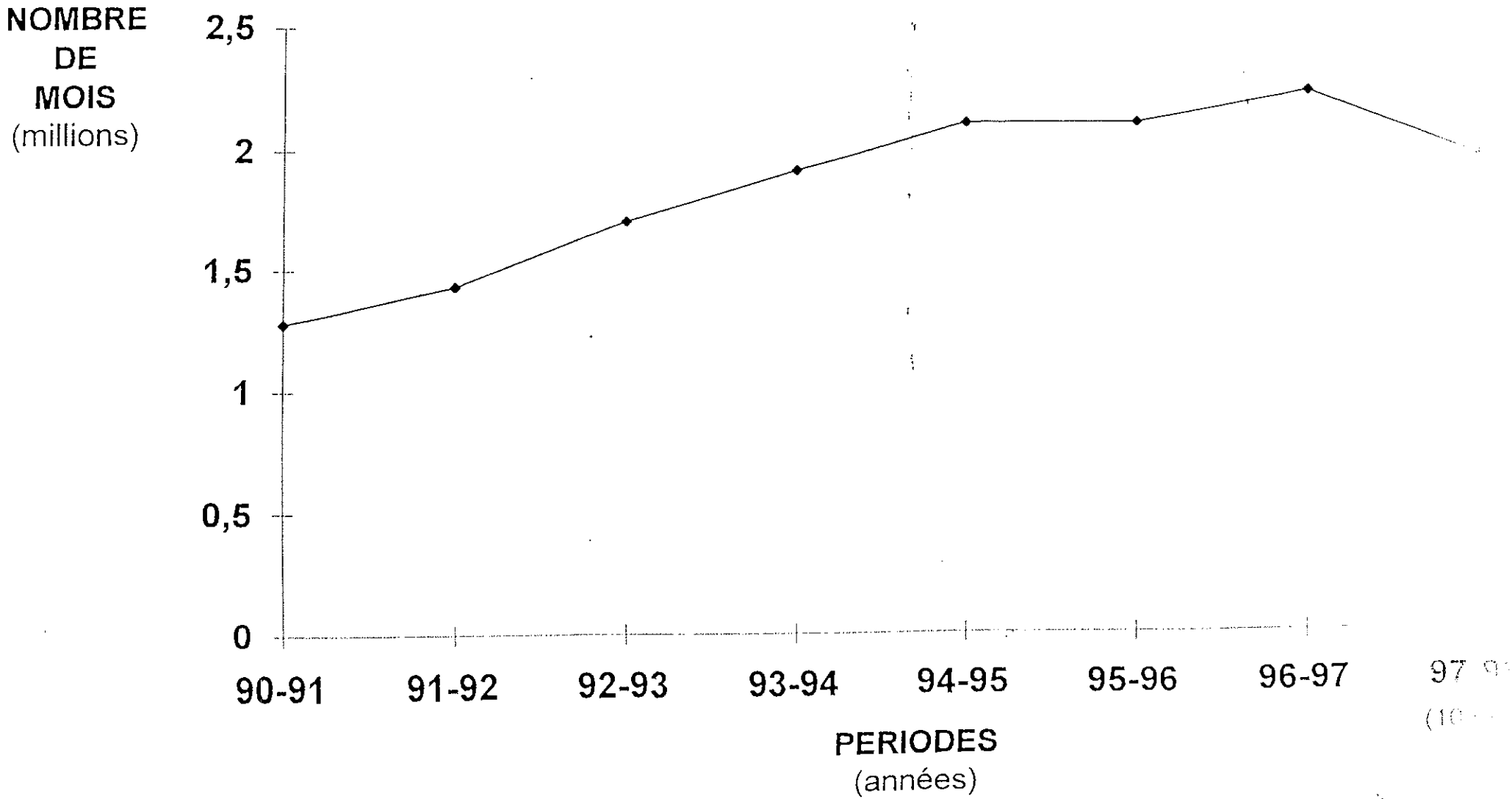
VERTIGE, TROUBLE DE L'EQUILIBRE

BX8500092 =060141	M,34	3 mois	C3,S2		A	
MA8800356	F,60	1 j	C2,S2		A	
MA8800929	F,47	1 cp	C2,S2	DAFLON, C1,S1	A	
NC9000297	F,58	15 j	C3,S2		A	
LL9200133	F,63	2 j	C1,S1		U	
NY9306790	F,77	2 j	C1,S2		A	
LM9500091	F,84		C2,S1	SOTALEX, C1,S1 LOXEN, C1,S1 ALDACTONE, C1,S1 CORDIPATCH, C1,S1 PREVISCAN, C1,S1	U	
TS9600227	F,64	4 sem.	C3,S1	RENITEC, C1,S1 LIPANTHYL, C1,S1	A	
BX9701040	M,74	4 sem.	C2,S1	PREVISCAN, C1,S1 DAONIL, C1,S1 CAPTOLANE, C1,S1 GLUCOPHAGE, C1,S1	A	
BX9701041	M,78	10 j	C2,S1	DAONIL CORDARONE ASPEGIC GLUCOR	A	
NC8900097	F,60	1 cp	C2,S2		A	
MA8700143	F,66	?	C1,S1	FLUVERMAL, C1,S1	F	
BX9701023	F,63	9 sem.	C2,S1	AVLOCARDYL DAFLON DAONIL LASILIX GLUCOR TRANXENE IMOVANE	A	
BX9700381	M,63	4 sem.	C2,S1	DAONIL	A	
BX9700301	M,71	6 sem.	C2,S1	LOPRIL CORDARONE VASTAREL PRAXILENE EUGLUCAN	A	
BX971022	F,74	7 mois	C2,S1	DIAMICRON MOPRAL TILDIEM ALDACTAZINE LYSANXIA	A	
10060F71	F,47	?	C2,S1	TAGAMET, C1,S1 JONCTUM, C1,S1 LEXOMIL, C1,S1	A	+ prurit + érythème
10060499	F,40	1 semaine	C3,S1	LEVOTHYROX, C1,S1	A	
10060J48	F,74	2 j	C2,S1	MODURETIC, C1,S1 LOXEN, C1,S1 DETENSIEL, C1,S1	A	
123T12	F,74	?	C1,S1	GLUCOPHAGE DIAMICRON TILDIEM KERLONE RISORDAN ALDACTAZINE MOPRAL	A	*trouble de la démarche*

ANNEXES

Benfluorex MEDIATOR®

Chiffres de vente
(nombre de mois de traitement)



1204

Annexe 3-16

REPARTITION DES PRESCRIPTIONS DE MEDIATOR EN FONCTION DES INDICATIONS

Source : DOREMA Médicaments - Printemps - Cumuls 12 mois

INDICATIONS	Juin 94 à Mai 95		Juin 95 à Mai 96			Juin 96 à Mai 97			Juin 97 à Mai 98		
	Prescriptions	Répart. %	Prescriptions	Répart. %	évol. an-1	Prescriptions	Répart. %	évol. an-1	Prescriptions	Répart. %	évol.
Total Prescriptions	893 000	100,0%	821 000	100,0%	-8,1	897 000	100,0%	9,3	948 000	100,0%	
Diabète et apparentés*	389 000	43,6%	407 000	49,6%	4,6	376 000	41,9%	-7,6	420 000	44,3%	
Lipides (Diag. 272)	151 000	16,9%	174 000	21,2%	15,2	248 000	27,6%	42,5	268 000	28,3%	
Obésité (Diag. 278)	212 000	23,7%	124 000	15,1%	-41,5	123 000	13,7%	-0,8	100 000	10,5%	

* Diag. 250-259 + 277 + 790-2

Direction de l'Evaluation
Unité de Pharmacovigilance

FAX

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
Agence du Médicament

DATE : 09

Pages (incl. cover) :

TO : **Fax N° :**

Italy : Dr Giuseppe PLUCHINO 39-6-5994.3554
..... 39-6-5994.3456
..... 39-6-5994.3365

SUBJECT / OBJET : Benfluorex

Dear colleague,

I don't forget you. First I would like to review each case report discussed in your draft, especially those related to a possible cardiovascular and pulmonary toxicity of benfluorex. For this purpose, I am waiting for the narratives.

Best regards.

Dr Anne CASTOT

Nom : PHARMACOVIGILANCE Numéro : 055873532 Date : 12-02-99 09:23

Date/Heure	12-02 9:22
Numéro composé	000390659943365
Correspondant	0039 6 59943456
Durée	0'45"
Mode	NORMAL
Pages	1
Résultat	Correct

AGENCE DU MEDICAMENT
Direction de l'Evaluation
Unité de Pharmacovigilance

RÉPUBLIQUE FRANÇAISE

FAX

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
Agence du Médicament

DATE : 09 [illegible] 99

Pages (incl. cover) :

TO : Fax N° :

Italy : Dr Giuseppe PLUCHINO 39-6-5994.3554
..... 39-6-5994.3456
..... 39-6-5994.3365

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Best regards.

Dr Anne CASTOT

143/145, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

Nom : PHARMACOVIGILANCE Numéro : 0558723532 Date : 12-02-99 09:15

Date/Heure	12-02 9:14
Numéro composé	000390659943456
Durée	0'21"
Mode	NORMAL
Pages	1
Résultat	Correct

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT
Direction de l'Evaluation
Unité de Pharmacovigilance

FAX

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
Agence du Médicament

DATE : 09 [illegible] 99

Pages (incl. covet) :

TO : Fax N° :

Italy : Dr Giuseppe PLUCHINO 39-6-5994.3554
..... 39-6-5994.3456
..... 39-6-5994.3365

SUBJECT / OBJET : Benfluorex

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Best regards.

Dr Anne CASTOT

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél : 01.55.87.30.00

*** RAPPORT 1210 EMISSION *** Annexe 3-17

Nom : PHARMACOVIGILANCE Numéro : 0155873532 Date : 12-02-99 09:52

Date/Heure	12-02 9:51
Numéro composé	000390659943554
Durée	0'00"
Mode	
Pages	0
Résultat	Code 01

*** Code 01 : Occupé ou pas de réponse fax ***

RÉPUBLIQUE FRANÇAISE

AGENCE DU MEDICAMENT
Direction de l'Evaluation
Unité de Pharmacovigilance

FAX

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
Agence du Médicament

DATE : 09 [illegible] 99

Pages (incl. cover) :

TO : Fax N° :

Italy : Dr Giuseppe PLUCHINO 39-6-5994.3554
..... 39-6-5994.3456
..... 39-6-5994.3365

SUBJECT / OBJET : Benfluorex

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I don't forget you. First I would like to review each case report discussed in your draft, especially those related to a possible cardiovascular and pulmonary toxicity of benfluorex. For this purpose, I am waiting for the narratives.

Best regards.

Dr Anne CASTOT

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél : 01.55.87.30.00

Annexe 3-18

AGENCE

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance
523

Saint-Denis, le 19 FEV. 1999

Dr Giuseppe PLUCHINO
Head Pharmacovigilance Unit
Pharmaceutical Department
Ministerio della Sanita
Viale della Civilta Romana 7
00144 ROME
ITALIA

SUBJECT / OBJET : Benfluorex

Dear colleague,

Further to my fax dated 9th February 1999, please find enclosed a line-listing with CIOMS forms concerning serious adverse drug reactions reported with benfluorex (MEDIATOR) in France.

Some CIOMS forms are not translated in English : these cases have been classified not related to benfluorex by the rapporteur of the French national inquiry (Pr. Bechtel).

Moreover, I send you a CIOMS form for a new serious case reported last week to a French Regional Center for Pharmacovigilance. This is a case of aortic insufficiency reported with benfluorex, without previous nor concomitant anorectic drug.

Best regards.

Le Chef de l'unité de Pharmacovigilance
P.

Dr Anne CASTOT

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIAL	1a.. COUNTRY	2. DATE OF BIRTH			2a. AGE Years	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
	France	28	10	1955	43	M	17	10	1998	

7-13 DESCRIBE REACTION(S) (including test/lab data)

Event : AORTIC INSUFFICIENCY

Comment :
This case involves a 43 year- old male patient (167 centimeters, 72 kg) with a history of smoking, hypercholesterolemia.
January 1992 : lower myocardial infarction not complicated. Coronarography : anterior interventricular lesion 50 %, minor mitral insufficiency, no aortic insufficiency detected.

The patient had been treated with benfluorex (300 MG / Day) from July 1992 to October 1998 (indications : overweight, hypercholesterolemia, hypoglycemic symptoms) and with pravastatine, atenolol and DL lysine acetylsalicylate since 1992.

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- X☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

MEDIATOR (benfluorex)

20.DID REACTION ABATE AFTER STOPPING DRUG ?
☐ YES X☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21.DID REACTION REAPPEAR AFTER REINTRO-DUCTION?
300 MG	PO	☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE Overweight, hypercholesterolemia, hypoglycemic symptoms		
18. THERAPY DATES (from/to) From July 1992 to October 1998	19. THERAPY DURATION 6 years	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

ASPEGIC (DL Lysine acetylsalicylate) 250MG / day since 1992
VASTEN (pravastatine) 20 MG / day since January 1993
TENORMINE (aténolol) 100 MG / day since January 1992

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc...)

Smoking, hypercholesterolemia, myocardial infarction in January 1992 : minor mitral insufficiency, no aortic insufficiency.
No previous intake of anorectic drugs.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		*Subsidiary Reference Number* *Other references*
	24b. MFR CONTROL N°	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE X☐ HEALTH PROFESSIONAL	CRPV Marseille Obs n° MA9900176 Date received by CRPV : 10th February1999
DATE OF THIS REPORT 18th February 1999	25a. REPORT TYPE X☐ INITIAL ☐ FOLLOWUP	

**This form is for expedited reporting of serious adverse events following the use of a drug/vaccine. Temporal relationship does not mean causality*

Annexe 3-18

Describe reaction (continuation) :

In October 1998, during a systematic clinical examination, a diastolic murmur, easy to discern, evocating an aortic insufficiency was discovered.
Systolic murmur (mitral insufficiency could be related to the ischemic sequella of myocardial infarction ?).
No functional sign.
Echocardiography (17th October 1998) : aortic insufficiency with"large jet", minor mitral insufficiency.

There is no argument for a chronic endocarditis.
No previous intake of anorectic drugs.

The aortic insufficiency did not exist in 1992. No murmur was detected at the clinical examination in March and April 1993. Stress test in June 1993 : no abnormality.

Outcome : in January 1999, aortic insufficiency well clinically tolerated.

BENFLUOREX

Spontaneous Reports of Serious Adverse Reactions

FRANCE

The following table is a listing of all the serious adverse reactions reported in France with Benfluorex (Mediator®), including :

- all serious reactions reported directly to the French Regional Centres for Pharmacovigilance (CRPV) in patients who had received Benfluorex (suspected drug or associated drug). After review (Pr P. Bechtel & Coll.), a number of them (marked with an asterisk – * – on the table) have been classified not related to Benfluorex (associated to other suspected drug(s)).
- all serious reactions reported to the Company.

CIOMS forms are provided for all reactions with Benfluorex considered as a suspected drug.

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Nervous System									
120M85	France	HP	70	M	300mg	11d	Amnesia, confusion, (malaise)	Improvement	Cerebrovascular insufficiency .
122K33	France	CRPV BX9701023	63	F	450mg	9w	Balance impaired, somnolence	Recovery	Liver cirrhosis, hypertension & diabetic neuropathy associated. Published (DOERMAN 1998).
122N89	France	CRPV BX9701041	77	M	450mg	10d	Balance impaired, neuropathy	Recovery	Diabetes & axonal neuropathy associated. Published (DOERMAN 1998).
121O17	France	HP-CRPV BX9700301	71	M	450mg	38d	Balance impaired, neuropathy	Recovery	Published (DOERMAN 1998). Glibenclamide associated.
121O16	France	HP-CRPV BX9701040	73	M	300mg	1m	Balance impaired, vertigo	Recovery	Hx of coronary & cerebrovascular insufficiency. Published (DOERMAN 1998)
540V17	France	CRPV RN9500096	59	F	450mg	2m	Confusion	Recovery	Amfepramone associated .
540V13	France	CRPV PB9300028	62	M	250mg	16d	Confusion, (hepatopathy)	Recovery	Several drugs associated . Intermittent alcoholism .
540D89	France	CRPV GR8700216	45	M	450mg	16d	Confusion, delirium	Recovery	
*540D68 **	*France*	*CRPV DJ8800309*	*74*	*F*	*u*	*4y*	*Confusion, hallucination*	*Unknown*	*Viloxazine associated. Hx of liver cirrhosis & diabetes.*
530V20	France	CRPV DJ8800131	76	F	150-300mg	5d	Confusion, somnolence, (lymphopenia)	Recovery	Several drugs associated. Diabetes.
*540D70 **	*France*	*CRPV CF8900109*	*46*	*F*	*300mg*	*1d*	*Convulsion*	*Recovery*	*Buspirone and amineptine associated .*
540D71	France	CRPV CF9000137	79	F	450mg	u	Delirium, disorientation	Recovery	Several drugs associated .
*540D97 **	*France*	*CRPV LL9000165*	*43*	*F*	*u*	*years*	*Delirium, insomnia*	*Recovery*	*Amfepramone associated.*
030345	France	HP	80	F	450mg	13d	Disorientation aggravated	Recovery	Positive rechallenge. Hx of cerebrovascular disorders.
540J08	France	HP-CRPV TS9300183	68	M	300-450mg	<1m	Polyneuropathy	Unknown	Several drugs associated. Hx of diabetes & chronic bronchitis.
*540J04 **	*France*	*CRPV MP9400396*	*73*	*F*	*300mg*	*26d*	*Polyneuropathy*	*Persistency*	*Almitrine associated . Alcoholism .*

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
J-C	FRANCE	Day Month Year 21-Jun-26	Years 70	M	Year Month Day 96/05/30	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

Repetitive AMNESIC MALAISES with CONFUSION and MALAISE requiring hospitalisation on 31-May-96. Mediator was stopped. ENT exam , biologic tests , EEG : NAD ;
Brain scan : cortico-sub-cortical atrophy , calcifications of lenticular nodes , no ischemic or hemorrhagic lesions .
Discharge on 21-Jun-96. Improvement but persistency of memory disorders.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
300MG	ORAL

17. INDICATION(S) FOR USE
POLYMETABOLIC DISORDERS

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 20.05.96 to 31.05.96	11D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
PREVISCAN (FLUINDIONE) from 01.96
CORDARONE (AMIODARONE) from 01.96

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Cardiovascular disorders since 1987 ,carotid stenosis operated in 1996, prostatic adenoma , aortic valve replacement(01.96), thoracic aorta aneurysm operated at the end of Jan-96 , COPD .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

COMMENTS

	24b. MFR CONTROL NO. 120M85
24c. DATE RECEIVED BY SERVIER Oct 10, 1996	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Oct 14, 1996	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
M-B	FRANCE	Day Month Year	Years 63	F	Year Month Day 97/04/03	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalisation for SOMNOLENCE and WALK DISORDERS (ATAXIA) and unstable NIDDM investigations. On admission, glycemia normal, anemia Hb 9g/dl, microcytosis at 78fl. Hypersplenic signs, moderate thrombocytopenia 82000/mm3. Coloscopy: NAD. Upper-digestive fibroscopy: oesophageal varix (grade I), fundic and antral gastritis. Neurologic exam: loss of equilibrium, enlarged polygone of sustentation, Romberg's signs positive, muscular force normal, LL reflexes abolition, probable posterior cordonal syndrome. Recovery after stopping the drug. NB: previous hospitalisation from 12 to 23-Jan-97 for NIDDM, cirrhosis and right ankle pain (canalar syndrome).

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
NIDDM

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 01.02.97 to 10.04.97	9W

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
AVLOCARDYL, DAFLON, DAONIL, LASILIX, GLUCOR, TRANXENE, IMOVANE

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Alcoholic cirrhosis, hypertension, basocellular exerese (1994), diabetic neuropathy.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

	24b. MFR CONTROL NO. 122K33	COMMENTS
24c. DATE RECEIVED BY SERVIER Oct 24, 1997	24d. REPORT SOURCE ☐ STUDY ■ LITERATURE ■ HEALTH PROFESSIONAL	*This report was received from the French Medicines Agency (Ref N° BX9701023).* *Published (Doerman 1998).*
DATE OF THIS REPORT Jun 15, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
J-R	FRANCE	Day Month Year 28-JUL-19	Years 77	M	Year Month Day 97/05/16	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalisation from 6 to 16-May-97 for unstable NIDDM investigations and GAIT DISORDERS AGGRAVATION with unstability, left LL hypoesthesia especially vibratory sensitivity. No Achille's reflex. No cerebellous syndrome. Motor deficiency of flexors especially of left lower limb. No monoclonal gammapathy.Pelvis echo normal. Glycemia 2g/l resulted in insulinotherapy with oral treatment. EMG (28/05/97): slight axonal NEUROPATHY with sensitive predominancy.Regression to his initial status after stopping Mediator.NB: previous hospitalisation from 23 to 30-Apr-97 for unstable NIDDM investigations and gait disorder. BP 15/8, no distal pulse, bilateral femoral murmur. Glycosylated Hb 7.3%, no dyslipidemia. Eye fundus:cataract, no retinopathy. No pathologic micro-albuminuria.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S) 450MG	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE NIDDM		
18. THERAPY DATES (from/to) from 07.05.97 to 16.05.97	19. THERAPY DURATION 10D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

DAONIL 4/D , CORDARONE , ASPEGIC , GLUCOR 300MG/D

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

NIDDM (88), 3 coronary by-pass (96), gastrectomy (2/3) for ulcers (53), aneurysm of abdominal aorta, CA/AF.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier F- 92200 -- Neuilly-sur-Seine		*This report was received from the French Medicines Agency (Ref N° BX9701041).* *Published (Doerman 1998).*
	24b. MFR CONTROL NO. 122N89	
24c. DATE RECEIVED BY SERVIER Nov 06, 1997	24d. REPORT SOURCE ☐ STUDY ■ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jun 15, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
M-F	FRANCE	Day Month Year 24-Sep-25	Years 71	M	Year Month Day 97/02/24	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Concomitantly to the beginning of Mediator and Euglucan treatment,neurologic troubles: disequilibrium when walking (EQUILIBRIUM DISORDER), falls and amnesia (loss of memory for recent facts), concentration difficulties, dysarthria. Hospitalisation from 27-Feb to 10-mar-97. Neurologic exam: slight distal hypoesthesia at left malleola, sensitivity and motricity normal, no Babinski, no extrapyramidal syndrome, no cerebellous or vestibular syndrome, no Romberg. No disorientation in time and space, no confusion. Favourable outcome after stopping Mediator. Re-hospitalisation from 5 to 6-May-97 for NIDDM investigations. Neurologic improvement.Abdominal echo: bilateral renal lithiasis, prostatic hyperthrophy (adenoma type). NIDDM still unstable resulting in insulinotherapy. EMG (22-May-97): demyelinising NEUROPATHY of LL with diffuse slowing down of motor and sensitive conduction (dysmetabolic origin).

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
NIDDM		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
from 17.01.97 to 24.02.97	38D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

EUGLUCAN, LOPRIL, LASILIX, CORDARONE, VASTAREL, PRAXILENE, DIGITALINE, DIFFU-K, ASPEGIC

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Hypertension, CA/AF, infarction (71), coronary by-pass (94), NIDDM (70), lower limbs arteritis, aorto-femoral bypass for aneurysm (96).

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier F- 92200 – Neuilly-sur-Seine		*The follow-up report was received from the French Medicines Agency (Ref N° BX9700301). Published (Doerman 1998).*
	24b. MFR CONTROL NO. 121017	
24c. DATE RECEIVED BY SERVIER Jun 04, 1997	24d. REPORT SOURCE ☐ STUDY ■ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jun 15, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
G-M	FRANCE	Day Month Year 17-APR-23	Years 73	M	Year Month Day 97/01/29	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

VERTIGO requiring hospitalisation for 2 days . Favourable outcome . Add. inf. (6.11.97): hospitalisation from 3 to 5-Feb-97 for unstable diabetes, malaise type vertigo with GAIT DISORDER and blurred vision. Neurologic exam normal except unstability standing. No Achille's reflex. Eye fundus: no diabetic retinopathy. Symptoms abated after stopping Mediator. Re-hospitalisation from 30-Oct to 10-Nov-97 for NIDDM investigations. Glycosylated Hb 9.6% resulted in insulinotherapy and biguanide treatment.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
300MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
NIDDM

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)
from 05.01.97 to 03.02.97

19. THERAPY DURATION
1M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
DAONIL , GLUCOPHAGE , AMLOR , CAPTOLANE, PREVISCAN

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hypertension , Wallenberg's syndrome (1984), NIDDM (1978), double coronary by-pass (1991), cataract.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

24b. MFR CONTROL NO.
121016

24c. DATE RECEIVED BY SERVIER
Jun 04, 1997

24d. REPORT SOURCE
☐ STUDY ■ LITERATURE ■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Jun 15, 1998

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This follow-up report was received from the French Medicines Agency (Ref N° BX9701040).
Published (Doerman 1998).

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 59	F	Year Month Day 95/06/07	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data
Hospitalisation for acute delirium flush: CONFUSION, disorientation in time and space, agitation. Neurologic investigations, scan, calcemia normal. On 7-Jun, Pilosuryl, Canol, Oliviase and amfepramone were stopped. On 9-Jun-95, cessation of MEDIATOR and Lipanthyl. Return to normal state within 8d after withdrawal of treatments and intake of neuroleptics .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ☐ NA
MEDIATOR (BENFLUOREX)		
15. DAILY DOSE(S) 450MG	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE CURE OF LOSS OF WEIGHT		
18. THERAPY DATES (from/to) from 27.03.95 to 09.06.95	19. THERAPY DURATION 2M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
PILOSURYL (PILOOSELLA , PHYLLANTUS) from 27.03.95 to 07.06.95
CANOL (CYNARA , LAWSONIA , CHYMAPHYLLA , APHLOIA) from 27.03.95 to 07.06.95
OLIVIASE (OLIVE) from 27.03.95 to 07.06.95, AMFEPRAMONE, LIPANTHYL.

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
No psychiatric past history .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° RN9500096). Amfepramone also suspected.*
	24b. MFR CONTROL NO. 540V17	
24c. DATE RECEIVED BY SERVIER Jun 28, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jul 07, 1995	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
W-Z	FRANCE	Day Month Year 08-May-33	Years 62	M	Year Month Day 93/03/08

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalisation for CONFUSION SYNDROME. Cerebellous syndrome, flapping. EEG: several irregularities, no epileptic signs. Cerebral scan normal. Liver biopsy normal.

	ASAT	ALAT	GGT	Alk Ph	Bili total
8-Mar	87	234	81	56	14
9-Mar	69	175	68	43	10
12-Mar	61	145	64	45	7
15-Mar	37	108	60	51	12
20-Mar	54	112	48	44	6

HBs Ag, anti-HBs antibodies negative, anti-HBc antibodies, anti-HVC antibodies positive. On 12-Mar, EEG negative. On 18-Mar, prescription of Prozac. On 19-Mar, the patient feels better.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
250MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: OBESITY		
18. THERAPY DATES (from/to): from 20.02.93 to 08.03.93	19. THERAPY DURATION: 16D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
MAGISTRAL PREP P 5CAP/D (METFORMINE 0.25G, DEXFENFLURAMINE 0.007G, BENFLUOREX 0.05G,ACETYLSALICYLIC ACID 0.10G) & C 3CAP/D (LYOPHILISATED THYROID 0.08G, YOHIMBINE 0.01G,GINSENG 0.10G) SINCE 20/02/93,ANAFRANIL,URBANYL,TTD-B3-B4.

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Intermittent alcoholism since Jun-92, depression (hypersomnia, speech disorders, incapacity to decide, walk slowly).

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

24b. MFR CONTROL NO.	COMMENTS
540V13	*This report was received from the French Medicines Agency (Ref N° PB9300028). Anafranil, Urbanyl, TTD-B3-B4, Tanakan and magistral preparation also suspected.*
24c. DATE RECEIVED BY SERVIER: Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
?-V	FRANCE	Day Month Year	Years 45	M	Year Month Day 87/07/10	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Sudden behavior disorders, with speech disorders (DELIRIUM) and DISORIENTATION IN TIME AND SPACE. Mediator was stopped on 11-Jul: in the evening, no improvement resulting in hospitalisation. Neurologic exams: astereognosis, no motor deficiency. Coordination normal. No oculo-motor deficiency. Photomotor reflex positive. No notion of cranial trauma. Cranial x-ray: NAD. On 12-Jul, disorientation improved but perisitency of confusion. No delirium, no thymic disorders. Blood toxics (barbiturics, aspirin, benzodiazepines & antidepressive drugs): negative. Alcoholemia negative. On 13-Jul:EEG: a few low bitemporal alterations (slightly superior from right side). Tomodensitometry normal. On 14-Jul, mystic DELIRIUM. Treatment with Valium, Droleptan, Barnetil and Nozinan. On 15-Jul, patient quiet. Chloroquine, benzodiazepine, amphetamines urine screening: positive. Administration of Temesta 2.5mg in the evening. On 16-Jul, patient quiet. On 17-Jul, scan with injection normal. Discharge on 18-Jul. On 25-Aug, no recurrence of symptoms. NB: symptoms should occurr after a sudden weight loss

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)	■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 25.06.87 to 11.07.87	16D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

COLLAGENAN 6/D SINCE 25/06/87, NICOBION 1.5G/D SINCE 25/06/87, GAVISCON

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Gastritis, hiatus hernia, obesity. No psychiatric history.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**	*This report was received from the French Medicines Agency (Ref N° GR8700216).*

	24b. MFR CONTROL NO.
	840D89
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
S-D	FRANCE	Day Month Year 01-Dec-12	Years 76	F	Year Month Day 88/04/25

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalization(25-Apr-88) for unbalanced diabetes (glycemia 6.4). Third administration of MEDIATOR on 27-Apr-88 (150mg/d). Important veinitis since 27-Apr-88. On 28-Apr: SOMNOLENCE, apathy. Patient was previously hospitalized: Mediator has been stopped after 3-4 days of intake. On 29-Apr, Mediator 300mg/d. On 02-May-88: fever 40°C without infectious site: tx with Rocephine 2g/d. Mediator was stopped. On 03-May, 37°C (at 8 a.m.), then at 10 a.m., chills, CONFUSION, knee mottling. Peripheral catheter culture: Staphylococcus epidermidis. LYMPHOPENIA.

Date	25-Apr	03-May	04-May	09-May
leukocytes	9200	8000	4800	8300
Hb	11	10.5	9.9	10.1
lymphocytes	1300	700	1000	2600
neutrophils	7410	7100	3100	5050
platelets		198000	168000	273000
SR	60/100	97/133	95/134	
glycemia	6.44	3.40	1.58	1.56
creatinine	20	17.5	15	17

Improvement of confusion on 04-May-88.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
150-300MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
NIDDM

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)
from 27.04.88 to 02.05.88

19. THERAPY DURATION
5D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
DIGOXIN, LASILIX, RYTHMODAN, DAONIL.

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
NIDDM, pericarditis (84), undetermined chronic inflammatory syndrome.
Behavior disorder. Cholelithiasis.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

24b. MFR CONTROL NO.
540V20

24c. DATE RECEIVED BY SERVIER
Jul 03, 1995

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Feb 16, 1999

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicines Agency (Ref N° DJ8800131).

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
E-T	FRANCE	Day Month Year 06-Dec-11	Years 79	F	Year Month Day 90/03/17	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life-threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

Hospitalisation for CONFUSION, DISORIENTATION, mnesic disorders and DELIRIUM. For 15 days, progressive disorientation in time and space. Neurologic exam normal. Thyroid and biologic exams normal. Cerebral tomodensitometry: sub-cortical cortical atrophy related to the patient's age; beginning of leucoaraiosis; basillar trunk terminaison aneurysm previously known. On 18-Mar, Mediator was stopped (patient with diet only). On 26-Mar, Catapressan was stopped and replaced by Adalate LP. Progressive stop of Haldol and Seresta on 21-Mar. Psychic disorders abated within 10 days. Dementia score 26 on admission and normalised on 30-Mar. Discharge on 4-Apr-90 with Sectral, Aldactazine, Aspegic 250, Lipanthyl, Adalate LP and diabetic diet.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
NIDDM		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
from U to 18-MAR-90	U	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

CATAPRESSAN (CLONIDINE) FROM UNKNOWN TO 26/03/90, ADALATE LP (NIFEDIPINE) FROM UNKNOWN TO 26/03/90, HALDOL (HALOPERIDOL) FROM UNKNOWN TO 21/03/90, SERESTA (OXAZEPAM) FROM UNKNOWN TO 21/03/90, PRAXILENE, ZESTRIL, SERMION

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Hypertension, hypercholesterolemia, hysterectomy, cataract surgery, syncope investigations in May-89.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier F- 92200 – Neuilly-sur-Seine		*This report was received from the French Medicines Agency (Ref N° CF9000137). Catapressan, Adalate LP, Haldol and Seresta also suspected.*
	24b. MFR CONTROL NO. 840D71	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
E-F	FRANCE	Day Month Year	Years 80	F	Year Month Day 84/02/10	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

4 or 5 days after treatment with Mediator, Kerlone & Mogadon in Feb-84, DISORIENTATION IN SPACE AND TIME AGGRAVATION, sphincter incontinency, obnubilation, and walk incapacity. Hypotension was noted (BP 160/90 to 120/70). Nootropyl infusion and administration per os of Pervincamine. Progressively symptoms abated. In jun-84, Mediator was readministred and symptoms reappeared. Mediator was stopped after 7 days of treatment.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	
17. INDICATION(S) FOR USE: HYPERCHOLESTEROLEMIA		■ YES ☐ NO ☐ NA
18. THERAPY DATES (from/to): from FEB-84 to U	19. THERAPY DURATION: 13D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
KERLONE, MOGADON IN FEB-84

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hypertension, hyperuricemia, sequelae of cerebrovascular accident with right hemiplegia in 78.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		*Positive rechallenge.*
	24b. MFR CONTROL NO. 010345	
24c. DATE RECEIVED BY SERVIER Sep 24, 1984	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Dec 05, 1984	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
B-B	FRANCE	Day Month Year 26-Oct-24	Years 68	M	Year Month Day 93/04/04	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

On 4-Apr-93 , gait disorders. Prescription of Anginotri-B and Uteplex on 14-May-93. On 29-May, hospitalisation for a few days. EMG: signs of symetrical bilateral sensitivo-motor NEUROPATHY. Glucophage was stopped on 29-May, Mediator and Azantac on 3-Jun. Equilibrium disorders abated on 9-Jun.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
300-450MG	ORAL

17. INDICATION(S) FOR USE
NIDDM .

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 09-MAR-93 to APR-93	<1M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
GLUCOPHAGE RETARD 2TAB/D (METFORMINE) FROM 09/03/93 TO 21/05/93, 3ATB/D FROM 22/05/93 TO 29/05/93, AZANTAC (RANITIDINE) FROM 01/93 TO 03/06/93, SURBRONC, CYCLOSPASMOL, TIMOPTOL, ISOPTOPILOCARPINE, DOLIPRANE & ATROVENT

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Gastrointestinal ulcer, chronic bronchitis, hiatus hernia.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

	24b. MFR CONTROL NO. 540J08
24c. DATE RECEIVED BY SERVIER Aug 30, 1993	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

COMMENTS
The follow-up report was received from the French Medicines Agency (Ref N° TS9300183).

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : DJ8800309 Centre de : DIJON Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 74 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 07/10/1988 Durée :

	Date de survenue
DELIRE	
HALLUCINATION	

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO		1 J		07/10/1988					1	1		1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

VIVALAN 50 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO		1 J		07/10/1988					1	1		1	S

Indication : PSYCHOSE NON PRECISEE

COMMENTAIRES

DELIRE HALLUCINATOIRE SOUS VIVALAN ET MEDIATOR.MAIS PROBLEME DE LA RESPONSABILITE DES MEDICAMENTS DANS UN SYNDROME QUI SEMBLAIT AVOIR DEBUTE AVANT LE DEBUT DU TRAITEMENT (TERRAIN:ETHYLISME).

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

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Fiche N° : CF8900109 Centre de : CLERMONT FERRAND Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 46 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 04/01/1989 Durée :

Date de survenue

CONVULSIONS

MEDICAMENT(S)

BUSPAR 5 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J		03/01/1989	005 J				2	1	2	1	S

Indication TROUBLES DEPRESSIFS NON CLASSES AILLEURS

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO									2	1	1	1	S

Indication

SURVECTOR 50, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	0.5 DF	1 J		03/01/1989	1.0 J				2	1	3	1	S

Indication

ATARAX 25 mg, comprimé pelliculé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication

BEFIZAL, comprimé PELLICULE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication

CALCIBRONAT 0,124 g/ml, solution injectable IV

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication

COMMENTAIRES

CRISE TONICOCLONIQUE AVEC PERTE BRUTALE DE CONNAISSANCE
FUGACES EXAMENS NEURO:NORMAL EEG:POTENTIELS PIONTUS TEMPORAUX DROITS

Edité le : 18/02/1999

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

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Fiche N° : LL9000165 Centre de : LILLE Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 43 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 01/04/1990 Durée :

	Date de survenue
DELIRE	
INSOMNIE	

MEDICAMENT(S)

AMFEPRAMONE (CHLORHYDRATE D')

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	135 MG	1 J		06/04/1990	008 J				2	1	3	1	S

Indication

TRANCOPAL 200 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/04/1990					2	1	1	1	S

Indication

TRINORDIOL, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/04/1990					2	1	1	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		06/04/1990					2	1	1	1	S

Indication

UTEPLEX 2 mg, solution buvable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/04/1990					2	1	1	1	S

Indication

CHYMODREX, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		06/04/1990	8.0 J				2	1	1	1	S

Indication

COMMENTAIRES

Edité le : 18/02/1999

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SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MP9400396 Centre de : MONTPELLIER Dossier Complet

Date de notification : 22/11/1994 Date de mise à jour :

PATIENT

Age : 73 A Sexe : F Taille : 158 cm Poids : 70 kg

Antécédents

FIEVRE TYPHOIDE
DIABETE SUCRE SANS MENTION DE COMPLICATIONS
SYNDROME DE DEPENDANCE ALCOOLIQUE
HYPERTENSION ESSENTIELLE SANS PRECISION

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Invalidité ou incapacité permanente Evolution : Guérison avec séquelle

Date apparition : 07/11/1994 Durée : 08 J

Date de survenue

POLYNEVRITE

MEDICAMENT(S)

DUXIL, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	02 DF	01 J	09/09/1994	09/11/1994	62 J	60 J	1	3	2	1	3	1	S

Indication

HEMIDAONIL 2,5 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	0,5 DF	01 J		15/10/1994			1	3	2	1	1	1	S

Indication DIABETE SUCRE SANS MENTION DE COMPLICATIONS

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	02 DF	01 J	15/10/1994	09/11/1994	26 J	24 J	1	3	2	1	1	1	S

Indication DIABETE SUCRE SANS MENTION DE COMPLICATIONS

PRAXILENE 200 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	02 DF	01 J		09/11/1994			1	3	2	1	1	1	S

Indication

ALDACTONE 75 mg, comprimé PELLICULE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	03 DF	1 J		09/11/1994			1	3	2	1	2	1	S

Indication HYPERTENSION ESSENTIELLE SANS PRECISION

COMMENTAIRES

Régression totale des troubles des membres supérieurs et des douleurs mais une aréflexie des membres inférieurs persiste

BENF ...orts of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Cardiovascular System									
123125	France	CRPV LY9700643	25	F	u	9m	Atrial fibrillation paroxystic	Recovery	Several drugs associated.
*[illegible] *	*France*	*CRPV RS9000184*	*62*	*F*	*450mg*	*4m*	*Cerebrovascular accident*	*Death*	*Diabetes, hypertension & hyperlipidemia associated.*
124809	France	CRPV PB9800124	72	F	450mg	2y	Cerebrovascular accident	Improvement	Hx of diabetes & hypertension. several drugs associated.
[illegible]	France	CRPV LL9700372	39	F	450mg	3m	Cerebrovascular accident	Recovery	Diuretics associated.
[illegible] *	*France*	*CRPV TO9800916*	*54*	*M*	*450mg*	*10y*	*Hemorroid disease aggravation (surgery)*	*Recovery*	*Several drugs associated*
540W55	France	CRPV GR9500235	52	F	u	u	Palpitation	Recovery	Sotalol associated . Drugs maintained .
540E02	France	CRPV PP9010597	37	F	150-450mg	10d	Syncope, (hypokalemia)	Recovery	Xipamide & several other drugs associated.
[illegible] *	*France*	*CRPV LY9500642*	*59*	*F*	*150mg*	*5m*	*Torsade de pointes*	*Recovery*	*Several drugs associated .*
121097	France	CRPV MP9700134	58	F	150mg	6d	Vasculitis	Improvement	Several drugs associated
[illegible]	France	CRPV RE9420042	41	F	450mg	3d	Vasculitis	Recovery	Several drugs associated.

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Annexe 3-18

SERVIER
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Pharmacovigilance Department
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 25	F	Year Month Day 97/10/21	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Paroxystic ATRIAL FIBRILLATION while patient treated with Mediator, Moderatan to lose weight. In the same time prescription of Canol and Tealine . Recovery without sequelae.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 02.01.97 to 20.10.97	9M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
CANOL FROM 02/01/97 TO 20/10/97, MODERATAN (AMFEPRAMONE) FROM 01/04/97 TO 20/10/97, TEALINE (GREEN TEA, ORTHOSIPHON) 02/01/97 20/10/97

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Obesity, nevrotic depression.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 123I25	COMMENTS
24c. DATE RECEIVED BY SERVIER Mar 30, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	*This report was received from the French Medicines Agency (Ref N° LY9700643). All the drugs are suspected.*
DATE OF THIS REPORT Mar 30, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 72	F	Year Month Day 97/06/27	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Left HEMIPARESIS while unstable hypertension. CT scan: ischemic CEREBROVASCULAR ACCIDENT of internal capsula, anterior lacuna. Hospitalisation. Recovery of motor disorders, persistency of left sensitive disorders with progressive improvement.
Indication of a further insulin therapy.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
GLIBENESE (GLIPIZIDE)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
15MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: NIDDM		
18. THERAPY DATES (from/to): from U to U	19. THERAPY DURATION: 2Y	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
MEDIATOR (BENFLUOREX) 450MG/D FOR 2Y, GLUCOR (ACARBOSE) 150MG/D

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
NIDDM (>20Y), severe retinopathy (micro & macro angiopathy), labile hypertension, obesity.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 124B09	COMMENTS
24c. DATE RECEIVED BY SERVIER: Jul 08, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	*This report was received from the French Medicines Agency (Ref N° PB9800124). All the drugs are suspected.*
DATE OF THIS REPORT: Aug 05, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 39	F	Year Month Day 97/09/22	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Ischemic CEREBROVASCULAR ACCIDENT, after sudden occipital headache on 22-Sep-97. Left cinetic cerebellar syndrome with dysarthria, facial asymetry, and diplopia. IRM: cerebellar infarction. Echo: mitral valve hypertrophy and aneurysm of IAS.
Recovery without sequelae.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
SPIRONONE (SPIRONOLACTONE)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 15.06.97 to 22.09.97	3M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
MEDIATOR (BENFLUOREX) 450MG/D FROM 15/06/97 TO 22/09/97

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**	*This report was received from the French Medicines Agency (Ref N° LL9700372). Mediator also suspected.*
24b. MFR CONTROL NO. 123F41	
24c. DATE RECEIVED BY SERVIER Mar 09, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Mar 09, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
?-?	FRANCE	Day Month Year	Years 52	F	Year Month Day 95/	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Onset of PALPITATIONS .
Hospitalisation or prolonged hospitalisation .
Treatments are maintained .
Favourable outcome .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 20.07.95 to MAINTAINED	U

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
SOTALEX (SOTALOL) from 15.06.94

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 540W55	COMMENTS
24c. DATE RECEIVED BY SERVIER Aug 24, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	*This case was received from the French Medicines Agency (Ref N° GR9500235).*
DATE OF THIS REPORT Aug 29, 1995	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
G-L	FRANCE	Day Month Year 26-Apr-53	Years 37	F	Year Month Day 90/03/06	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Treatment prescribed on 07-Mar-90: amfepramone 100mg/d, boldine 6mg/d, passiflore 200mg/d, aubepine 200mg/d as a magistral preparation; Lumitens 20-30mg/d, MEDIATOR 1 tab/d then 2 & 3tabs/d; Ribomunyl; Ginkor Fort. Ten days later, on 16-Mar-90: brief LOSS OF CONSCIOUSNESS (twice) requiring hospitalization. EKG: ventricular hyperexcitability, prolonged QT 0.48 (N=0.37): possible torsade de pointes. HYPOKALEMIA (K: 3.1 mEq/L).
Treatment stopped. Holter monitor (at 48th hr): polymorphic ventricular hyperexcitability. EKG normal three days after stopping the drugs.
Tx: heparin, potassium, magnesium. Neurological exam: negative.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)	■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150-450MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to) from 07.03.90 to 16.03.90	19. THERAPY DURATION 10D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

SINCE 7-MAR-90: LUMITENS (XIPAMIDE), MAGISTRAL PREPARATION INCLUDING AMFEPRAMONE 50MG, BOLDINE 3MG, PASSIFLORA 100MG, AUBEPINE 100MG (2CAPS/D) RIBOMUNYL, GINKOR FORT

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Gout. Obesity.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**	*This report was received from the French Medicines Agency (Ref N° PP9010597).*

	24b. MFR CONTROL NO.
	840E02
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 58	F	Year Month Day 96/12/10	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

PAPULAR , ERYTHEMATOUS PURPURA and ANGEITIS of feet spreading to the upper body (3 recurrent successive eruptions on 24-Dec and also on 1-Jan-97 .
2 days before the first eruption , right gonalgia treated with Niflugel .
On 8-Jan-97 , histology : diagnosis of acute leucocytoclasic vasculitis . Biologic tests : NAD except proteinuria 0.32g/l .
On 18-Jan-97 , no improvement (segmental edematous fits and arthritis with abdominal pain) . Treatment with Cortancyl 80mg/d and Zovirax for labial herpes , activating only on fever (38°) .
On 22-Jan-97 , hospitalisation in dermatologic ward . On 2-Feb-97 , persistent eruption with increased diameter of purpuric lesions on legs , thighs , trunk and back .
On 7-Feb-97 , discharged with cortisone decreased dose to 50mg/d and colchicine 1tab/d .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA
BOP (BIRCH TREE AND OLIVE TREE NEBULISAT)		
15. DAILY DOSE(S) 6TAB	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to) from 19.11.96 to 24.11.96	19. THERAPY DURATION 6D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

MEDIATOR (BENFLUOREX) from 19.11.96 to 24.11.96
NIFLUGEL (NIFLUMIC ACID) from 08.12.96 to 10.12.96
LEVOTHYROX 50UG (LEVOTHYROSIN) from 15.06.93 to CONTINUES

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Chronical thyroiditis , hypertension and history of medications allergies .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° MP9700134).*
	24b. MFR CONTROL NO. 121D97	
24c. DATE RECEIVED BY SERVIER Mar 19, 1997	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Mar 21, 1997	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
?-?	FRANCE	Day Month Year 01-Dec-52	Years 41	F	Year Month Day 93/11/25	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalization (until 03-Dec-93) for abdominal pain. Abdominal echo: no cholecystitis.
While hospitalized, dx of IDDM. Tx: MEDIATOR 3 tabs/d since 22-Nov-93, Sorbitol 2/d since 17-Nov-93, Insulatard, Actrapid; Virlix on 30-Nov-93. On 25-Nov-93, onset of cutaneous disorder. Dx(dermatologist): purpuric, papulous, vesiculous & pruriginous VASCULITIS. Latex, Waaler-Rose, C3, C4, CH50: negative. Biopsy(26-Nov-93): acute leucocytoclasic vasculitis with sub-epidermic pustules. Mediator stopped on 25-Nov-93. Improvement. Sorbitol & Virlix stopped on 30-Nov-93. 03-Dec-93: Direct Coombs' test: negative, Complement dosage: normal. Complete recovery on 07-Dec-93.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
DIABETES

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 22.11.93 to 25.11.93	3D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
SORBITOL 2/D SINCE 17-NOV-93, INSULATARD, ACTRAPID

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
None.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° RE9420042).*
	24b. MFR CONTROL NO. 840E00	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : RS9000184 Centre de : RENNES Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 62 A Sexe : F Taille : cm Poids : kg

Antécédents

DIABETE SUCRE SANS MENTION DE COMPLICATIONS

Cause de décès

ACCIDENT VASCULAIRE CEREBRAL

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Décès du à l'effet

Date apparition : 03/12/1990 Durée :

Date de survenue

ACCIDENT VASCULAIRE CEREBRAL

MEDICAMENT(S)

CEBUTID 50 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/11/1990	015 J				2	1	2	1	S

Indication

BAYPRESS 10 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/11/1990	4.0 M				1	1	2	1	S

Indication

DAONIL FAIBLE 1,25 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/11/1990	4.0 M				1	1	2	1	S

Indication

LOPRIL 25 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/11/1990	4.0 M				1	1	2	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/11/1990	4.0 M				1	1	0	1	A

Indication

LIPANOR, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/11/1990	4.0 M				1	1	0	1	A

Indication

COMMENTAIRES

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ARRET DE FELDENE POUR DU CEBUTID 13 JOURS AVANT LE DECES. HYPOTHESE DE DESEQUILIBRE DU TRAITEMENT HYPERTENSEUR ET HYPOGLYCEMIANT PAR LE CEBUTID.

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1242

Fiche N° : TO980916 Centre de : TOULOUSE Dossier Complet

Date de notification : 23/10/1998 **Date de mise à jour :** 28/01/1999

PATIENT

Age : 54 A Sexe : M Taille : cm Poids : kg

Antécédents

DIABETE SUCRE SANS MENTION DE COMPLICATIONS
HEMORROIDE SANS PRECISION SANS MENTION DE COMPLICATION

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation **Evolution :** Guérison sans séquelle

Date apparition : 10/12/1996 **Durée :**

	Date de survenue
AGGRAVATION DE LA MALADIE	

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	450 MG	J	14/03/1996			9 M	3	4	1	1	0	1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

GLUCOR 100 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	300 MG	J	26/11/1996			15 J	3	4	1	1	0	1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

GLUCOPHAGE 850 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3 DF	J	15/06/1995			18 M	3	4	0	1	0	0	A

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

COMMENTAIRES

Aggravation des signes fonctionnels et de l'importance anatomique d'une maladie hémorroïdaire ancienne. Patient hospitalisé pour le traitement chirurgical de celle-ci. Bonne évolution. Evènement indésirable déclaré dans le cadre de l'étude EPIDOR (BAYER PHARMA).

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SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : LY9500642 Centre de : LYON Dossier Complet

Date de notification : 11/10/1995 Date de mise à jour : 22/01/1996

PATIENT

Age : 59 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Mise en jeu du pronostic vital Evolution : Guérison sans séquelle

Date apparition : 08/10/1995 Durée :

Date de survenue

TORSADE DE POINTES

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	150 MG	J	01/05/1995	07/10/1995	5 M	5 M	1	3	2	2	1	2	S

Indication

DI ANTALVIC ADULTE, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3 DF	J	01/10/1995	07/10/1995	7 J	8 J	1	3	2	2	2	2	S

Indication

FELDENE 20 mg, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	20 MG						3	4	1	2	1	1	A

Indication

OLIGOSOL FLUORURE DE SODIUM, solution injectable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	IM			30/08/1995			6 S	3	2	1	2	1	1	A

Indication

COMMENTAIRES

Survenue de torsades de pointe et d'un arrêt circulatoire, le 8 octobre 1995 chez une femme de 59 ans à la suite de la prise de Di-Antalvic*, Oligosol*, Médiator* et Féldène*. La kaliémie était normale et la patiente ne présentait pas, a priori, d'allongement de QT long congénital ou acquis. Arrêt du Médiator à l'entrée. L'arrêt de l'administration de Di-Antalvic* a permis la régression des troubles malgré la poursuite de l'administration des autres produits.

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Respiratory System									
12SD63	France	CRPV NT9800036	69	M	150mg	10y	Pneumonitis	Persistency	Bisoprolol associated.
124U12	France	CRPV LM9800297	75	M	u	u	Pneumonitis	Unknown	Glimepiride associated.
540V90	France	CRPV SE9400175	46	F	u	3m	Pneumopathy	Recovery	Dexfenfluramine & clobenzorex associated. Reversible with anti-tuberculous agents.
54aV06	France	CRPV PP8990081	40	F	150mg	u	Pulmonary hypertension	Unknown	Clobenzorex & amfepramone intake.

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 69	M	Year Month Day 97/08/15	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

Recent dyspnea worsened rapidely for 1 month resulting in hospitalisation at the beginning of Sep-97.
Etiologic research: no infectious pathology, nor immun, nor professional (the patient was refrigerist then worked in farm-produce industry). PULMONARY INTERSTITIAL FIBROSIS, DIFFUSE INTERSTITIAL PNEUMOPATHY. Treatment with steroids and Endoxan. In Dec-97, the patient seems to be stable.
Add inf (7-Apr-98): In Mar-98, still no improvement . Pt's HP noted that the Pt's general status was slowly worsening. The Pt is incharged in a private centre.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
DETENTIEL (BISOPROLOL)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
☐ YES ■ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
15MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: HYPERTENSION		
18. THERAPY DATES (from/to): from 01.03.97 to 01.09.97	19. THERAPY DURATION: 6M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
LEXOMIL 0.25TAB/D (BROMAZEPAM) FROM UNKNOWN TO 01/01/98, MEDIATOR 150MG/D (BENFLUOREX) FROM UNKNOWN TO 01/09/97 FOR 10Y, JOSIR 0.2MG/D FROM 01/03/97 TO 01/09/97

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Prostatic disorder.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 123D63	COMMENTS
24c. DATE RECEIVED BY SERVIER: Feb 19, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	*This report was received from the French Medicines Agency (Ref N° NT9800036). Lexomil, Mediator and Josir also suspected.*
DATE OF THIS REPORT: Apr 10, 1998	25a. REPORT TYPE ☐ INITIAL ■ FOLLOWUP	

Annexe 3.18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 75	M	Year Month Day 98/07/15	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Massive bilateral alveolo-intertitial syndrome (major hypoxia) (except upper area) (DIFFUSE INTERTITIAL PNEUMOPATHY). Unknown outcome after stopping Amarel.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 15.06.98 to U	U

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
AMAREL (GLIMEPIRIDE) FROM 15/06/98 TO 22/08/98 FOR 9W

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Heart failure.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° LM9800297). Glimepiride also suspected.*
	24b. MFR CONTROL NO. 124U12	
24c. DATE RECEIVED BY SERVIER Oct 13, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Oct 20, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
Z-B	FRANCE	Day Month Year 28-Sep-48	Years 46	F	Year Month Day 94/04/??

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Apr-94 : chest pain. CXR on 14-Apr-94 showed evidence of diffuse widespread images.
Lung CT-scan (5-May-94) : presence of about 10 nodules (diameter 0.5 to 2cm).
Bronchoscopy (18-May-94): inflammatory mucosae of benign aspect; purulent sputum (PNEUMOPATHY).
Bronchial biopsy (19-May-94): suacute inflammation of mucosae.
Thoracoscopy : no suspect lesions.
Biology (26-May-94): Fbg 4.99 (N 2.5-4.5), SGPT 33 (N<30), GGT 50 (N<40).
Pleural biopsy (27-May-94): slight congestive and macrophagic alveolitis.
No BK (31-May-94).
Mediator, Dinintel and Isomeride (?) were stopped on 16-May-94.
Tx with Rimifon, Rifadine and Pirilene since 10-Jun-94.
Recovery within 1 month.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)	■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 02.94 to 16.05.94	3M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
DININTEL AND ISOMERIDE SINCE FEB-94
NOCTAMIDE, VISCERALGINE F, DIANTALVIC, CALCITONINE

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hystrectomy, unilateral ovariectomy. Cholecystectomy. Preventive tx with Rimifon in 1990 (father had tuberculosis). MVA in Oct-93 (CXR showed diffuse widespread images at this time).

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**	*This report was received from the French Medicine Agency (Ref N° SE9400175).*

	24b. MFR CONTROL NO.
	540V90
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
C-C	FRANCE	Day Month Year 21-Sep-47	Years 40	F	Year Month Day 88/07/??	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Reintake of anorexiants in Apr-88.
Jul-88 : diagnosis of PULMONARY HYPERTENSION revealed by dyspnea.
Hospitalization on 29-Feb-89 for pre-graft investigations.
Abdominal CT-scan : hepatomegalia with ascites.
Platelets 71,000.
Myelogram & bone marrow biopsy (31-Jan-89) : suggestive of dysmyelopoeisis.
Biology : abnormal liver function tests (Bili T 67, Bili C 46, SGOT 44, SGPT 40, PT 50%).
First injection of Imovax.
Outcome not specified.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)	☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: OBESITY		
18. THERAPY DATES (from/to): from 09.87 to U	19. THERAPY DURATION: U	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

FROM 1970 OR 1972, ALTERNATIVE INTAKE 2MONTHS/4 OF DININTEL, FRINGANOR & TENUATE DOSPAN. HAVLANE 1TAB/D SINCE SEP-87. MAGISTRAL PREP.INCLUDING AMFEPRAMONE 17MG/CAPS,METFORMINE 50MG/CAPS,THEOPHYLLINE,FUCUS VESICULUS

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

D8 fracture. CXR in 1980 judged normal but 'a posteriori suggestive of pulmonary hypertension'.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**	*This report was received from the French Medicine Agency (Ref N° ~~PP8990081~~).*

	24b. MFR CONTROL NO.
	540V06
24c. DATE RECEIVED BY SERVIER: Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Dexfenfluramine and Pulmonary Hypertension : Benfluorex exposure

Ref. N° Age, sex Body Mass Index	Timing				Underlying Cardio-pulmonary or Collagen vascular Diseases	Other Drugs	Outcome
	First dose	Last dose	First symptoms	Diagnosis			
VIGI 10052454 France 48, male BMI = 31	Dexfenfluramine 12-88	04-91	04-91 (SOB)	12-91	Dyslipidemia		Death (18m)
	Benfluorex 06-86	02-92					
	appropriate				no	no	
VIGI 10052455 France 46, female BMI = 23 (history of obesity)	Dexfenfluramine 06-90	09-92	09-92 (SOB)	01-93	Systemic hypertension	Anti-obesity (< 06-90) Estrogen therapy (ovariectomy)	No follow-up
	Benfluorex 10-90	12-92					
	appropriate				no	yes	
VIGI 10052733 France 71, female BMI = 38	Dexfenfluramine 03-92	04-92	06-92 (SOB)	(02-93)	Systemic hypertension Respiratory failure (obstructive, with thyroid hypertrophy) Diabetes (NIDDM)	Diet pills	No follow-up
	Benfluorex 1987	?					
	appropriate				no	no	
VIGI 10840193 France 47, female BMI = 39	Dexfenfluramine 09-91	11-93	03-93 (SOB)	12-93	Systemic hypertension Diabetes (NIDDM)		Status-quo (17m)
	Benfluorex 03-93	09-93					
	appropriate (dF only)				no	no	
VIGI 10840255 France 57, female BMI = 32	Dexfenfluramine 1986	1986	01-93 (SOB)	11-93		Fenfluramine (15 years ago)	Status-quo (7m)
	Benfluorex 09-93	?					
	appropriate (dF only)				no	no	

Dexfenfluramine and Pulmonary Hypertension . Benfluorex exposure (Cont'd)

Ref. N° Age, sex Body Mass Index	Timing				Underlying Cardio-pulmonary or Collagen vascular Diseases	Other Drugs	Outcome
	First dose	Last dose	First symptoms	Diagnosis			
VIGI 10840663 France 48, male BMI = 35	Dexfenfluramine 09-90	04-91	?	06-93	Systemic hypertension Respiratory sequelae of a chest trauma chronic obstructive lung disease		Status-quo (16m)
	Benfluorex 02-92	?					
	unassessable				yes	no	
VIGI 10840770 France 66, female BMI = 27	Dexfenfluramine 04-91	05-91	1985	11-91	Past history of phlebitis (post-partum) Chronic obstructive lung disease Systemic hypertension	Fenproporex (1985)	Status-quo (36m)
	Benfluorex 1985	1985					
	unappropriate				yes	yes	
VIGI 10840954 France 54, female Body weight unknown	Dexfenfluramine 1992	1992	11-93	07-94	Diabetes (NIDDM) Mitral stenosis with left ventricular hypertrophy		Improvement (4m)
	Benfluorex ?	?					
	appropriate (dF only)				yes	no	
VIGI 10840B19 France 51, female BMI = 37	Dexfenfluramine 1985	1989	08-94 Sjögren syndrome	08-94	Systemic hypertension Venous problem Hyperlipidemia Mitral and aortic valves incontinence	Mefenorex (1974)	Status-quo (5m)
	Benfluorex 1989	1-95					
	appropriate				yes	yes	
VIGI 10840D01 France 59, female BMI = 27	Dexfenfluramine 04-91	01-93	10-93	05-95	Ischemic and hypertensive cardiopathy	Fenfluramine (11-92 to 11-93)	Death (9m)
	Benfluorex 1990	1994					
	appropriate				yes	no	

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Hemic and Lymphatic System									
[illegible] *	*France*	*CRPV TS9600117*	*73*	*F*	*150mg*	*u*	*Agranulocytosis*	*Recovery*	*Several drugs associated .*
[illegible] *	*France*	*CRPV BX9800512*	*72*	*M*	*450mg*	*3m*	*Agranulocytosis*	*Recovery*	*Several drugs associated.*
[illegible] *	*France*	*CRPV MP9800040*	*68*	*M*	*u*	*u*	*Agranulocytosis*	*Recovery*	*Several drugs associated. Mediator maintained.*
[illegible]	France	HP	70	F	450mg	3w	Anemia, thrombopenia	Recovery	
[illegible] *	*France*	*CRPV BX9700357*	*75*	*F*	*450mg*	*3m*	*Neutropenia*	*Persistency*	*Several drugs associated .*
[illegible] *	*France*	*CRPV TS9300053*	*72*	*F*	*300mg*	*1y*	*Neutropenia, (cough)*	*Persistency*	*Several drugs associated .*
[illegible]	France	CRPV NC8900022	71	M	450mg	>6m	Neutropenia, thrombopenia	Unknown	Glibenclamide associated . Drugs maintained .
[illegible]	France	CRPV PS9400301	61	F	300mg	u	Thrombocytopenia	Recovery	Retinol associated .
[illegible]	France	CRPV NC9400153	19	F	450mg	2m	Thrombocytopenia	Recovery	Spironolactone & clobenzorex associated.
[illegible] *	*France*	*CRPV CF8800375*	*85*	*F*	*75mg*	*u*	*Thrombocytopenia*	*Recovery*	*Several drugs associated.*
[illegible] *	*France*	*CRPV NT9800026*	*73*	*F*	*u*	*9w*	*Thrombopenia*	*Persistency*	*Several drugs associated.*
[illegible] *	*France*	*CRPV MP9400244*	*69*	*M*	*300mg*	*u*	*Thrombopenia*	*Recovery*	*Glibenclamide associated.*
[illegible]	France	CRPV LY8500365	50	M	300mg	3m	Thrombopenia	Unknown	Several drugs associated.

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Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
N-B	FRANCE	Day Month Year	Years 70	F	Year Month Day 86/06/??	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Treatment with MEDIATOR 450mg/d (date U, associated tx U).
In Jun-86, after 3 weeks of tx, onset of purpura & digestive hemorrhage with melaena. THROMBOPENIA (Platelets < 5000/mm3), ANEMIA (Hb 9 g/dl). Myelogram: numerous megacaryocytes. Antiplatelets antibodies: positive (Coombs' platelet test I125). Mediator stopped. Favourable outcome: Platelet count 220,000(07-Jul); 247,000 (15-Jul). Antiplatelets antibodies: negative. Hb: normal.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG		☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: HYPERLIPEMIA		
18. THERAPY DATES (from/to): from U to U	19. THERAPY DURATION: 3W	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Angor, HTN, gastric ulcer.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier F- 92200 -- Neuilly-sur-Seine	

	24b. MFR CONTROL NO.
	050F09
24c. DATE RECEIVED BY SERVIER: Aug 18, 1986	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Sep 08, 1986	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

CIOMS FORM

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
J-L	FRANCE	Day Month Year ??-???-17	Years 71	M	Year Month Day 87/01/??

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

NEUTROPENIA & THROMBOPENIA:

Date	1985	Jan-86	Jan-87	03-Dec-88	Jan-89
Platelets	158	?	46	45	48
WBC	?	3030	3120	3710	2900

Hospitalization (date U). Myelogram(14-Dec-88): important monocytosis & blasts at the upper limit of normal. Myelogram(18-Jan-89): myelodysplasia (Refractory Anemia with Partial Myeloblastosis), monocytosis & sideroblastosis (ring sideroblasts: 30%).MEDIATOR & Hemidaonil maintained. Diantalvic was stopped at the end of Dec-88. Unknown outcome.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 07.86 to CONTINUES	>6M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
HEMIDAONIL 3/D (SINCE 06.83),DIANTALVIC (SINCE 12.88).

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

	24b. MFR CONTROL NO. 540V26
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicines Agency (Ref N° NC8900022).

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
M-R	FRANCE	Day Month Year 05-Apr-33	Years 61	F	Year Month Day 94/05/26

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

On 21-May-94, onset of ulorrhagia (while brushing teeth), LL then generalized petechiae. Tx: Betametazone. Slight decrease of symptoms. Gerimax was stopped on 24-May-94. On 26-May-94: platelet count 3000/mm3 (THROMBOPENIA). Hospitalization in emergency for thrombopenic purpura. BP 120/90. Generalized petechial purpura,predominant on LL, hemorrhage stomatitis, cutaneous & mucous pallor. MEDIATOR was stopped on 26-May-94. During the night (26/27-May-94): generalized pruritus with maculo-papulous eruption, face & eyelids edema, BP 120/80. Tx: Polaramine. Platelet count (27-May) 2000/mm3, no hemorrhage. Bone-marrow smear:numerous granulocytes, erythroblasts moderately present. Platelet count(28-May) 8000/mm3.

Date	30-May-94	06-Jun-94
Hb g/L	8	9
WBC /mm3	8500	9900
Platelets /mm3	133000	305000

Immunoglobulins were stopped on 02-Jun-94. End of hospitalization: 07-Jun-94.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
300MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
NIDDM

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from U . to 26.05.94	U

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
GERIMAX (SINCE 15.05.94),OROCAL 500/D,LEVOTHYROX 50/D

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hypothyroidism, NIDDM, pleurisy(at age 19).

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

24b. MFR CONTROL NO.	COMMENTS
540V28	*This report was received from the French Medicines Agency (Ref N° PS9400301).*
24c. DATE RECEIVED BY SERVIER: Jul 03, 1995	24d. REPORT SOURCE: ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Feb 16, 1999	25a. REPORT TYPE: ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
C-F	FRANCE	Day Month Year ??-???-75	Years 19	F	Year Month Day 94/05/11	☐ Patient died ☐ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalization(11-May-94/20-May-94) for LL purpura. Platelet count: 3000/mm3 (THROMBOPENIA), Prothrombin index 77%, APTT 39 sec., SR 8. Note: 3 weeks ago, acne: tx were stopped; Doxycline prescribed from 6-May to 10-May-94.Myelogram(13-May-94): numerous megacaryocytes. Rheumatoid factor (date U): 38 (N: 0-20). HBV, HCV, CMV, HIV & EBV: negative. Tx: Veinoglobuline, Solumedrol. Rapid platelet increase. Favourable outcome.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 02.94 to 04.94	2M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
CLOBENZOREX 60MG/D,ALDACTONE 75 1/D: SINCE FEB-94.
DOXYCLINE 1/D (06.05.94 TO 10.05.94).

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° NC9400153).*
	24b. MFR CONTROL NO. 540V27	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
R-P	FRANCE	Day Month Year 25-Dec-34	Years 50	M	Year Month Day 85/09/05	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
NIDDM treated with MEDIATOR 300mg/d for 3 months.
Onset of ulorrhagia & moderate epistaxis. Hospitalization:
THROMBOPENIA (between 10,000 & 14,000). Myelogram: megacaryocytes
growth disorder. All drugs were stopped on 05-Sep-85. Platelet
count(12-Sep-85): 15,000. Tx: corticoids. Unknown outcome.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
300MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: NIDDM		
18. THERAPY DATES (from/to): from U to 05.09.85	19. THERAPY DURATION: 3M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
SECTRAL 400MG/D (FOR 3Y),TILDIEM 3/D(FOR 2M),MODURETIC 1/D (FOR 2Y),
RISORDAN 20 (FOR 4Y).

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Angor, HTN.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F- 92200 – Neuilly-sur-Seine

COMMENTS
This report was received from the French Medicines Agency (Ref N° LY8500365).

	24b. MFR CONTROL NO. 540V21
24c. DATE RECEIVED BY SERVIER: Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1257

Fiche N° : TS9600117 Centre de : TOURS Dossier Complet

Date de notification : 12/03/1996 Date de mise à jour :

PATIENT

Age : 73 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Guérison sans séquelle

Date apparition : 02/02/1996 Durée :

	Date de survenue
AGRANULOCYTOSE	

MEDICAMENT(S)

SALAZOPYRINE 500 mg, comprimé enrobé gastro-résistant

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	500 MG	4 J		02/02/1996			1	3	1	1	3	1	S

Indication

PROZAC 20 mg, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	20 MG	1 J					1	3	1	1	2	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO							1	3	1	1	1	1	S

Indication

CIBADREX 10 mg/12,5 mg, comprimé pelliculé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J					1	3	1	1	3	1	S

Indication

COMMENTAIRES

M.A: Témesta, Amlor, Ikorel.
Le 02/02/1996: leuco 640/mm3, neutro 19/mm3.
Le 28/02/1996: leuco 8600/mm3, neutro 7700/mm3.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1268

Fiche N° : BX9800512 Centre de : BORDEAUX Dossier Complet

Date de notification : 26/05/1998 Date de mise à jour : 24/07/1998

PATIENT

Age : 72 A Sexe : M Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Guérison sans séquelle

Date apparition : 18/05/1998 Durée :

Date de survenue

AGRANULOCYTOSE

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	450 MG	J	01/02/1998	18/05/1998	3 M	3 M	1	3	2	1	1	1	S

Indication

NOCERTONE 60 mg, comprimé pelliculé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	J	01/02/1998	18/05/1998	3 M	3 M	1	3	2	1	1	1	S

Indication

PENTASA 500 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	4 GM	J	04/03/1998	18/05/1998	10 S	10 S	1	3	2	1	3	1	S

Indication

ARESTAL, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3 MG	J	11/02/1998	18/05/1998	3 M	3 M	1	3	2	1	1	1	S

Indication

COMMENTAIRES

Observation recueillie dans le cadre de l'étude EURONET.
Patient aux antécédents de DNID, d'adénome prostatique, de diarrhée chronique, revient le 14 mai d'un voyage aux USA de 15 jours. Dans le nuit du 14 au 15 mai, température à 39-39,5°. La numération réalisée le 18 mai montre des globules blancs (GB) à 700/mm3 et des neutrophiles à 56/mm3 (la dernière numération du 20 mars était normale : GB : 6300/mm3, PNN à 4851/mm3). La numération se normalise le 2 juin. GB : 5200/mm3 ; PNN : 2444/mm3. La ponction sternale du 29 mai évoque une origine toxique. Son hospitalisation met, par ailleurs, en évidence : une pneumopathie lobaire droite hypoxomiante, un adénome de la prostate, une tumeur carcinoïde duodénale.
Autres médicaments utilisés : MOPRAL, DAONIL, LIPANOR, ZYLORIC, PERMIXON, PRAZINIL, OSSOPAN, NORMISSON.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MP9800040 Centre de : MONTPELLIER Dossier Complet

Date de notification : 28/01/1998 Date de mise à jour :

PATIENT

Age : 68 A Sexe : M Taille : 174 cm Poids : 70 kg

Antécédents

DIABETE SUCRE SANS MENTION DE COMPLICATIONS
HYPERCHOLESTEROLEMIE ESSENTIELLE
INSUFFISANCE AORTIQUE RHUMATISMALE
CARDIOMYOPATHIE AU COURS D'AUTRES MALADIES CLASSEES AILLEURS
FIBRILLATION ET FLUTTER AURICULAIRES

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation **Evolution :** Guérison sans séquelle

Date apparition : 24/12/1997 **Durée :**

	Date de survenue
AGRANULOCYTOSE	

MEDICAMENT(S)

PREVISCAN 20 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	15 MG	1 J	27/10/1997	23/12/1997	8 S	8 S	1	3	1	1	3	1	S

Indication : CARDIOMYOPATHIE AU COURS D'AUTRES MALADIES CLASSEES AILLEURS

ZESTRIL 20 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J	27/10/1997	23/12/1997	8 S	8 S	1	3	1	1	2	1	S

Indication : CARDIOMYOPATHIE AU COURS D'AUTRES MALADIES CLASSEES AILLEURS

DAONIL 5 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO							3	4	1	1	3	1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO							3	4	1	1	1	1	S

Indication : HYPERCHOLESTEROLEMIE ESSENTIELLE

LASILIX 40 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J	22/10/1997	23/12/1997	8 S	9 S	1	3	1	1	3	1	S

Indication : CARDIOMYOPATHIE AU COURS D'AUTRES MALADIES CLASSEES AILLEURS

CORDARONE 200 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO			15/10/1997			10 S	3	4	1	1	1	1	S

Indication : FIBRILLATION ET FLUTTER AURICULAIRES

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COMMENTAIRES

Agranulocytose est accompagnée d'une fièvre à 39° sans point d'appel infectieux clinique particulier + aphtes. Aucun germe n'a été retrouvé (hémoculture, ECBU, aphtes buccaux). Le myélogramme est normal ainsi que transaminases. Sérologies MNI, hépatite A et B non faites.

	GB	PW
25/12/97	2000	0
7/1/98	6500	3900

Dossier complet.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : BX9700357 Centre de : BORDEAUX Dossier Complet

Date de notification : 13/01/1997 Date de mise à jour :

PATIENT

Age : 75 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Sujet non encore rétabli

Date apparition : 03/01/1997 Durée :

Date de survenue

AGRANULOCYTOSE

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3 DF	J	01/10/1996	07/01/1997	3 M	3 M	2	3	1	1	1	1	S

Indication

VASTAREL 1 mg, COMPRIME

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3 DF	J		14/01/1997			2	3	1	1	1	1	S

Indication

LASILIX FAIBLE, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	J	01/01/1991	14/01/1997	6 A	6 A	2	3	1	1	3	1	S

Indication

LIPANTHYL 200 micronisé, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	J	01/01/1991	07/01/1997	6 A	6 A	2	3	1	1	3	1	S

Indication

HYPERIUM 1 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication

MONO TILDIEM LP 200 mg, gélule à libération prolongée

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication

COMMENTAIRES

Annexe 3-18

Début octobre 96 : asthénie + anorexie -> numération formule sanguine normale. Visite mensuelle chez son médecin traitant le 03/01/97. NFS : globules blancs à 2900/mm3, neutrophile à 493/mm3.
LASILIX remplacé par ALDACTONE le 16/01/97.
Arrêt du LIPANTHYL, MEDIATOR puis du LASILIX et VASTAREL. La ponction sternale du 08/01/97 montre une hyperéosinophilie marquée (signe d'irritation médullaire) snas véritable signe de toxicité médullaire.
Persistance de l'agranulocytose : le 26/01/97 : GB : 2100/mm3, neutrophile : 294/mm3, le 19/03/97 : GB : 2190/mm3.
Prenait de plus du LOPRIL 2cp/jour depuis 1991 et du STILNOX 2 cp/jour depuis 07/95 (non arrêtés).

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : TS9300053 Centre de : TOURS Dossier

Date de notification : Date de mise à jour : 28/07/1997

PATIENT

Age : 72 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Sujet non encore rétabli

Date apparition : 16/11/1992 Durée :

	Date de survenue
TOUX	
NEUTROPENIE	

MEDICAMENT(S)

SIBELIUM 10 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	10. MG	1 J			1.0 A				1	1	1	1	S

Indication

SERC 8 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	16. MG	1 J			1.0 A				1	1	1	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	300 MG	1 J		18/11/1992	1.0 A				1	1	1	1	S

Indication

PRIMPERAN 100 mg/100 ml, solution buvable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				16/11/1992	6.0 M				1	1	1	1	S

Indication

DIFRAREL 100 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		16/11/1992	1.0 A				1	1	1	1	S

Indication

CIBACENE 10 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	10. MG	1 J			001 M				1	1	3	1	S

Indication

COMMENTAIRES

MED ASSOCIE / ETIOVEN

Edité le : 18/02/1999

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SYSTEME NATIONAL DE PHARMACOVIGILANCE

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Fiche N° : CF8800375 Centre de : CLERMONT FERRAND Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 85 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 14/10/1988 Durée :

Date de survenue

THROMBOCYTOPENIE

MEDICAMENT(S)

FLUDEX 2,5 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 S		19/10/1988					2	2	0	2	S

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

ACYLANIDE 0,2 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	0.5 DF	1 J		19/10/1988					2	2	3	2	S

Indication : INSUFFISANCE CARDIAQUE SANS PRECISION

CORDARONE 200 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	5.0 DF	1 S		19/10/1988					2	2	3	2	S

Indication :

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication :

VASTAREL 1 mg, COMPRIME

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication :

NOOTROPYL 400 mg, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication :

COMMENTAIRES

Edité le : 18/02/1999

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THROMBOPENIE ISOLEE AVEC MYELOGRAMME NORMAL.

MEDICAMENTS

ASSOCIES:LIBRAX,MOTILIUM.

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Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

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Fiche N° : NT9800026 Centre de : NANTES Dossier Complet

Date de notification : 27/01/1998 Date de mise à jour : 05/05/1998

PATIENT

Age : 73 A Sexe : F Taille : 155 cm Poids : 60 kg

Antécédents

DIABETE SUCRE SANS MENTION DE COMPLICATIONS
HYPERTENSION ESSENTIELLE SANS PRECISION

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Sujet non encore rétabli

Date apparition : 08/01/1998 Durée :

	Date de survenue
THROMBOPENIE	

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO			01/11/1997	04/01/1998	9 S	9 S	4		1	1	1	1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

ALDACTONE 50 mg, comprimé PELLICULE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	J	01/11/1997			9 S	3	3	1	1	0	1	S

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

LOGIMAX 5 mg/47,5 mg, comprimé pelliculé à libération prolonlée

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO							3	3	1	1	2	1	S

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

EURELIX 6 mg LP, gélule à libération prolongée

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	J		01/11/1997				3	0	1	2	0	A

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

COMMENTAIRES

Thrombopénie découverte vers le 08 01 98 environ 30 000/mm3
le 14 01 : 35 000 arrêt du MEDIATOR vers le 10 01
le 19 01 : 90 000 mais le 26 01 : 33 000

Dossier peu documenté contradiction entre la patiente et ses médecins.
en attente exploration.

Mai 98 :
Rien de plus le 04 05 98 n'a pas reconsulté et nie tout en bloc selon le médecin généraliste : a entendu parler du MEDIATOR (confond sans doute avec 'SURVECTOR' car s'est faché et a déclaré ne pas être une toxico !!!)

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SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MP9400244 Centre de : MONTPELLIER Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 69 A Sexe : M Taille : cm Poids : kg

Antécédents

DIABETE SUCRE SANS MENTION DE COMPLICATIONS
PSYCHOSE NON PRECISEE

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 30/05/1994 Durée :

	Date de survenue
THROMBOCYTOPENIE	
THROMBOPENIE	

MEDICAMENT(S)

HEMIDAONIL 2,5 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.5 DF	1 J		30/05/1994					2	1	3	1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

TEMESTA 1 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J							1	1	3	1	A

Indication : ETATS ANXIEUX

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J							1	1	1	1	A

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

TERALITHE 250 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J							1	1	1	1	A

Indication : PSYCHOSE NON PRECISEE

PRAXILENE 200 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J							1	1	1	1	A

Indication :

COMMENTAIRES

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BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Body as a Whole									
[illegible]	France	CRPV MA9700036	60	F	150mg	2d	Anaphylactic reaction	Recovery	Published (CHAINE 1998). Positive rechallenge.
[illegible]	France	CRPV MA9300723	41	F	150mg	1d	Anaphylactic reaction	Recovery	Negative prechallenge .
[illegible]	France	CRPV NC8900097	60	F	150mg	1d	Anaphylactic reaction	Recovery	
[illegible]	France	CRPV LY9800499	36	M	150mg	1d	Anaphylactic reaction	Recovery	
[illegible]	France	CRPV NC9800400	36	F	150mg	1d	Anaphylactic reaction	Recovery	
[illegible]	France	CRPV PA9200399	41	F	150mg	1d	Anaphylactic shock	Recovery	Metformine associated.
[illegible]	France	HP	38	F	150mg	1d	Anaphylactic shock	Recovery	Carbocisteine interaction suspected.
[illegible]	France	CRPV MA9300967	50	F	150mg	8d	Anaphylactic shock	Recovery	Positive rechallenge .
[illegible]	France	CRPV DJ9200119	79	F	150mg	2d	Anaphylactic shock	Recovery	Positive rechallenge .
[illegible]	France	CRPV MA9400018		F	u	days	Anaphylactic shock	Recovery	Positive rechallenge .
[illegible]	France	CRPV PA9735052	27	M	1350mg	6m	Drug abuse, (headache, manic reaction, mydriasis after withdrawal)	Unknown	Drug abused by a sportsman.
[illegible]	France	HP	2	M	450mg	1d	Overdosage accidental	Recovery	No signs/symptoms .
[illegible]	France	HP	37	F	4500mg	1d	Overdosage intentional (hypotension, obnubilation)	Recovery	
[illegible]	*France*	*CRPV RS9800096*	*77*	*F*	*300mg*	*20y*	*Photosensitivity*	*Recovery*	*Several drugs associated.*

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 60	F	Year Month Day 96/12/18	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

On 18-Dec-96 , URTICARIA generalised and BRONCHOSPASM after taking Rulid, Mediator (first tab), Surgam and Efferalgan. Admitted to emergency room.
On 6-Jan-97 , oral provocation test with Mediator : 1 hour later, palmar pruriginous rash, then generalised pruritus, slight pulmonary edema requiring antihistaminic IV and 1.5 hour later ANAPHYLACTIC SHOCK with BP 7/4, impregnable pulse and abdominal pain: infusion of adrenaline at 0.05%, dexchlorpheniramine infusion, steroids, and oxygenotherapy. Favourable outcome within one hour. NB : previous intake of Mediator, 5 years ago .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S) 150MG	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ■ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE NIDDM		
18. THERAPY DATES (from/to) from 18.12.96 to 06.01.97	19. THERAPY DURATION 2D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° MA9700036). Published (Chaine 1998). Positive rechallenge .*
	24b. MFR CONTROL NO. 121D94	
24c. DATE RECEIVED BY SERVIER Mar 19, 1997	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Apr 17, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 41	F	Year Month Day 93/??/??	☐ Patient died ☐ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ■ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

During 1993, the patient was hospitalised in emergency room for ANAPHYLACTIC SHOCK, one hour and a half after taking one tablet of Mediator and one tablet of Hexalyse. BP 12/6, shiver, malaise, cold extremities, maculo-erythematous rash on thorax, infiltrated erythema (non pruriginous). No edema, no respiratory disorders. Symptoms abated with steroids and Polaramine. NB: previously, the patient was treated with Mediator without problems.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
from 1993 to 1993	1D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
No hx of allergy.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicine Agency (Ref N°MA9300723 & MA9322478).*
	24b. MFR CONTROL NO. 840D41	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

Institut de Recherches Internationales Servier
Pharmacovigilance Department
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
M-F	FRANCE	Day Month Year 24-Mar-29	Years 60	F	Year Month Day 89/01/20	☐ Patient died ☐ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ■ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

ANAPHYLACTIC REACTION .
On 20-Jan-89 , first intake of Mediator .
Three hours after the intake , vertigo .
During the night , feeling of suffocation , generalised pruritus , anguish , tachycardia .
On 22-Jan-89 at 3H am , moderate tachycardia ; no rash nor dyspnea .
Normal auscultation . Agitation . Feeling of suffocation when lying .
Mediator was stopped . IM Solumedrol 40mg .
Asthenia for the 3 following days .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 20.01.89 to 20.01.89	1D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
CERVOXAN (VINBURNINE)
DIGOXINE

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier F-92200 Neuilly-sur-Seine	*This case was received from the French Medicines Agency (Ref N° NC8900097).*
24b. MFR CONTROL NO. 840D44	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 36	M	Year Month Day 98/07/25	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

The patient was treated with Mediator until Apr-98 for weight loss. On 25-Jul-98, 10 minutes after taking one tablet of Mediator with greek coffee, he presented malaise, with face edema (ANAPHYLACTOID SHOCK), DYSPNEA and generalised pruritus. Hospitalisation. On admission, BP 4mmHg, spontaneously increased to 8mmHg within 10 minutes. No treatment with steroids nor antiH1. NB: no previous known allergies, no insect bite and usual BP 12/8. Favourable outcome.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
WEIGHT LOSS

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 25.07.98 to 25.07.98	1D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

COMMENTS
This report was received from the French Medicines Agency (Ref N° LY9800499).

	24b. MFR CONTROL NO.
	124F81
24c. DATE RECEIVED BY SERVIER Aug 21, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Aug 26, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
	FRANCE	Day Month Year	Years 36	F	Year Month Day 98/08/01

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

In Jun-98, after taking one tablet of Mediator, the patient presented urticaria. On 1-Aug-98, 5 hours after taking Mediator, the patient presented URTICARIA, CHEST OPPRESSION, HYPOTENSION, MALAISE without loss of consciousness, and tongue edema. Treatment with Celestene 2mg and one tablet of Clarytine. Symptoms abated rapidely.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ☐ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ■ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: U		
18. THERAPY DATES (from/to): from 01.08.98 to 01.08.98	19. THERAPY DURATION: 1D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier F-92200 Neuilly-sur-Seine		*This report was received from the French Medicines Agency (Ref N° NC9800400).*
	24b. MFR CONTROL NO.: 125E48	
24c. DATE RECEIVED BY SERVIER: Dec 28, 1998	24d. REPORT SOURCE: ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT: Dec 30, 1998	25a. REPORT TYPE: ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
S-V	FRANCE	Day Month Year	Years 41	F	Year Month Day 91/12/30	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Diabetes treated with Glucinan 2tab/d for years. It was stopped one week. On 30-Dec-91, the patient took Glucinan and one tablet of Mediator at 13h. At 15h, pruritus of hands. At 18h, geant urticaria, Quincke's edema, and loss of consciousness. Hospitalisation in emergency room. Intubation and ventilation. Symptoms abated after steroids administration. Discharged on 31-Dec-91.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
150MG	ORAL

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 30.12.91 to 30.12.91	1D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
Glucinan (metformine) for several years

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
No atopy. Overweight.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

COMMENTS
This report was received from the French Medicine Agency (Ref N° PA9200399). Metformine also suspected.

	24b. MFR CONTROL NO.
	840D42
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
B-A	FRANCE	Day Month Year 18-JUN-59	Years 38	F	Year Month Day 98/01/06

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Cough and mucous expectoration treated by Bronchokod syrup. On 6-Jan-98, the Pt decided to loss weight and took concomitantly to Bronchokod, 1 tab of Mediator (given by her neighbour). 2 hours later, generalised rash, malaise sensation then collapsus. She was hospitalised with persistent collapsus, bronchospasm and vasoconstriction of extremities (ANAPHYLACTIC SHOCK). Pulmonary rate 24/mn, BP 60/40, HR 128/mn, PaO2 (with 6l O2) 144mmHg, PaCO2 36, AR 20mmol/l. Favourable outcome with adrenaline IV, oxygenotherapy, steroids and bronchodilatators.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
150MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
OVERWEIGHT

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES (from/to)
from 06.01.98 to 06.01.98

19. THERAPY DURATION
1D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
BRONCHOKOD (CARBOCISTEINE) from 04.01.98 to 06.01.98

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Chronic asthmatiform bronchitis, heavy smoker, overweight.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

COMMENTS
Drug interaction with carbocisteine suspected.

	24b. MFR CONTROL NO. 123K59
24c. DATE RECEIVED BY SERVIER Apr 14, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Apr 17, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
	FRANCE	Day Month Year	Years 50	F	Year Month Day 93/??/??

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Several days after starting Mediator, onset of palmar and solar pruritus and Quincke's edema (ANAPHYLACTIC SHOCK). mediator was stopped after 8days of treatment.
1 week later, reintake of 1 tablet of Mediator. 1 hour later : anaphylactic shock requiring one injection of Adrenaline.
Cutaneous tests were performed :
benfluorex : negative — glycerol oleate : positive
beeswax : strongly positive — S422 chlorhydrate: positive
talc : positive — polysorbate 80 : negative

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ☐ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ■ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
150MG	ORAL

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
■ YES ☐ NO ☐ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 1993 to 1993	8D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
NONE

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO.
	840D39
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicine Agency (Ref N° MA9300967).

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
M-M	FRANCE	Day Month Year 17-Aug-13	Years 79	F	Year Month Day 92/03/11	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

On 20-Feb-92, 4 hours after the first intake of one tablet of Mediator, onset of extremities pruritus and face tumefaction.
The patient stopped the drug on her own.
On 11-Mar-92, reintake of 1 tablet at 12h.
Other treatment : Veinotonyl for more than one year.
15 minutes later : erythema of the face then generalized with malaise and collapse (BP 6), visual flash, nausea, vigil coma for 30 minutes (ANAPHYLACTIC SHOCK).
Hospitalization. Treatment with sub-cutaneous adrenaline and vascular fluids. Recovery.
On 11-Mar-92 : IgE 91iu/L (N<120).

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	■ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE: HYPERLIPIDEMIA		
18. THERAPY DATES (from/to): from 20.02.92 to 11.03.92	19. THERAPY DURATION: 2D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
VEINOTONYL FOR MORE THAN A YEAR

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier F-92200 Neuilly-sur-Seine		*This report was received from the French Medicine Agency (Ref N° DJ9200119).*
	24b. MFR CONTROL NO.: 840D40	
24c. DATE RECEIVED BY SERVIER: Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT: Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years	F	Year Month Day 94/??/??	☐ Patient died ☐ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ■ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

A few days after starting Mediator, Fucus and an unspecified diuretic, onset of ANAPHYLACTIC SHOCK.
Hospitalization for 24 hours.
All drugs were stopped : recovery.
Afterwards, in 1994, reintake of 1 tablet of Mediator at 8AM.
At 8.30AM, eyelids edema and watering eyes. Recovery following injection of Soludecadron.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	
17. INDICATION(S) FOR USE		■ YES ☐ NO ☐ NA
WEIGHT LOSS		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
from 1994 to 1994	DAYS	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		*This report was received from the French Medicine Agency (Ref N° MA9400018).*
	24b. MFR CONTROL NO. 840D38	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 27	M	Year Month Day 97/11/03	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Medical prescription of Mediator to a sportsman with progressive increased dosage from 1tab/week to 9 tablets/day for weight loss or doping (DRUG OVERDOSE).
When he stopped Mediator, he experienced a weaning syndrom: HEADACHE, MANIC EXCITATION, MYDRIASIS. Previous similar episode a few months ago. Hospitalisation.
ECG: normal, hyperalbuminuria and hematocrite 18.5.
Unknown outcome.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		☐ YES ☐ NO ■ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
1350MG	ORAL	
17. INDICATION(S) FOR USE		☐ YES ☐ NO ■ NA
18. THERAPY DATES (from/to) from 01.05.97 to 03.11.97	19. THERAPY DURATION 6M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° PA9735052).*
	24b. MFR CONTROL NO. 123S98	
24c. DATE RECEIVED BY SERVIER May 28, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jun 03, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
?-V	FRANCE	Day Month Year	Years 2	M	Year Month Day 94/09/07	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

ACCIDENTAL ABSORPTION on 07-Sep-94 , by a 2years1/2-old child of 3 tablets of MEDIATOR 150mg .
Hospitalization the same day .
Supervision of respiratory and cardiac functions and of the consciousness during 3hours : E-C-G , BP , pulse and consciousness : normal .
No gastric lavage nor symptomatic treatment were realized .
Favourable outcome .
Patient discharged on 07-Sep-94 .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE: ACCIDENTAL OVERDOSE		
18. THERAPY DATES (from/to): from 07-SEP-94 to 07-SEP-94	19. THERAPY DURATION: 1D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**	
	24b. MFR CONTROL NO.: 540022
24c. DATE RECEIVED BY SERVIER: Sep 08, 1994	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Sep 19, 1994	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
J-A	FRANCE	Day Month Year	Years 37	F	Year Month Day 79/06/25	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

OVERDOSAGE: intake of one box of MEDIATOR. Hospitalization (ICU): obnubilation, reactive dilated pupils, regular pulse (75/min), BP 90/70mmHg. Gastric lavage, neutral diuresis. Stable pulse (80). Maximum BP 90 - 120. 4 hours later: patient can keep up a conversation.
The following day (at 7 a.m.): HR 80/min, max. BP 110, diuresis 1.8L, normal consciousness. Biological data: WNL. EKG: normal, except microvoltage.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		☐ YES ☐ NO ■ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
4500MG	PO	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
from 25.06.79	1D	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F- 92200 – Neuilly-sur-Seine**		
	24b. MFR CONTROL NO. 060051	
24c. DATE RECEIVED BY SERVIER Jun 26, 1979	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT May 07, 1985	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1282

Fiche N° : RS9800096 Centre de : RENNES Dossier Complet

Date de notification : 30/04/1998 Date de mise à jour : 12/01/1999

PATIENT

Age : 77 A Sexe : F Taille : cm Poids : kg

Antécédents

HYPERTENSION ESSENTIELLE SANS PRECISION
ANGINE DE POITRINE
AUTRES MALADIES DU SYST. VASCULAIRE PERIPHERIQ. SANS PRECIS.

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Guérison sans séquelle

Date apparition : 19/03/1998 Durée :

	Date de survenue
REACTION DE PHOTOSENSIBILITE	
PRURIT	
ERYTHEME	

MEDICAMENT(S)

DIOSMIL 300 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	DF	2 J	01/01/1978			20 A	3		1	1	1	1	S

Indication

MODURETIC, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	DF	2 J	01/01/1978			20 A	3		1	1	3	1	S

Indication

NITRIDERM TTS 5 mg/24 H, dispositif transdermique

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	ID	1 DF	1 J	01/01/1993			5 A	3		1	1	2	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	01 DF	02 J	01/01/1978			20 A	3		1	1	1	1	S

Indication

ALDOMET 250 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	01 DF	01 J	01/01/1978			20 A	3		1	1	3	1	S

Indication

HYDERGINE 1,5 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO			01/01/1978			20 A	3		1	1	1	1	S

Indication

COMMENTAIRES

Patiente hospitalisée le 13/03/98 pour des lésions macérées des pieds et ulcération malléolaire gauche. Eruption erythèmatosquameuse prurigineuse du décolleté apparue, au cours de l'hospitalisation. L'erythème avait disparu lors d'une consultation du 17/04/98.
Traitement des lésions par DIPROSONE crème, 1 application/j jusqu'au 24/03/98, puis 1j/2 pendant une semaine.
Tests trés positifs au baume du Perou, au fragrance mix et au Wool Alcohols. Tests positifs pour Neomycine sulfate, Paraphenyldiamine, colophane.
DOUBLON AVEC DOSSIER RS9800107

Annexe 3-18

1284

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Digestive System									
[illegible]X08	France	CRPV BX8800309	57	M	150mg	13y	Cirrhosis	Unknown	Chronic alcoholism. Several drugs associated.
[illegible]30	France	HP	64	F	300mg	3m	Gastric ulcer	Recovery	Several drugs associated.
[illegible]35 *	*France*	*CRPV PP8980920*	*57*	*F*	*u*	*#3y*	*Hepatitis*	*Recovery*	*NIDDM . Aldomet associated .*
[illegible]37 *	*France*	*CRPV NT8800125*	*49*	*F*	*450mg*	*u*	*Hepatitis*	*Recovery*	*Plethoryl & several other drugs associated.*
[illegible]51 *	*France*	*CRPV LY9300470*	*45*	*F*	*u*	*u*	*Hepatitis*	*Persistency*	*Alpidem & fluoxetine associated.*
[illegible]K94	France	HP-CRPV NY8804047	47	M	450mg	9m	Hepatitis	Recovery	
[illegible]29 *	*France*	*CRPV MA8900165*	*33*	*F*	*u*	*#1m*	*Hepatitis*	*Persistency*	*History of hepatitis with plethoryl . Several drugs associated .*
[illegible]A14	France	CRPV RE8660098	82	M	150mg	1m	Hepatitis	Recovery	Several drugs associated.
[illegible]025	France	CRPV DJ9100164	61	M	150mg	#4y	Hepatitis	Death	Chronic alcoholism. Enalapril & several other drugs associated.
[illegible]26 *	*France*	*CRPV GR8700067*	*70*	*F*	*300mg*	*16d*	*Hepatitis*	*Persistency*	*Diazepam associated.*
[illegible]20 *	*France*	*CRPV LY9800317*	*49*	*F*	*450mg*	*3m*	*Hepatitis*	*Persistency*	*Several drugs associated.*
[illegible]07 *	*France*	*CRPV AN8600104*	*73*	*M*	*450mg*	*4m*	*Hepatitis acute*	*Death*	*Tienilic acid associated. alcohol abuse.*
[illegible]818	France	CRPV NC9200360	85	F	150mg	3m	Hepatitis cholestatic	Recovery	Cicletamine & several other drugs associated.
[illegible]10 *	*France*	*CRPV MP8900016*	*62*	*M*	*150mg*	*30d*	*Hepatitis cholestatic*	*Recovery*	*Several drugs associated .*
[illegible]09 *	*France*	*CRPV MA8700958*	*50*	*F*	*450mg*	*34d*	*Hepatopathy*	*Recovery*	*Plethoryl & several other drugs associated.*
[illegible]35 *	*France*	*CRPV NC8900509*	*62*	*F*	*300mg*	*13m*	*Hepatopathy*	*Unknown*	*Plethoryl & carbutamide associated.*
[illegible]853	France	CRPV NY9608618	36	F	450mg	4m	Hepatopathy	Recovery	Likely liver steatosis .
[illegible]325	France	HP	42	M	450mg	3w	Hepatopathy	Recovery	Diabetes associated. Likely alcohol abuse.
[illegible]33	France	CRPV PA8851623	61	M	450mg	#3y	Liver function abnormal	Improvement	History of amibiasis ; NIDDM , gastric ulcer .
[illegible]W00	France	CRPV MA9000382	40	M		6m	Pancreatitis	Recovery	Dexfenfluramine associated.
[illegible]44	France	CRPV MA9700296	54	F	150mg	8d	Pancreatitis acute	Recovery	Cholecystectomy was subsequently performed.

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
A-A	FRANCE	Day Month Year	Years 57	M	Year Month Day 88/05/??

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

End of May-88 : edemato-ascitic decompensation of CIRRHOSIS of undetermined origin.
Treatment with Flagyl, Clamoxyl, Gentamycine from 10-Jun to 14-Jun-88. Hospitalization on 6-Jul-88.
On 13-Jun-88 : ASAT 33 (NR 8-30), ALAT 24 (NR 3-35), Bili T 24 (NR 5-20), Bili C 15 (NR 3-15), Alk Ph 126 (NR 6-210), GGT 57 (NR 8-37), PT 41%, factor V 45%.
Immunological tests (10-Jun-88): ANA negative, anti-SM Ab positive , HBs Ag negative, hepatitis A IgM negative, anti-VCA IgG positive at 1280, anti-EBNA 40. HIV negative. MNI test and PBD positive.
Liver echotomography (1-Jun-88): ascites, homogeneous liver, slightly atrophic.
Abdominal CT-scan : ascites, otherwise normal.
Outcome not specified.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
150MG	ORAL

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 1975 to 1988	13Y

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
TENSIGRADYL 1TAB/D FROM 1975 TO 1986, VISKEN 15 1/4TAB/D SINCE 1975, ZYLORIC 300MG 1D/2 SINCE 1975, ALDACTONE SINCE 8-JUIL-88, DESOMEDINE, SOLUPSAN, TAO, MAXILASE (FROM TIME TO TIME)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Anorexia (no meat intake for 5y), hypertension, hyperuricemia, alcoholism.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.	COMMENTS
540V08	*This report was received from the French Medicine Agency (Ref N° BX8800309).*
24c. DATE RECEIVED BY SERVIER: Jul 03, 1995	24d. REPORT SOURCE: ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT: Feb 16, 1999	25a. REPORT TYPE: ■ INITIAL ☐ FOLLOWUP

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
H-D	FRANCE	Day Month Year	Years 64	F	Year Month Day 91/03/27	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

On 27-Mar-91 , after 3months of treatment , hospitalization for GASTRIC ULCER . Transfusion . Stop of Mediator . Treatment with antiacids and adsorbents .
Discharged 7days later . Stomach ulcer healed .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
300MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
OBESITY . DIABETES . HYPERLIPEMIA .

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 01-JAN-91 to 27-MAR-91	3M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
GLUCOPHAGE RETARD (METFORMINE) from 1990
EUGLUCAN (GLIBENCLAMIDE) from 1990
ZESTRIL (LISINOPRIL) from 1990

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hypercholesterolemia . Hypertension . Obesity.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		
	24b. MFR CONTROL NO. 540930	
24c. DATE RECEIVED BY SERVIER Jan 02, 1992	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jan 15, 1992	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
B-W	FRANCE	Day Month Year	Years 47	M	Year Month Day 87/12/30	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Tx with Mediator from Jan-87 to Jun-87 then Oct-87 to Dec-87.
On 30-Dec-87 : moderate hepatomegalia. Mediator was stopped this day.
Hospitalization on 4-Jan-88 : good general status, slight subicterus, BP 12/8. Abdominal echography suggestive of a steatosis.
Biology : ASAT 106 (NR<25), ALAT 375 (NR<29), GGT 182 (NR<38), amylasemia WNL (HEPATITIS).
Serology positive for a past CMV infection and a past hepatitis A. Otherwise negative.
Favourable outcome : discharge on 9-Jan-88 (tx : Laroscorbine).
End of Jan-88 : decreased transaminases (not yet normalized).
9-Mar-88 : full recovery.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S) 450MG	16. ROUTE(S) OF ADMINISTRATION PO	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to) from JAN-87 to 30-DEC-87	19. THERAPY DURATION 9M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
NONE

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Obesity. Pneumonia in 1983 followed by a rash.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier F-92200 Neuilly-sur-Seine		
	24b. MFR CONTROL NO. 060K94	
24c. DATE RECEIVED BY SERVIER Sep 02, 1988	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
E-C	FRANCE	Day Month Year 19-May-04	Years 82	M	Year Month Day 86/06/09	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

HEPATITIS . On 8-Jun-86 , epigastric pain . Hospitalisation on 9-Jun. On that date : ASAT 497 , ALAT 318 , bili 77mcmol/l , Alk Phosp 250 , GGT 376 . Mediator stopped on 9-Jun . 16-Jun-86 ; no more jaundice , normalisation of transaminases (ASAT 22 , ALAT 75) , improved Alk Ph 134 & GGT 221 . 17-Jun : normal bili . Viral serologies : neg. AgHBs , positive antiHBs and antiHbc antibodies .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
150MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
DYSLIPIDEMIA

18. THERAPY DATES (from/to)
from 09.05.86 to 09.06.86

19. THERAPY DURATION
1M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
CORVASAL (MOLSIDOMINE) & ADALATE (NIFEDIPINE) FROM 84 , DIAMICRON (GLICLAZIDE) FROM 84 , TADENAN (PYGEUM AFRICANUM) FROM MAR-86

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
NIDDM . Coronary insufficiency . Cholecystectomy in 86 . Hypophyse adenomectomy .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.
540V14

24c. DATE RECEIVED BY SERVIER
Jul 03, 1995

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Feb 16, 1999

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This case was received from the French Medicines Agency (Ref N° RE8660098).

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
A-C	FRANCE	Day Month Year 02-Jun-30	Years 61	M	Year Month Day 91/07/27

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalized on 27-Jul-91 for violent abdominal pain, icterus then somnolence. HEPATITIS was diagnosed :

	27-07	28-07	29-07	01-08	02-08	04-08	05-08
SGOT	410	210	135		30	64	79
SGPT	1350	904	620		210	104	106
GGT	280	262	240		119		82
Alk Ph	98	104	113		125		132
amylasemia	19	12					
lipasemia	336	328					
Bili T	150	160	182		293	260	260
Bili C	123	125	138		213	212	200
TP		25%	30	48	53	56	57

Serology negative for hepatitis A,B,C. Asterixis. Moreover gynecomatia. Mediator, Dogmatil, Lasilix, Hepacholine and Natirose were stopped on 27-Jul-91. Renitec and Rythmodan were stopped on 28-Jul-91. Improvement of liver function tests. Then onset of a purulent orchiepididymitis with septicemia (Staphylococcus aureus) and kidney failure. Death.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ■ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
☐ YES ☐ NO ■ NA

15. DAILY DOSE(S)
150MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
OBESITY

18. THERAPY DATES (from/to)
from 1988 to 27.07.91

19. THERAPY DURATION
#4Y

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
RENITEC 1TAB/D SINCE 1987, RYTHMODAN SINCE 1990, DOGMATIL 1TAB/D SINCE 1987, LASILIX 40MG/D SINCE 1987, NATIROSE, HEPACHOLINE

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Cut off R finger. Hypertension. CAD. Chronic alcoholism.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.
840D25

24c. DATE RECEIVED BY SERVIER
Jul 03, 1995

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Feb 16, 1999

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicine Agency (Ref N° DJ9100164).

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
V-D	FRANCE	Day Month Year 05-Sep-07	Years 85	F	Year Month Day 92/09/21

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalization on 20-Sep-92 for L ileo-femoral phlebitis and erysipelas on leg ulcer. Coincidental evidence of CHOLESTATIC HEPATITIS.

	21-Sep	25-Sep	1-Oct
Transaminases	WNL	WNL	
GGT (n 5-30)	67		66
Alk Ph	increased		WNL
Bili T (n<13)	43	24	28
Bili C (n<3)	17	8	10

Viral serology negative.
CXR : R pleural effusion.
Abdominal CT-scan : WNL.
Favourable outcome.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ?
■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
150MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)
from <JUN-92 ? to 20-SEP-92

19. THERAPY DURATION
3M+

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
TENSTATEN FOR >6M (SINCE <MAR-92 ?), LONG-TERM TX WITH ESTULIC, FONZYLANE, TORENTAL, ESBERIVEN

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
NIDDM, obesity, hypertension. Recent history of thrombocytopenia related to Fraxiparine.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.
061S18

24c. DATE RECEIVED BY SERVIER
Jul 03, 1995

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Feb 16, 1999

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicine Agency (Ref N° NC9200360).

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 36	F	Year Month Day 95/11/22	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

LIVER DISORDERS : bilirubin 17mg/l , SGOT 198IU/l , SGPT increased 113IU/l , hypertrophy and hyperechogen liver on echography , suggestive of diffuse fibro steatosis . Normal HSV1 , CMV , VZV serologies . No liver biopsy . Biology was normal 2 days after drug cessation (except SGPT at 71UI/l) .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 15.07.95 to 25.11.95	4M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 120I53
24c. DATE RECEIVED BY SERVIER Aug 26, 1996	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Aug 26, 1996	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medecine Agency (Ref N° NY9608618) .

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
T-B	FRANCE	Day Month Year	Years 42	M	Year Month Day 84/04/??

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

3 weeks after starting Mediator, the patient was hospitalized for asthenia, feber and subicterus.
Biological investigations showed evidence of moderate cytolysis and slight cholestasis (HEPATOPATHY).
Etiological investigations were negative (HbS antigen, echography).
Favourable outcome after stopping Mediator.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ☐ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
450MG

16. ROUTE(S) OF ADMINISTRATION
PO

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
MODERATE HYPERTRIGLYCERIDEMIA & DIABETES

18. THERAPY DATES (from/to)
from U to U

19. THERAPY DURATION
3W

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Probable alcoholism.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

COMMENTS

24b. MFR CONTROL NO.
010325

24c. DATE RECEIVED BY SERVIER
May 25, 1984

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Dec 03, 1984

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
?-R	FRANCE	Day Month Year	Years 61	M	Year Month Day 88/11/21

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Long-standing treatment with Myocoril for 10y, Mediator for 3y and Phosphalugel.
Mid Oct-87 : LL edema. Proteinuria 0.35G/24h.
Hospitalized on 21-Nov-88 for investigations. Good general status, no fever. No LL edema. Urine cultures negative.
Biological testing : proteinuria <0.10G/l (twice); hypoalbuminemia 34g/L, creatininemia 135mcmol/L, thrombocytopenia 98,000 on 21-Nov and 131,000 on 22, protides electrophoresis WNL,slight cytolisis and cholestasis (LIVER FUNCTION ABNORMAL).
Liver echography : no biliary duct dilation.
Mediator was stopped and liver function tests were normalized.
Discharged on 25-Nov-88 (tx : Myocoril, Phosphalugel).
20-Dec-88 : Alk Ph slightly increased, GGT high. Myocoril was stopped.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
450MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
DIABETES

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)
from U to 21.11.88

19. THERAPY DURATION
#3Y

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
MYOCORIL 2/D FOR 10Y, PHOSPHALUGEL 2BAGS/D

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Amibiasis in 1951. Myocardial infarction in 1977. Glaucoma diagnosed in 1971; gastric ulcer in 1951. No alcoholism.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

COMMENTS
This report was received from the French Medicine Agency (Ref N° PA8851623).

24b. MFR CONTROL NO.
840D33

24c. DATE RECEIVED BY SERVIER
Jul 03, 1995

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Feb 16, 1999

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER

Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
J-P-G	FRANCE	Day Month Year	Years 40	M	Year Month Day 1990	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Coincident with 6 months of therapy , PANCREATITIS . Hospitalisation for 2 months .
Investigations ruled out lithiasis .
Hyperlipidemia suspected .
Mediator , Isomeride and Mopral were stopped .
Recovery .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
	ORAL	☐ YES ☐ NO ☐ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
	6M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
ISOMERIDE (DEXFENFLURAMINE)
MOPRAL (OMEPRAZOLE)
TOPAAL (ALUMINIUM HYDROXYDE, MAGNESIUM HYDROCARBONATE , AL)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hyperlipidemia , no alcoholism .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° MA9011983 or MA9000382).*
	24b. MFR CONTROL NO. 540W00	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 07, 1997	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
	FRANCE	Day Month Year	Years 54	F	Year Month Day 97/02/26

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalized on 26-Feb-97 for acute necrotizing and hemorrhagic PANCREATITIS (abdominal pain, hyperamylasemia 6100).
Mediator was stopped on 26-Feb-97.
Transfer to ICU for 48 hours (symptomatic treatment and IV nutrition).
In Gastroenterology Ward , a biliary etiology was suggested (gallbladder sludge).
On 13-Mar-97 : amylasemia 456.
Cholecystectomy was performed on 26-Mar-97.
Discharged 1 month after admission.

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
150MG

16. ROUTE(S) OF ADMINISTRATION
PO

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
HYPERCHOLESTEROLEMIA & OBESITY

18. THERAPY DATES (from/to)
from 19-FEB-97 to 26-FEB-97

19. THERAPY DURATION
8D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.
121V44

24c. DATE RECEIVED BY SERVIER
Aug 12, 1997

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Aug 14, 1997

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicine Agency (Ref N° MA9700296).

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1296

Fiche N° : PP8980920 Centre de : PITIE SALPETRIERE Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 57 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison avec séquelle

Date apparition : 19/09/1988 Durée :

Date de survenue

HEPATITE

MEDICAMENT(S)

METHYLDOPA

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/10/1988	005 M				2	2	3	2	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				27/09/1988	3.0 A				2	2	1	2	S

Indication

DIAMICRON, comprimé sécable en croix

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														A

Indication

COMMENTAIRES

HEPATITE SURVENUE SOUS DIAMICRON, MEDIATOR ET ALDOMET (CYTOLYSE: 20 N, BILI CONJUGUEE A 304 UMOL/L, TP= 60 %, FACTEUR V= 50 %, PBH: HEPATITE GRAVE EN COURS DE RESOLUTION AVEC FIBROSE A TENDANCE CIRRHOGENE). BILAN ETIOLOGIQUE: IGM HAV, AGHBS, ACANTIHBC, ACANTIHBS NEGATIFS, PAS D'ARGUMENTS EN FAVEUR D'UNE HEPATITE NON A NON B. ANTICORPS ANTITISSUS NEGATIFS, ECHOGRAPHIENORMALE. QUASI NORMALISATION DU BILAN HEPATIQUE EN TROIS MOIS. REINTRODUCTION DU DIAMICRON SANS PROBLEME.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1297

Fiche N° : NT8800125 Centre de : NANTES Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 49 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 01/04/1988 Durée :

HEPATITE TOXIQUE	Date de survenue

MEDICAMENT(S)

MADECASSOL 10 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	6.0 DF	1 J		01/04/1988	4.0 M				3	2	1	3	S

Indication OBESITE

PLETHORYL, COMPRIME ENROBE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J		07/05/1988	7.0 J				3	2	3	3	S

Indication OBESITE

PLETHORYL, COMPRIME ENROBE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		01/04/1988	004 M				3	2	3	3	S

Indication OBESITE

IODORGANINE AUGOT A LA CASEINE IODEE, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		01/04/1988	4.0 M				3	2	1	3	S

Indication OBESITE

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J		07/05/1988	7.0 J				3	2	1	3	S

Indication OBESITE

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		01/04/1988	4.0 M				3	2	1	3	S

Indication OBESITE

COMMENTAIRES

APPARITION D'UN ICTERE PRECEDE DE NAUSEES ET VOMISSEMENTS CHEZ UNE FEMME PRENANT : PLETHORYL*, MEDIATOR*,MADECAMOL*, IODORGANINE*, UN RECHALLENGE PLUS A ETE FAIT ET LE DECHALLENGE A ETE FAVORABLE (AVEC L'ENS. DES MEDIC.).

Edité le : 18/02/1999

1298

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : LY9300470 Centre de : LYON Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 45 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison avec séquelle

Date apparition : 22/05/1993 Durée :

Date de survenue

HEPATITE

MEDICAMENT(S)

PROZAC 20 mg, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	20. MG	1 J		22/05/1993	14. M				1	2	3	1	S

Indication

ANANXYL 50 mg, comprimé pelliculé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	100 MG	1 J		22/05/1993	014 M				1	2	3	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO									1	2		1	S

Indication

SOTALEX 80 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO									1	2		1	S

Indication

COMMENTAIRES

HEPATITE FULMINANTE -> TRANSPLANTATION HEPATIQUE.

1299

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MA8900165 Centre de : MARSEILLE Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 33 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 14/01/1989 Durée :

	Date de survenue
HEPATITE	
ELEVATION DU TAUX DE LA SGOT	
ELEVATION DU TAUX DE LA SGPT	

MEDICAMENT(S)

TRIACANA, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		06/02/1989					2		3		S

Indication

PONDERAL 20 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/02/1989					2				S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/02/1989					2				S

Indication

VANILONE FORT 100 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				06/02/1989					2		3		S

Indication

COMMENTAIRES

ANTECEDENTS D'HEPATITE AU PLETHORYL IL Y A DEUX ANS.

~~1300~~

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : GR8700067 Centre de : GRENOBLE Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 70 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Inconnu

Date apparition : 23/03/1987 Durée :

Date de survenue

HEPATITE CHOLOSTATIQUE

MEDICAMENT(S)

VALIUM ROCHE 5 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	4.0 DF	1 J			010 J				2	2	3	2	S

Indication TROUBLES DEPRESSIFS NON CLASSES AILLEURS

RUFOL, comprimé PELLICULE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO					16. J				1	2	2	1	A

Indication

SEGLOR, solution buvable, gouttes

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J			13. J				1	2	1	1	A

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J			16. J				1	2	1	1	A

Indication

PRAGMAREL 100 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J			10. J				1	2	2	1	A

Indication

COMMENTAIRES

Annexe 3-18

1301

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : LY9800317 Centre de : LYON Dossier Complet

Date de notification : 15/04/1998 Date de mise à jour : 05/08/1998

PATIENT

Age : 49 A Sexe : F Taille : 169 cm Poids : 71 kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Sujet non encore rétabli

Date apparition : 01/04/1998 Durée :

Date de survenue	
HEPATITE	

MEDICAMENT(S)

MAXEPA 500 mg, capsule

Lot	Voie	Dose		Fréquence		Du	au	Durée		Délai surv.		Dech	Rech	C	S	B	I	OMS
	PO	6	DF		J	15/12/1997	03/04/1998	3	M	4	M	1	3	2	2	0	2	S

Indication

STAGID, comprimé

Lot	Voie	Dose		Fréquence		Du	au	Durée		Délai surv.		Dech	Rech	C	S	B	I	OMS
	PO	2	DF		J	15/12/1997	03/04/1998	3	M	4	M	1	3	2	2	0	2	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose		Fréquence		Du	au	Durée		Délai surv.		Dech	Rech	C	S	B	I	OMS
	PO	3	DF		J	15/12/1997	03/04/1998	3	M	4	M	1	3	2	2	0	2	S

Indication

COPALTRA, mélange de plantes pour tisane

Lot	Voie	Dose		Fréquence		Du	au	Durée		Délai surv.		Dech	Rech	C	S	B	I	OMS
	PO					15/01/1998	03/04/1998	11	S	3	M	1	3	2	2	1	2	S

Indication

LIPANTHYL 200 micronisé, gélule

Lot	Voie	Dose		Fréquence		Du	au	Durée		Délai surv.		Dech	Rech	C	S	B	I	OMS
	PO	1	DF	1	J	15/12/1997	03/04/1998	3	M	4	M	1	3	2	2	3	2	S

Indication

AGREAL, gélule

Lot	Voie	Dose		Fréquence		Du	au	Durée		Délai surv.		Dech	Rech	C	S	B	I	OMS
	PO	2	DF		J	15/12/1997	03/04/1998	3	M	4	M	1	3	2	1	0	1	A

Indication

COMMENTAIRES

Edité le : 18/02/1999

Femme de 49 ans. ATCD d'appendicectomie en 1970, de césarienne en 1989, pas de prise d'alcool, tabagisme et hypercholestérolémie diagnostiqués en Décembre 1997, mise sous Maxépa*, Stagid*, Agréal*, Médiator*, Lipanthyl*.

A partir du mois de Janvier 1998, prise de Tisane Copaltra pour maigrir, 4 fois par semaine, 6 cuillères à café dans un litre et demi d'eau.

Le 01 / 04 / 98, apparition d'un ictère conjonctival, perturbation du bilan hépatique avec élévation des transaminases, ASAT à 96 N, ALAT à 97 N, bilirubine à 22 N à prédominance conjuguée.

Hospitalisation le 03 / 04 / 98. Arrêt des prises médicamenteuses et de la tisane, remplacé par l'Insuline.

Bilan effectué, évolution durant l'hospitalisation :

- Echographie : hépatomégalie modérée, homogène, avec épaississement de la paroi vésiculaire, sans lithiase, sans dilatation des voies biliaires.
- Fibroscopie : RAS:.
- Bilan hépatique :
  - ASAT oscillant aux alentours de 80 N du 06 au 16 / 04, à 43 N le 18 / 04 / 98, à 42 N le 20 / 04, à 36 N le 22 / 04, à 26 N le 27 / 04 / 98.
  - ALAT entre 80 et 90 N du 06 / 04 au 16 / 04, à 62 N le 18 / 04, à 53 N le 20 / 04, à 46 N le 22 / 04, à 34 N le 24 / 04, à 28 N le 27 / 04.
  - BT de 20 à 31 N du 06 / 04 au 20 / 04, à 22 N le 27 / 04.
- Coagulation : TP à 85 % à l'entrée, à 58 % le 16 / 04; facteur V à 100%, fibrinogène normal, chute des facteurs VII et X à 50%.(mise sous vitamine K, remontée du TP à 100%).
- Sérologies A et C négatives, Ac anti- HBS positif 18 UI (début de vaccination), HIV négatives, sérologies EBV, CMV, herpès, en faveur d'une immunité ancienne, sérologie des mycoplasmes positive au 1/16, de la toxoplasmose positive pour les IgG.
- Recherche d'auto-Ac : anti-nucléaires, anti-ADN natifs, anti-mitochondries, anti-microsomes, négative. Recherche d'Ac anti-muscles lisses positive à 1/20.
- PBF (prélevé le 27 / 04 / 98) : aspect d'hépatite aigue commune résolutive.

Sortie du CH le 29 / 04 / 98, conclusion du dossier : hépatite toxique probablement au Lipanthyl*, possiblement à la tisane.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : AN8600104 Centre de : ANGERS Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 73 A Sexe : M Taille : cm Poids : kg

Antécédents

SYNDROME DE DEPENDANCE ALCOOLIQUE

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Décès du à l'effet

Date apparition : 25/07/1986 Durée :

	Date de survenue
HEPATITE	
ELEVATION DU TAUX DE LA SGOT	
ELEVATION DU TAUX DE LA SGPT	
ELEV TAUX PHOSPHATASE ALCALINE	
INSUFFISANCE HEPATIQUE	

MEDICAMENT(S)

DIFLUREX 250 mg, COMPRIME

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J		30/07/1986	075 J				1	2	3	1	S

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

CATAPRESSAN 0,15 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J		30/07/1986	9.0 M				1	1		1	S

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		30/07/1986	75. J				1	1		1	S

Indication :

COMMENTAIRES

PAS DE TRANSFUSION RECENTE. HEPATIE B- ECHOTOMO DES VB NORMALE AC ANTIRE - ALCOOLISME + PBH COMPATIBLE AVEC UNE HYPOTHESE MEDICAMENTEUSE.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MP8900016 Centre de : MONTPELLIER Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 62 A Sexe : M Taille : cm Poids : kg

Antécédents

DIABETE SUCRE SANS MENTION DE COMPLICATIONS

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 30/01/1989 Durée :

Date de survenue

HEPATITE CHOLOSTATIQUE

MEDICAMENT(S)

DIOVENOR 300 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.8 GM	1 J		03/02/1989	11. S				3	2	1	3	S

Indication

DIABINESE 250MG, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	750 MG	1 J		03/02/1989	037 J				3	2	3	3	S

Indication DIABETE SUCRE SANS MENTION DE COMPLICATIONS

LIPUR 450 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	900 MG	1 J		03/02/1989	8.0 J				2	2	3	2	S

Indication AUTRES TROUBLES DU METABOLISME DES LIPIDES

RECTOQUOTANE, suppositoire

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PR				03/02/1989	8.0 J				2	2	1	2	A

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	150 MG	1 J		27/01/1989	30. J				2	2	1	2	A

Indication AUTRES TROUBLES DU METABOLISME DES LIPIDES

COMMENTAIRES

AUTRES MEDICAMENTS : TITANOREINE, PHLEBOI-DINE, TAMARINE. COTATION : C2 (CAR ON NE CONNAIT PAS LA DATE D'ARRET DE CES MEDICAMENTS) S2, B1. CE MALADE FAIT L'OBJET D'UN SECOND DOSSIER CONCERNANT UNE ERUPTION TYPE TOXIDERMIQUE MP 89 00038.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1305

Fiche N° : MA8700958 Centre de : MARSEILLE Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 50 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Sujet non encore rétabli

Date apparition : 12/11/1987 Durée :

	Date de survenue
PRURIT	
SELLES PALES	
HEPATITE	
ICTERE	

MEDICAMENT(S)

TOFRANIL 10 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		12/11/1987	34. J				2	2	3	2	S

Indication

PLETHORYL, COMPRIME ENROBE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		12/11/1987	34. J				2	2	3	2	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		12/11/1987	034 J				2	2	1	2	S

Indication

HEPANEPHROL 10 ml, solution buvable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		12/11/1987	34. J				2	2	1	2	S

Indication

COMMENTAIRES

HEPATITE CHRONIQUE AGRESSIVE A POTENTIALITE CIRRHOGENE D'ORIGINE POSSIBLEMENT MEDICAMENTEUSE

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : NC8900509 Centre de : NICE Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 62 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Sujet non encore rétabli

Date apparition : 07/11/1989 Durée :

Date de survenue

HEPATITE

MEDICAMENT(S)

GLUCIDORAL 500 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J			2.0 A				1	2	1	1	S

Indication

PLETHORYL, COMPRIME ENROBE

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		31/01/1987	001 M				1	2	3	1	S

Indication

GLUCOPHAGE 850 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J			2.0 A				1	2	1	1	S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				01/03/1986	1.0 A				1	2	3	1	S

Indication

COMMENTAIRES

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Skin and Appendages									
[illegible]	France	CRPV NC9300394		F	450mg	3y	Eczema	Improvement	Vitamins associated.
[illegible]	France	CRPV NY9809751	70	M	300mg	10m	Eczema	Persistency	Acarbose & omeprazole associated.
[illegible] *	*France*	*CRPV PA8745961*	*50*	*F*	*300-450mg*	*u*	*Epidermal necrolysis, (liver function abnormal)*	*Recovery*	*Chlormezanone & several other drugs associated.*
[illegible] *	*France*	*CRPV MP8900301*	*71*	*F*		*1d*	*Face edema*	*Recovery*	*History of drugs allergy. Several drugs associated.*
[illegible]	France	HP	59	F	150mg	1d	Face edema, urticaria	Recovery	
[illegible]	France	CRPV TS9400194	79	F	450mg	>9m	Fixed eruption	Persistency	Several drugs associated. Drug continued.
[illegible]	France	CRPV DJ9100155	31	M	u	u	Rash erythematous, (malaise, vomiting)	Unknown	
[illegible]	France	CRPV PA9739366	65	M	u	>8m	Rash lichenoid	Recovery	Allopurinol, losartan & several other drugs associated. Drug continued.
[illegible]	France	CRPV CF9200106	66	F	u	years	Rash purpuric	Recovery	Several drugs associated.
[illegible]	France	CRPV PP8990384	75	F	450mg	3w	Rash purpuric	Recovery	
[illegible]	France	CRPV NC9100505	48	F	450mg	40d	Rash pustular	Recovery	Bisoprolol associated.
[illegible] *	*France*	*CRPV BX9400599*	*68*	*F*	*300mg*	*u*	*Skin reaction*	*Death*	*Allopurinol & several other drugs associated. Hx of diabetes & renal failure.*
[illegible]	France	CRPV CF8500013	50	M	u	years	Urticaria	Recovery	

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
C-P	FRANCE	Day Month Year	Years	F	Year Month Day 93/09/21

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

ECZEMA .
Hospitalisation for rash evolving by fits since Jun-93 : papulo vesicu lar lesions of forearms , thighs and flanks (palmoplantar dyshidrosis)
Resolution on dermosteroids but recurrence when stop .
Biopsy (date ?) : lymphocytic dermitis suggestive of toxiderma .
Speckled antinuclear antibodies positive (1/50°) . No other abnormalities . Negative inflammatory investigations .
Mediator and vitamins definitively stopped on 10-Nov-93 .

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
450MG	ORAL

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
to 10.11.93	3Y

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
8 VITAMINS ECLAT & VITALITE 2/D FROM JUN-93 TO 10-NOV-93

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 540W03
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

COMMENTS
This case was received from the French Medicines Agency (Ref N° NC9300394).

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 70	M	Year Month Day 96/07/30	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
For 18 months, PRURIGINOUS ECZEMA lesions on trunk, bottom, thigh, pubis, and right wirst. Slight decrease in Sep-97 after Kanacort injection. On 18-Oct-97, the patient still presented erythema on her face with eczematiform rash purpuric and a few vesicles on her sides. Symptoms reduced with Nerisone. No allergic tests.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MOPRAL (OMEPRAZOLE)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ■ NO ☐ NA

15. DAILY DOSE(S)
20MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

17. INDICATION(S) FOR USE
GASTRITIS

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)
from 15.01.96 to U

19. THERAPY DURATION
#6M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
MEDIATOR (BENFLUOREX) 300MG/D FROM 15/01/96 TO 14/11/96, GLUCOR 200MG/D (ACARBOSE)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
NIDDM, hypercholesterolemia, alcohol abuse, gastritis, gastro-duodenitis.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.
123F60

24c. DATE RECEIVED BY SERVIER
Mar 06, 1998

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Mar 11, 1998

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicines Agency (Ref N° NY9809751). Mediator and Glucor also suspected.

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
J-P	FRANCE	Day Month Year 27-Mar-37	Years 59	F	Year Month Day 97/01/08

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

GENERALIZED URTICARIA and FACE EDEMA with thoracic oppression and malaise requiring hospitalisation for 36 hours .
WBC 14000 .
Treatment with steroids IV and antihistaminic therapy .
Recovery within 3 days .
NB : 1 month before , episode of urticaria after intake of 1 tab of Mediator and 1 tab of an unspecified medication which was suspected and stopped . Several courses with Mediator , before Nov-96 , without problems .

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
150MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 08.01.97 to 08.01.97	1D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
ART 50 (DIACERHEINE)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Smoking , overweight .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
Les Laboratoires Servier F-92200 Neuilly-sur-Seine	

	24b. MFR CONTROL NO.
	120T66
24c. DATE RECEIVED BY SERVIER Jan 29, 1997	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 03, 1997	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
E-C	FRANCE	Day Month Year 06-Dec-14	Years 79	F	Year Month Day 93/09/20	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

FIXED ERUPTION .
Nov-92 : pigmentary lesions on forearms , then subaxillar , on groin , between buttocks , sub mammar and on shoulders (at that time ,patient received Lipanthyl , catapressan , Natisedine , Nitriderm) .
Natisedine , Lipanthyl & Nitriderm stopped . Skin biopsy (31-Dec-92) : superficial dermatitis with lin like aspect of interface and pigmentary incontinence .
Compatible with toxiderma (aspect between fixed eruption and lichen like toxiderma). Abdominal echography : nl. Apr-93 : treatment for 8d with Oroken and Mucomyst for bronchitis .
Hospitalisation on 20-Sep-93 for persistent cutaneous lesions .
Brown cyclic maculae on forarms and rachis ; maculae with clear centers , confluent , polycyclic on armpits , inguinal , buttocks , submammar folds . Normal biological examination (electrolytes , liver , electrophoresis proteins , FBC , hemoastasis) . Glucose tolerance test: no diabetes mellitus .
Skin biopsy (21-Sep-93) : persistency of infiltrates . Suggestive of fixed eruption .Discharge on 23-Sep-93 on Mediator 450mg/d , Isoptine , Catapressan .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		☐ YES ☐ NO ■ NA
15. DAILY DOSE(S) 450MG	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to) from 02.93 to CONTINUED	19. THERAPY DURATION >9M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
ISOPTINE (VERAPAMIL) from FEB-93
CATAPRESSAN (CLONIDINE) from 1991

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Eczema 30 years ago. Diabetes diagnosed 3 months ago.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This case was received from the French Medicines Agency (Ref TS9400194).*
	24b. MFR CONTROL NO. 840E10	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
M-T	FRANCE	Day Month Year	Years 31	M	Year Month Day 91/06/30	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

30-Jun-91 : ERYTHEMATOUS RASH on the whole body . Regression within few hours after injection of ? . Further asthenia , sweating , vertigo and headache . SInus X Ray : left sinusitis .
13-Jul-91 : recurrence of eruption with pruritus , malaise , fall when standing , vomiting . NB :* Mediator had been stopped 10d before and readministered for 2d .*12-Jul evening , alcohol absorption.
* Diarrhea for 15 last days .
Hospitalisation . On admission , fever . WBC 23000 on 13-Jul (92% PNN) , 9400 on 14-Jul . K+ 3.2mmol/l then normal . Normal liver function tests . Serologies were negative (hepatitis A (IgM) , typhoid , antinuclear antibodies). Negative urine culture .
Chest X Ray , ECG : no particularities .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	■ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
	U	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This case was received from the French Medicines Agency (Ref N° DJ9100155).*
	24b. MFR CONTROL NO. 840D63	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE	Day Month Year	Years 65	M	Year Month Day 97/10/01	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

GENERALISED SQUAMOUS and ERYTHEMATOUS RASH, with LICHENS, HYPERKERATOSIS and PRURITUS except on mucous, face, palms and sole of feet. Cozaar was stopped (it was the more recent treatment prescribed): no improvement. Treatment with local steroids then ineffective emoluants. Cutaneous biopsy was done. Diagnosis accepted by the dermatologist was Lichen plan.
Recovery without sequelae.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
DAONIL (GLIBENCLAMIDE)		☐ YES ☐ NO ■ NA
15. DAILY DOSE(S) U	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
17. INDICATION(S) FOR USE DIABETES		☐ YES ☐ NO ■ NA
18. THERAPY DATES (from/to) from 01.02.97 to CONTINUES	19. THERAPY DURATION >8M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

MEDIATOR (BENFLUOREX) SINCE 01/02/97, COZAAR (LOSARTAN) 1/D FROM 27/09/97 TO 05/12/97, ZYLORIC (ALLOPURINOL) SINCE 01/01/95, LOXEN (NICARDIPINE) SINCE 01/01/95, GLUCOPHAGE SINCE 01/02/97

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° PA9739366). All the drugs were suspected. Only Cozaar was stopped.*
	24b. MFR CONTROL NO. 122X93	
24c. DATE RECEIVED BY SERVIER Jan 12, 1998	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jan 14, 1998	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
S-N	FRANCE	Day Month Year 20-Aug-25	Years 66	F	Year Month Day 92/05/05	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

RASH PURPURIC . On 5-May-92 , purpura of lower limbs for one month , extending to upper limbs . Hospitalisation on 7-May-92 . On the other hand , urinary tract infection (E Coli) and left sural thrombosis (?) (doppler) , possible phlebitis (?) . Abdo pelvian echography : normal . Gastroscopy: normal . Immunological and thyroid investigations : normal . Electrophoresis and biology (?) : normal . Drugs were stopped . Recovery within one week .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)	■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
NIDDM		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
to 07.05.92	YEARS	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

ELISOR FROM NOV-91 , DAFALGAN PRN
VASTAREL FOR SEVERAL YEARS

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Phlebitis, cholecystectomy.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This case was received from the French Medicines Agency (Ref N° CF9200106)*
	24b. MFR CONTROL NO. 540V18	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
O-A	FRANCE	Day Month Year	Years 75	F	Year Month Day 89/05/02	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

RASH PURPURIC .
On 2-May-89 , hosp. for sudden vascular purpura of lower limbs with inflammatory edema of ankles . Clinical examination : bullous necrotic purpura . No signs of collagenosis . Antinuclear factor , latex Waaler Rose : negative . Complement & circulating immune complexes : negative .Negative AgHBs . No dysglobulinemia . ESR 22 / Nl FBC . Platelets 200 000 . No eosinophils . Well controlled diabetes . SKin biopsy not suggestive of vasculitis . Mediator stopped . Spontaneous favourable outcome .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
450MG

16. ROUTE(S) OF ADMINISTRATION
ORAL

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE
NIDDM

18. THERAPY DATES (from/to)
from 04.89 to 02.05.89

19. THERAPY DURATION
3W

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
CAPTOPRIL SINCE 78 , TILDIEM AND NATIROSE
DAONIL , STAGID

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Hypertension.Angina pectoris since 78.Raynaud syndrome .NIDDM known for 10y .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

24b. MFR CONTROL NO.
840E01

24c. DATE RECEIVED BY SERVIER
Jul 03, 1995

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE
■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Feb 16, 1999

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

COMMENTS
This report was received from the French Medicine Agency (Ref n° PP8990384).

SERVIER
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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET
M-D	FRANCE	Day Month Year	Years 48	F	Year Month Day 91/11/14

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

Hospitalisation for generalized PUSTULAR ERYTHRODERMA : for 3days , severe pruritus then erythematous plaques generalized and pustules (burning sensation) . Temperature 38° , ALAT 74 , ASAT 32 , total bili 16 . Negative AgHBs . Mediator and Soprol stopped on 14-Nov-91 . 18-Nov-91 , ALAT 69 , ASAT 27 , Alk phosph. 82 . No Sezary cells . Negative immunological investigations : antinuclear , anti epiderm interstitial , basal membrane , subbasal area , intracytoplasmic antibodies . Sign of Nickolsky . Skin biopsy (25-Nov-91) : pustular toxiderma without depots . On 4-Dec-91 , patient felt well .

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ Patient died
- ■ Involved or prolonged inpatient hospitalisation
- ☐ Involved persistence or significant disability or incapacity
- ☐ Life threatening
- ☐ Important medical event

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
450MG	ORAL

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 10.91 to 14.11.91	40D

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
SOPROL (BISOPROLOL) from OCT-91 to 14-NOV-91

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 540W06
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP

COMMENTS
This case was received from the French Medicines Agency (Ref N° NC9100505).

Annexe 3-18

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
R-L	FRANCE	Day Month Year	Years 50	M	Year Month Day 84/11/06	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

URTICARIA .
6-Nov-84 : giant urticaria on trunk then the whole body .
Maculo papulous rash with peeling , pruritus .
Hospitalisation on 9-Nov-84 :
clinical exam without particularities .
biological testings : WBC 8600 , no eosinophiles . Platelets 240 000.
GGT 119 (N 6-36) . Negative Coombs test . Macrocytosis (107).
7 and 9-Nov-84 : 1 injection of Celestene and Celestamine Polaramine .
Sermion , Lexomil and Mediator stopped on 8-Nov-84 .
9-Nov-84 , Atarax . Recovery within 3days . Discharge on 13-Nov-84 .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		■ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
U	ORAL	☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
to 8-NOV-84	YEARS	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
SERMION & LEXOMIL , LONG-STANDING ; STOPPED ON 8-NOV-84

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Alcoholism . Overworking .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This case was received from the French Medicines Agency (Ref N° CF8500013).*
	24b. MFR CONTROL NO. 840D69	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : PA8745961 Centre de : FERNAND WIDAL Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 50 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 23/10/1987 Durée :

	Date de survenue
SYNDROME DE LYELL	
CONJONCTIVITE	
HEPATITE	
DIABETE SUCRE	
LYMPHOPENIE	

MEDICAMENT(S)

TRANCOPAL 200 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		25/10/1987	018 J				2	2	3	2	S

Indication : DOULEUR ARTICULAIRE

ASPEGIC 500, poudre orale

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				23/10/1987					1	2	1	1	A

Indication :

ISOMERIDE, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		25/10/1987	1.0 M				1	2	0	1	A

Indication : OBESITE

MAG 2, solution buvable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				25/10/1987					1	2	0	1	A

Indication :

DOLIPRANE, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		07/10/1987	12. J				1	1	1	1	A

Indication :

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		25/10/1987	1.0 M				1	2	0	1	A

Indication : OBESITE

Annexe 3-18

COMMENTAIRES

EVOLUTION FAVORABLE EN 10-15 JOURS SOUS CORTICOIDES ET INSULINE.ATTEINTE HEPATIQUE MIXTE.FONCTION RENALE NORMALE. COMPTE RENDU D'HOSPITALISATION EN ATTENTE.A COMPLETER.

1320

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MP8900301 Centre de : MONTPELLIER Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 71 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 15/07/1989 Durée :

	Date de survenue
PRURIT	
OEDEME	
TROUBLE RESPIRATOIRE	

MEDICAMENT(S)

PEFLACINE 400 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO									1	1	1	1	S

Indication : INFECTION DES VOIES URINAIRES DE SIEGE NON PRECISE

BEFIZAL 400 mg, comprimé enrobé à libération prolongée

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO					6.0 M				1	1	1	1	S

Indication : AUTRES TROUBLES DU METABOLISME DES LIPIDES

MINIDIAB, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO					001 M				1	1	2	1	S

Indication : DIABETE SUCRE SANS MENTION DE COMPLICATIONS

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO					1.0 M				1	1	1	1	S

Indication : AUTRES TROUBLES DU METABOLISME DES LIPIDES

TILDIEM 60 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO					6.0 M				1	1	1	1	S

Indication : INFECT. BACILL.FRIEDLANDER+MAL.CLASS.AILLEURS SIEG.NON PREC.

SOLUMEDROL 120 mg/2 ml, lyophilisat et solution pour usage parentéral

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	IV				15/07/1989	1.0 J				1	1	1	1	S

Indication : OEDEME

COMMENTAIRES

Edité le : 18/02/1999

Annexe 3-18

TRAITEMENT EGALEMENT PAR IMPUTATION : VIRLIX C1 S1 B1, VASOCALM C1S1B1, TRANXENE C1 S1 B1, CELESTAMINE C1S1B1, POLARAMINE C1 S1 B1.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : BX9400599 Centre de : BORDEAUX Dossier 1322

Date de notification : Date de mise à jour :

PATIENT

Age : 68 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Décès du à l'effet

Date apparition : 11/06/1994 Durée :

	Date de survenue
INSUFFISANCE RENALE AIGUE	
DECES	
ERUPTION BULLEUSE	

MEDICAMENT(S)

ALPRESS L P 5 mg, comprimé osmotique à libération prolongée

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	3.0 DF	1 J		28/06/1994					1	1	2	1	S

Indication

ZYLORIC 300 mg, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO		1 J		10/06/1994	003 M				1	1	3	1	S

Indication

CORDIPATCH 10 mg/ 24 heures, dispositif transdermique

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
										1	1		1	S

Indication

SOPROL 10 mg, comprimé pelliculé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														S

Indication

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
										1	1		1	S

Indication

LASILIX 40 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
														S

Indication

COMMENTAIRES

Edité le : 18/02/1999

Annexe 3-18

CALDINE

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Metabolic and Nutritional Disorders									
*[illegible] **	*France*	*CRPV CN9600038*	*66*	*F*	*150mg*	*2m*	*CPK increased*	*Recovery*	*Fenofibrate associated .*
[illegible]326	France	HP	61	M	u	u	Deshydratation, (confusion, fever)	Recovery	
[illegible]943	France	HP	60	M	450mg	days	Digitalin toxicity	Recovery	Suspected interaction with digitalin.
[illegible]24 *	*France*	*CRPV MP9400324*	*61*	*F*	*u*	*13d*	*Prothrombine time decreased*	*Recovery*	*Antivitamin K associated.*

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
A-C	FRANCE	Day Month Year	Years 61	M	Year Month Day 84/06/12	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

On 12-Jun-84 , hospitalisation for FEVER (38°) , DEHYDRATION , CONFUSION with disorientation in time and space without meningeal syndrome .
EEG : polymorphous symetrical activity with diffuse paroxysm .
Wright serodiagnosis was negative (neutropenia) and normal ammoniemia .
Mediator has been stopped . Favourable outcome after rehydration .
Normalisation of EEG within 3days .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
U

16. ROUTE(S) OF ADMINISTRATION

17. INDICATION(S) FOR USE

20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES (from/to)
from U to U

19. THERAPY DURATION
U

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
FONZYLANE (BUFLOMEDIL) , SINTROM (ACENOCOUMAROL)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
History of lung embolism and phlebitis .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

COMMENTS

24b. MFR CONTROL NO.
010326

24c. DATE RECEIVED BY SERVIER
Oct 01, 1984

24d. REPORT SOURCE
☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL

DATE OF THIS REPORT
Dec 03, 1984

25a. REPORT TYPE
■ INITIAL ☐ FOLLOWUP

Annexe 3-18

SERVIER

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SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4-6 REACTION ONSET	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
Z-Z	FRANCE	Day Month Year	Years 60	M	Year Month Day	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data

BRADYCARDIA and PSYCHIC TROUBLES (not specified) suggestive of digitalic overdosage .
Hospitalisation .
Mediator and acylanide were stopped .
Favourable outcome : complete regression of signs .
Further prescription of digoxine (lower doses) .

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
MEDIATOR (BENFLUOREX)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
450MG	ORAL	☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION DAYS	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
ACYLANIDE , LASILIX

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Heart failure (atrial fibrillation treated with digitalics for 7y).

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Les Laboratoires Servier
F-92200 Neuilly-sur-Seine

	24b. MFR CONTROL NO. 060943	COMMENTS
24c. DATE RECEIVED BY SERVIER Dec 02, 1986	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	*Suspected interaction with digitalin .*
DATE OF THIS REPORT Dec 12, 1986	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : CN9600038 Centre de : CAEN Dossier Complet

Date de notification : 08/02/1996 Date de mise à jour :

PATIENT

Age : 66 A Sexe : F Taille : cm Poids : kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Hospitalisation ou prolongation d'hospitalisation Evolution : Guérison sans séquelle

Date apparition : 01/02/1995 Durée :

	Date de survenue
ELEVATION DU TAUX DE LA SGOT	
ELEVATION DU TAUX DE LA SGPT	
RHABDOMYOLYSE	

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	150 MG	J			2 M		1	3	2	1	1	1	S

Indication HYPERCHOLESTEROLEMIE ESSENTIELLE

ALDACTAZINE, comprimé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	J			1 M		1	3	2	1	1	1	S

Indication HYPERTENSION ESSENTIELLE SANS PRECISION

LIPANTHYL 200 micronisé, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	200 MG	J			1 M		1	3	2	1	3	1	S

Indication HYPERCHOLESTEROLEMIE ESSENTIELLE

CATAPRESSAN 0,15MG/ml, solution injectable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	150 RG	J					3		1	1	2	1	A

Indication HYPERTENSION ESSENTIELLE SANS PRECISION

COMMENTAIRES

Elévation des CPK à 80 N (CPK-MB < 0,11 %).
Normalisaton 15 jours après arrêt de MEDIATOR*, LIPANTHYL*, ALDACTAZINE*.

Annexe 3-18

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MP9400324 Centre de : MONTPELLIER Dossier

Date de notification : Date de mise à jour :

PATIENT

Age : 61 A Sexe : F Taille : cm Poids : kg

Antécédents

INFECT. BACILL.FRIEDLANDER+MAL.CLASS.AILLEURS SIEG.NON PREC.
HYPERTENSION ESSENTIELLE SANS PRECISION
EMBOLIE PULMONAIRE
PHLEBITE ET THROMBOPHLEBITE DE SIEGE NON PRECISE
ULCERE DUODENAL EVOL.NON PREC.SANS HEMORRAGIE NI PERFORATION

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Evolution : Guérison sans séquelle

Date apparition : 19/08/1994 Durée :

	Date de survenue
PURPURA	
ECCHYMOSES	
HEMORRAGIE GINGIVALE	

MEDICAMENT(S)

PREVISCAN 20 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	0.6 DF	1 J		24/08/1994	008 M				2	3	3	3	S

Indication : PHLEBITE ET THROMBOPHLEBITE DE SIEGE NON PRECISE

DAFLON 500 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		18/08/1994					2	2	1	2	A

Indication :

LOPRIL 25 mg, comprimé sécable

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2.0 DF	1 J		18/08/1994					2	2	1	2	A

Indication : HYPERTENSION ESSENTIELLE SANS PRECISION

DICETEL 50 mg, comprimé pelliculé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				18/08/1994	7.0 J				2	2	1	2	A

Indication :

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO				18/08/1994	13. J				2	2	1	2	A

Indication :

ERCEFURYL 100 mg, gélule

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1.0 DF	1 J		18/08/1994	1.0 J				2	2	1	2	A

Indication : DIARRHEE D'ORIGINE PRESUMEE INFECTIEUSE

Annexe 3-18

COMMENTAIRES

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Urogenital System									
[illegible]	France	CRPV MA8901133	79		u	2m	Anuria (transient)	Death	Several drugs associated. Subsequent death due to cardio-respiratory failure.
[illegible]	France	CRPV LY8700356	52	M	300-450mg	5m	Glomerulonephritis	Unknown	Allopurinol & gliclazide associated.
[illegible]	France	CRPV BX9700689	71	F	300mg	u	Nephrotic syndrome	Persistency	Diabetes, hypertension & rheumatoid arthritis associated.

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Annexe 3-18

Annexe 3-18
CIOMS FORM

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH (Day Month Year)	2a. AGE (Years)	3. SEX	4-6 REACTION ONSET (Year Month Day)	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
H-M	FRANCE	??-???-35	52	M	87/04/??	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
In Apr-87, edema of lower limbs, nephrotic syndrome. Kidney biopsy: extramembranous GLOMERULONEPHRITIS. Unknown outcome.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG ?
MEDIATOR (BENFLUOREX)		☐ YES ☐ NO ■ NA
15. DAILY DOSE(S) 300-450MG	16. ROUTE(S) OF ADMINISTRATION ORAL	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐ YES ☐ NO ■ NA
17. INDICATION(S) FOR USE NIDDM		
18. THERAPY DATES (from/to) from 11.86 to 03.87	19. THERAPY DURATION 5M	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
ZYLORIC (ALLOPURINOL) SINCE 81, DIAMICRON (GLICLAZIDE) FROM 82 TO UNKNOWN (RECENT DATE)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
Gout.

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicine Agency (Ref N° LY8700356). Allopurinol and gliclazide also suspected.*
	24b. MFR CONTROL NO. 840D84	
24c. DATE RECEIVED BY SERVIER Jul 03, 1995	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ■ HEALTH PROFESSIONAL	
DATE OF THIS REPORT Feb 16, 1999	25a. REPORT TYPE ■ INITIAL ☐ FOLLOWUP	

Annexe 3-18

CIOMS FORM

SERVIER
Institut de Recherches Internationales Servier
Pharmacovigilance Department
Tel (33 1) 55 72 70 70 - Fax (33 1) 55 72 65 88

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first - last)	1a. COUNTRY	2. DATE OF BIRTH (Day Month Year)	2a. AGE (Years)	3. SEX	4-6 REACTION ONSET (Year Month Day)	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
	FRANCE		71	F	97/06/18	☐ Patient died ■ Involved or prolonged inpatient hospitalisation ☐ Involved persistence or significant disability or incapacity ☐ Life threatening ☐ Important medical event

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

Hospitalisation for lower limbs edema for 3 months and ascite for 2 months. Vein echodoppler (7-May-97): superficial vein insufficiency, no vein thrombosis or phlebitis sequelae. On 19-Jun-97, proteinuria 3.3g/l (N<0.10g/l), slight hematuria. Urea 7mmol/l (N 3.5-7). On 20-Jun proteinuria (24h) 7.5g/l, urin volume 2100ml, hematuria, microalbuminuria 42.2mg/l (N<20). NEPHROTIC SYNDROME. In Dec-96, there was no albuminuria. Favourable outcome for edema of lower limbs. Patient improved. Persistency of proteinuria on 30-Jun. Other possible etiology: NIDDM.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
TROLOVOL (PENICILLAMINE)

20 DID REACTION ABATE AFTER STOPPING DRUG ? ■ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	20 DID REACTION REAPPEAR AFTER REINTRODUCTION ?
900MG	ORAL	☐ YES ☐ NO ■ NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to)	19. THERAPY DURATION
from 01.01.95 to 18.06.97	29M

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
MEDIATOR (BENFLUOREX) 300MG/D FROM UNKNOWN TO 18/06/97, LASILIX (FUROSEMIDE) 40MG/D FROM UNKNOWN TO 20/06/97, MONOTILDIEM LP 200MG/D, TRINITRINE, GLUCOPHAGE 1.7G/D, DAONIL 12.5MG/D, VOLTARENE (50MG & 100MG),

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
NIDDM , hypertension , angina pectoris , rheumatoid polyarthritis, overweight .

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
Les Laboratoires Servier **F-92200 Neuilly-sur-Seine**		*This report was received from the French Medicines Agency (Ref N° BX9700689). Mediator and Lasilix also suspected .*
	24b. MFR CONTROL NO. 121S20	
24c. DATE RECEIVED BY SERVIER Jul 15, 1997	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ● HEALTH PROFESSIONAL	
DATE OF THIS REPORT Jul 16, 1997	25a. REPORT TYPE ● INITIAL ☐ FOLLOWUP	/

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Cardiovascular System									
123I25	France	CRPV LY9700643	25	F	u	9m	Atrial fibrillation paroxystic	Recovery	Several drugs associated.
*840E12 **	*France*	*CRPV RS9000184*	*62*	*F*	*450mg*	*4m*	*Cerebrovascular accident*	*Death*	*Diabetes, hypertension & hyperlipidemia associated.*
124B09	France	CRPV PB9800124	72	F	450mg	2y	Cerebrovascular accident	Improvement	Hx of diabetes & hypertension. several drugs associated.
123F41	France	CRPV LL9700372	39	F	450mg	3m	Cerebrovascular accident	Recovery	Diuretics associated.
*125J97 **	*France*	*CRPV TO9800916*	*54*	*M*	*450mg*	*10y*	*Hemorroid disease aggravation (surgery)*	*Recovery*	*Several drugs associated*
540W55	France	CRPV GR9500235	52	F	u	u	Palpitation	Recovery	Sotalol associated . Drugs maintained .
840E02	France	CRPV PP9010597	37	F	150-450mg	10d	Syncope, (hypokalemia)	Recovery	Xipamide & several other drugs associated.
*541083 **	*France*	*CRPV LP9500642*	*59*	*F*	*150mg*	*5m*	*Torsade de pointes*	*Recovery*	*Several drugs associated .*
121D97	France	CRPV MP9700134	58	F	150mg	6d	Vasculitis	Improvement	Several drugs associated
840E00	France	CRPV RE9420042	41	F	450mg	3d	Vasculitis	Recovery	Several drugs associated.

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BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Hemic and Lymphatic System									
*541259 **	*France*	*CRPV TS9600117*	*73*	*F*	*150mg*	*u*	*Agranulocytosis*	*Recovery*	*Several drugs associated .*
*124E45 **	*France*	*CRPV BX9800512*	*72*	*M*	*450mg*	*3m*	*Agranulocytosis*	*Recovery*	*Several drugs associated.*
*123E36 **	*France*	*CRPV MP9800040*	*68*	*M*	*u*	*u*	*Agranulocytosis*	*Recovery*	*Several drugs associated. Medicine maintenance*
050F09	France	HP	70	F	450mg	3w	Anemia, thrombopenia	Recovery	
*121L32 **	*France*	*CRPV BX9700357*	*75*	*F*	*450mg*	*3m*	*Neutropenia*	*Persistency*	*Several drugs associated .*
*540V30 **	*France*	*CRPV TS9300053*	*72*	*F*	*300mg*	*1y*	*Neutropenia, (cough)*	*Persistency*	*Several drugs associated .*
540V26	France	CRPV NC8900022	71	M	450mg	>6m	Neutropenia, thrombopenia	Unknown	Glibenclamide associated . Drugs maintained
540V28	France	CRPV PS9400301	61	F	300mg	u	Thrombocytopenia	Recovery	Retinol associated .
540V27	France	CRPV NC9400153	19	F	450mg	2m	Thrombocytopenia	Recovery	Spironolactone & clobenzorex associated.
*540V19 **	*France*	*CRPV CF8800375*	*85*	*F*	*75mg*	*u*	*Thrombocytopenia*	*Recovery*	*Several drugs associated.*
*123D62 **	*France*	*CRPV NT9800026*	*73*	*F*	*u*	*9w*	*Thrombopenia*	*Persistency*	*Several drugs associated.*
*540V25 **	*France*	*CRPV MP9400244*	*69*	*M*	*300mg*	*u*	*Thrombopenia*	*Recovery*	*Glibenclamide associated.*
540V21	France	CRPV LY8500365	50	M	300mg	3m	Thrombopenia	Unknown	Several drugs associated.

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BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Nervous System									
120M85	France	HP	70	M	300mg	11d	Amnesia, confusion, (malaise)	Improvement	Cerebrovascular insufficiency.
122K33	France	CRPV BX9701023	63	F	450mg	9w	Balance impaired, somnolence	Recovery	Liver cirrhosis, hypertension & diabetic neuropathy associated. Published (DOERMAN 1998).
122N89	France	CRPV BX9701041	77	M	450mg	10d	Balance impaired, neuropathy	Recovery	Diabetes & axonal neuropathy associated. Published (DOERMAN 1998).
121O17	France	HP-CRPV BX9700301	71	M	450mg	38d	Balance impaired, neuropathy	Recovery	Published (DOERMAN 1998). Chronic alcoholism associated.
121O16	France	HP-CRPV BX9701040	73	M	300mg	1m	Balance impaired, vertigo	Recovery	Hx of coronary & cerebrovascular insufficiency. Published (DOERMAN 1998).
540V17	France	CRPV RN9500096	59	F	450mg	2m	Confusion	Recovery	Amfepramone associated.
540V13	France	CRPV PB9300028	62	M	250mg	16d	Confusion, (hepatopathy)	Recovery	Several drugs associated. Intermittent alcoholism.
840D89	France	CRPV GR8700216	45	M	450mg	16d	Confusion, delirium	Recovery	
*840D68 **	*France*	*CRPV DJ8800309*	*74*	*F*	*u*	*4y*	*Confusion, hallucination*	*Unknown*	*Viloxazine associated. Hx of liver cirrhosis & diabetes.*
540V20	France	CRPV DJ8800131	76	F	150-300mg	5d	Confusion, somnolence, (lymphopenia)	Recovery	Several drugs associated. Diabetes.
*840D70 **	*France*	*CRPV CF8900109*	*46*	*F*	*300mg*	*1d*	*Convulsion*	*Recovery*	*Buspirone and amineptine associated.*
840D71	France	CRPV CF9000137	79	F	450mg	u	Delirium, disorientation	Recovery	Several drugs associated.
*840D97 **	*France*	*CRPV LL9000165*	*43*	*F*	*u*	*years*	*Delirium, insomnia*	*Recovery*	*Amfepramone associated.*
010345	France	HP	80	F	450mg	13d	Disorientation aggravated	Recovery	Positive rechallenge. Hx of cerebrovascular disorders.
540J08	France	HP	68	M	300-450mg	<1m	Polyneuropathy	Unknown	Several drugs associated. Hx of diabetes & chronic bronchitis.
*840E04 **	*France*	*CRPV MP9400396*	*73*	*F*	*300mg*	*26d*	*Polyneuropathy*	*Persistency*	*Almitrine associated. Alcoholism.*

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Digestive System									
540V08	France	CRPV BX8800309	57	M	150mg	13y	Cirrhosis	Unknown	Chronic alcoholism. Several drugs associated.
540930	France	HP	64	F	300mg	3m	Gastric ulcer	Recovery	Several drugs associated.
*840D35 **	*France*	*CRPV PP8980920*	*57*	*F*	*u*	*#3y*	*Hepatitis*	*Recovery*	*NIDDM . Aldomet associated .*
*840D37 **	*France*	*CRPV NT8800125*	*49*	*F*	*450mg*	*u*	*Hepatitis*	*Recovery*	*Plethoryl & several other drugs associated.*
*840D31 **	*France*	*CRPV LY9300470*	*45*	*F*	*u*	*u*	*Hepatitis*	*Persistency*	*Alpidem & fluoxetine associated*
060K94	France	HP	47	M	450mg	9m	Hepatitis	Recovery	
*840D29 **	*France*	*CRPV MA8900165*	*33*	*F*	*u*	*#1m*	*Hepatitis*	*Persistency*	*History of hepatitis with plethoryl . Several drugs associated .*
540V14	France	CRPV RE8660098	82	M	150mg	1m	Hepatitis	Recovery	Several drugs associated.
840D25	France	CRPV DJ9100164	61	M	150mg	#4y	Hepatitis	Death	Chronic alcoholism. Enalapril & several drugs associated.
*840D26 **	*France*	*CRPV GR8700067*	*70*	*F*	*300mg*	*16d*	*Hepatitis*	*Persistency*	*Diazepam associated.*
*123X20 **	*France*	*CRPV LF9800317*	*49*	*F*	*450mg*	*3m*	*Hepatitis*	*Persistency*	*Several drugs associated.*
*540V07 **	*France*	*CRPV AN8600104*	*73*	*M*	*450mg*	*4m*	*Hepatitis acute*	*Death*	*Tienilic acid associated. alcohol abuse*
061S18	France	CRPV NC9200360	85	F	150mg	3m	Hepatitis cholestatic	Recovery	Cicletamine & several other drugs associated.
*540V10 **	*France*	*CRPV MP8900016*	*62*	*M*	*150mg*	*30d*	*Hepatitis cholestatic*	*Recovery*	*Several drugs associated .*
*540V09 **	*France*	*CRPV MA8700958*	*50*	*F*	*450mg*	*34d*	*Hepatopathy*	*Recovery*	*Plethoryl & several other drugs associated.*
*540V15 **	*France*	*CRPV NC8900509*	*62*	*F*	*300mg*	*13m*	*Hepatopathy*	*Unknown*	*Plethoryl & carbutamide associated*
120I53	France	CRPV NY9608618	36	F	450mg	4m	Hepatopathy	Recovery	Likely liver steatosis .
010325	France	HP	42	M	450mg	3w	Hepatopathy	Recovery	Diabetes associated. Likely alcohol abuse
840D33	France	CRPV PA8851623	61	M	450mg	#3y	Liver function abnormal	Improvement	History of amibiasis : NIDDM . gastric ulcer
540W00	France	CRPV MA9000382	40	M		6m	Pancreatitis	Recovery	Dexfenfluramine associated.
121V44	France	CRPV MA9700296	54	F	150mg	8d	Pancreatitis acute	Recovery	Cholecystectomy was subsequently performed .

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Body as a Whole									
121D94	France	CRPV MA9700036	60	F	150mg	2d	Anaphylactic reaction	Recovery	Published (CHAINE 1998). Positive rechallenge.
840D41	France	CRPV MA9300723	41	F	150mg	1d	Anaphylactic reaction	Recovery	Negative prechallenge .
840D44	France	CRPV NC8900097	60	F	150mg	1d	Anaphylactic reaction	Recovery	
124F81	France	CRPV LY9800499	36	M	150mg	1d	Anaphylactic reaction	Recovery	
125E48	France	CRPV NC9800400	36	F	150mg	1d	Anaphylactic reaction	Recovery	
840D42	France	CRPV PA9200399	41	F	150mg	1d	Anaphylactic shock	Recovery	Metformine associated.
123K59	France	HP	38	F	150mg	1d	Anaphylactic shock	Recovery	Carbocisteine interaction suspected.
840D39	France	CRPV MA9300967	50	F	150mg	8d	Anaphylactic shock	Recovery	Positive rechallenge .
840D40	France	CRPV DJ9200119	79	F	150mg	2d	Anaphylactic shock	Recovery	Positive rechallenge .
840D38	France	CRPV MA9400018		F	u	days	Anaphylactic shock	Recovery	Positive rechallenge .
123S98	France	CRPV PA9735052	27	M	1350mg	6m	Drug abuse, (headache, manic reaction, mydriasis after withdrawal)	Unknown	Drug abused by a sportsman.
540O22	France	HP	2	M	450mg	1d	Overdosage accidental	Recovery	No signs/symptoms .
060051	France	HP	37	F	4500mg	1d	Overdosage intentional (hypotension, obnubilation)	Recovery	
*124Q44 **	*France*	*CRPV RS9800096*	*77*	*F*	*300mg*	*20y*	*Photosensitivity*	*Recovery*	*Several drugs associated.*

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BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Metabolic and Nutritional Disorders									
*541175 **	*France*	*CRPV CN9600038*	*66*	*F*	*150mg*	*2m*	*CPK increased*	*Recovery*	*Fenofibrate associated.*
010326	France	HP	61	M	u	u	Deshydratation, (confusion, fever)	Recovery	
060943	France	HP	60	M	450mg	days	Digitalin toxicity	Recovery	Suspected interaction with digitalin.
*540V24 **	*France*	*CRPV MP9400324*	*61*	*F*	*u*	*13d*	*Prothrombine time decreased*	*Recovery*	*Antivitamin K associated.*

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Respiratory System									
123D63	France	CRPV NT9800036	69	M	150mg	10y	Pneumonitis	Persistency	Bisoprolol associated.
124U12	France	CRPV LM9800297	75	M	u	u	Pneumonitis	Unknown	Glimepiride associated.
540V90	France	CRPV SE9400175	46	F	u	3m	Pneumopathy	Recovery	Dexfenfluramine & clobenzorex associated. Reversible with anti-tuberculous agents.
540V06	France	CRPV PP8990081	40	F	150mg	u	Pulmonary hypertension	Unknown	Clobenzorex & amfepramone intake

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Skin and Appendages									
540W03	France	CRPV NC9300394		F	450mg	3y	Eczema	Improvement	Vitamins associated.
123F60	France	CRPV NY9809751	70	M	300mg	10m	Eczema	Persistency	Acarbose & omeprazole associated
*840D34 **	*France*	*CRPV PA8745961*	*50*	*F*	*300-450mg*	*u*	*Epidermal necrolysis, (liver function abnormal)*	*Recovery*	*Chlormezanone & several other drugs associated.*
*840D43 **	*France*	*CRPV MP8900301*	*71*	*F*		*1d*	*Face edema*	*Recovery*	*History of drugs allergy. Several drugs associated.*
120T66	France	HP	59	F	150mg	1d	Face edema, urticaria	Recovery	
840E10	France	CRPV TS9400194	79	F	450mg	>9m	Fixed eruption	Persistency	Several drugs associated. Drug continued.
840D63	France	CRPV DJ9100155	31	M	u	u	Rash erythematous, (malaise, vomiting)	Unknown	
122X93	France	CRPV PA9739366	65	M	u	>8m	Rash lichenoid	Recovery	Allopurinol, losartan & several other drugs associated. Drug continued.
540V18	France	CRPV CF9200106	66	F	u	years	Rash purpuric	Recovery	Several drugs associated.
840E01	France	CRPV PP8990384	75	F	450mg	3w	Rash purpuric	Recovery	
540W06	France	CRPV NC9100505	48	F	450mg	40d	Rash pustular	Recovery	Bisoprolol associated.
*840D65 **	*France*	*CRPV BX9400599*	*68*	*F*	*300mg*	*u*	*Skin reaction*	*Death*	*Allopurinol & several other drugs associated Hx of diabetes & renal failure.*
840D69	France	CRPV CF8500013	50	M	u	years	Urticaria	Recovery	

BENFLUOREX - Spontaneous Reports of Serious Adverse Reactions - FRANCE *(Cont'd)*

Company ref.no.	Country	Source	Age	Sex	Total dose (mg/day)	Duration of treatment d/w/m/y	Reaction description	Outcome	Comments
Urogenital System									
540V99	France	CRPV MA8901133	79		u	2m	Anuria (transient)	Death	Several drugs associated. Subsequent death due to cardio-respiratory failure.
840D84	France	CRPV LY8700356	52	M	300-450mg	5m	Glomerulonephritis	Unknown	Allopurinol & gliclazide associated.
121S20	France	CRPV BX9700689	71	F	300mg	u	Nephrotic syndrome	Persistency	Diabetes, hypertension & rheumatoid arthritis associated.

Annexe 3-18

SERVIER

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER
I. R. I. S.

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Fax No : 01 55 87 35 32 **Total Pages :**

Message : Voici pour avis le document Beaufour, que vous complété par la fiche CIOMS 1 — Bien cordialement.

BENFLUOREX

Spontaneous Reports of Serious Adverse Reactions

FRANCE

The following table is a listing of all the serious adverse reactions reported in France with Benfluorex (Mediator®), including :

- all serious reactions reported directly to the French Regional Centres for Pharmacovigilance (CRPV) in patients who had received Benfluorex (suspected drug or associated drug). After review (Pr P. Bechtel & Coll.), a number of them (marked with an asterisk – * – on the table) have been classified not related to Benfluorex (associated to other suspected drug(s)).
- all serious reactions reported to the Company.

CIOMS forms are provided for all reactions with Benfluorex considered as a suspected drug.

Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) (IT)

From: IT
Sender:
Date: 03/03/1999

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

The Italian Member presented their Assessment Report. Marketing authorisations for benfluorex containing medicinal products exist in France, Greece, Italy, Luxembourg, Portugal and Spain, with highest consumption in France where the authorised indication is hyperlipidaemia. The PhVWP agreed that there was no major benefit-risk concern for benfluorex containing medicinal products. Italy is considering to withdraw the indication of obesity and to update the section on undesirable effects in their Summary of Product Characteristics with regard to potential cardiotoxicity. For June 1999, the Italian Member, in co-operation with the French colleagues, will circulate a revised Assessment Report taking into account the individual case safety reports submitted to the French authorities.

Proposed Issues for Discussion

Annexe 3-19

DRAFT
Non distribuer

ASSESSMENT REPORT

RELEVANCE OF METABOLIC PATHWAYS OF BENFLUOREX TO NORFENFLURAMINE

Medicinal products: Mediaxal®, Balans®

Manufacturing Authorisation Holder: Laboratoires Servier

Active constituent: benfluorex

Originating Member State: Italy

Assessors: Dr. Giuseppe Pimpinella, Dr. Renato Bertini Malgarini

Contact point: Italian Ministry of Health

Pharmacovigilance Unit

TEL: 0039 06 5994 3212

FAX: 0039 06 5994 3554

Confidential

1. INTRODUCTION

Benfluorex is indicated in the treatment of hyperlipidaemias that cannot be adequately controlled by diet alone. Adjuvant therapy in obesity associated to disorders of glyco-lipidic metabolism.

The hypolipemic action is currently attributed to impairment of intestinal absorption of triglycerides due to inhibition of pancreatic lipase activity. It reduces hepatic synthesis of cholesterol and triglycerides in the liver and increases cellular uptake and utilisation of glucose. It is unknown if benfluorex is effective in long-term prevention of atherosclerotic processes.

The matter of concern is that the pharmacological activities of benfluorex might depend on the metabolic biotransformation to norfenfluramine leading to an anorectic effect of the drug. Based on this hypothesis, and considering the actual referral of fenfluramine under art. 15a procedure, Prof. Garattini sent a letter to EMEA to consider the referral of benfluorex to CPMP according to art. 12 procedure.

2. REGULATORY HISTORY

Benfluorex is currently marketed in the following EU Countries through national procedures: FRANCE, LUXEMBOURG, PORTUGAL, SPAIN, GREECE, ITALY. It is authorised in other non EU countries including SWITZERLAND.

Proposals from MAH

The Company proposes to delete the wording related to obesity treatment in the indications.

3. METABOLIC PATHWAYS

Benfluorex is rapidly absorbed by the gastrointestinal tract and only 0,5% is found in faeces. Within the first 24 hours, 90% of the administered dose is eliminated in urine as metabolites.

Benfluorex is extensively metabolised in man so that the parent compound cannot be detected in body fluid. In humans (fig. 1), benfluorex is totally and rapidly hydrolysed by plasma esterases to the corresponding alcohol (S422). The alcohol deriving by complete hydrolysis of the ester is partially transformed to norfenfluramine that is an active metabolite of fenfluramine.

The percentage of norfenfluramine detected in urine is only 2%, but this percentage could not account for the real amount of norfenfluramine that is generated in the body. This is because norfenfluramine is metabolised to trifluoromethylketone that is further transformed into other demolition and/or conjugation compounds.

For this reason, the data obtained in urine analysis are not relevant to know the exact kinetic of norfenfluramine.

The results of the detection of plasma concentration of norfenfluramine in man after repeated doses administration of benfluorex is much more significant.

This level is of about 50 ng/ml (fig.2) and it is in the same magnitude order observed in plasma of patients receiving normal doses of fenfluramine.

4. PUBLISHED LITERATURE ON FENFLURAMINE PHARMACOKINETICS

After the administration of 20 mg of fenfluramine thrice in day, plasma levels of fenfluramine varying in the 40-120 ng/ml range have been described.

Another study, carried out in 41 subjects, describes plasma levels of fenfluramine and norfenfluramine after repeated doses of fenfluramine. Daily dose was decreased or increased to a maximum of 160 mg/die according to individual response. The mean fenfluramine intake was 142 ± 29 (23-107) mg/day. The mean of mean plasma fenfluramine was 158 ± 70 (35-299) ng/ml and the mean of mean plasma norfenfluramine was 72± 29 (22-144) ng/ml. In 13/41 subjects with a mean fenfluramine intake of 135 ± 33 mg/day the values of the above mentioned parameters were 78 ± 22 ng/ml for fenfluramine and 44 ± 17 for norfenfluramine.

5. TOXICOLOGICAL DATA FOR NORFENFLURAMINE

Fenfluramine and norfenfluramine are both neurotoxic in experiment animals, causing reduction in the serotonin axonal markers. Doses of fenfluramine found to be effective in this respect are in the same order of those utilised to achieve the anorectic effect in man, if corrected for body mass and pharmacokinetic differences.

Furthermore, the neurotoxic potential of norfenfluramine seems to be higher than for the parent compound.

6. PHARMACOVIGILANCE DATA

The PSURs covering the period since 1st of January 1992 to 15th December 1998 were considered.

Nervous system and cerebral circulation.

Two cases of cerebrovascular accident have been described:

Annexe 3-19

124B09	France	72	F	450	2y	**Cerebrovascular accident, ischemia of internal capsula.**

After analysis of complete case narratives provided by Agence du Medicament it must be pointed out that the causality assessment is complicated by the concomitant therapies and by the pre-existing conditions. In the case of the 39 years old patient, spironolactone was the drug indicated as suspected by the reporter and there is no clear indication of concomitant pathologies.

For the 72 years old patient case, there were underlying diabetes and unstable hypertension.

The following reports from the Company can be related to nervous system toxicity too:

(after analysis of French case narratives the following confounding factors have been added into brackets)

Company ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
540J08	France	68	M	450	1m	**Polyneuropathy** (pre-existing diabetes)
540V17	France	59	F	450	2m	**Delirium, agitation, disorientation** (Concomitant amfepramone)
541173	France	45	F	300	8d	**Hallucination, aggressiveness** (no complete case narrative available)
120M52	France	60	M	150	2d	**Somnolence, personality disorder** (no complete case narrative

Three cases of agranulocytosis, one of thrombocytopenia, one of neutropenia have been described.

Allergic reactions

Several cases of allergic reactions and three cases of anaphylactic shock have been reported. The Company proposes to add the allergic reactions in the undesirable effects section

Liver and biliary tract

Three cases of hepatopathy and one of hepatitis.

Respiratory system

One case of respiratory failure and two of pneumonitis have been reported, but there are too many confounding factors.

7. Patient exposure

8. DISCUSSION

The first element to be considered in the overall safety evaluation of benfluorex is that it cannot be ruled out that norfenfluramine is the responsible for the nervous system and cardiovascular adverse reactions reported in patients assuming benfluorex. It must be pointed out that these reactions have been described also for fenfluramine. It's well known that norfenfluramine is neurotoxic in animals and it's very likely it is also in humans.

Furthermore, adverse reactions such as cardiac arrhytmias, agranulocytosis, anaphylactic shock, hepatopathy have been reported several times and are not included in the Summary of Product Characteristics.

CONCLUSION

It is reasonable that, as proposed by Prof. Garattini, benfluorex is referred to CPMP under art. 12 procedure for complete risk/benefit reassessment.

In this respect, it should be asked to the Company to provide:

- complete case-reports for cerebrovascular, nervous, pulmonary and cardiac adverse reactions;
- confidence limits of norfenfluramine plasma levels after repeated doses of benfluorex
- further data on long-term efficacy of benfluorex therapy.

Dr. Renato Bertini Malgarini **Dr. Giuseppe Pimpinella**

MODULARIO

Ministero della Sanità

FB000/FS/4462 - 7 MAR. 1999

TO: Dr. A. CASTOT/Dr. C. FOSSET
HEAD OF PHARMACOVIGILANCE UNIT
AGENCE DU MEDICAMENT
FAX 0033 1 48 13 22 83

FROM: ITALIAN MINISTRY OF HEALTH
DRUG EVALUATION AND PHARMACOVIGILANCE DEPARTMENT
V.LE DELLA CIVILTA' ROMANA, 7
ROMA
FAX + 39 6 5994 3554

SUBJECT: ASSESSMENT REPORT FOR BENFLUOREX.

Dear Dr. Castot and Dr. Fosset,

Please find enclosed a copy of the revised Italian assessment report on benfluorex following the discussion at the Pharmacovigilance Working Party meeting on 3-4 March 1999, so that common measures can be adopted in co-operation between Italy and France.
Best regards.

HEAD OF UNIT
DR. GIUSEPPE FUCCHIDO

Ministero della Sanità

REVISED ASSESSMENT REPORT

RELEVANCE OF METABOLIC PATHWAYS OF BENFLUOREX TO NORFENFLURAMINE

Medicinal product: Mediaxal®

Manufacturing Authorisation Holder: Laboratoires Servier

Active constituent: benfluorex

Originating Member States: Italy, France

Assessors: Dr. Giuseppe Pimpinella, Dr. Renato Bertini Malgarini

Contact point: Italian Ministry of Health

Pharmacovigilance Unit

TEL: 0039 06 5994 3212

FAX: 0039 06 5994 3554

Confidential

Annexe 3-20

1. INTRODUCTION

This is the revised version of the assessment report on benfluorex following the discussion at the Pharmacovigilance Working Party held on 3-4 March 1999 and the analysis of complete case reports provided by Agence du Medicament.

Benfluorex is indicated in the treatment of hyperlipidaemias that cannot be adequately controlled by diet alone and for adjuvant therapy in obesity associated to disorders of glyco-lipidic metabolism.

The hypolipemic action is currently attributed to impairment of intestinal absorption of triglycerides due to inhibition of pancreatic lipase activity. It reduces hepatic synthesis of cholesterol and triglycerides in the liver and increases cellular uptake and utilisation of glucose. It is unknown if benfluorex is effective in long-term prevention of atherosclerotic processes.

The matter of concern is that the pharmacological activities of benfluorex might depend on the metabolic biotransformation to norfenfluramine leading to an anorectic effect of the drug. Based on this hypothesis, and considering the actual referral of fenfluramine under art. 15a procedure, Prof. Garattini sent a letter to EMEA to consider the referral of benfluorex to CPMP according to art. 12 procedure.

2. REGULATORY HISTORY

Benfluorex is currently marketed in the following EU Countries through national procedures: FRANCE, LUXEMBOURG, PORTUGAL, SPAIN, GREECE, ITALY. It is authorised in other non EU countries including SWITZERLAND.

Proposals from MAH

In the PSUR, the Company proposes to delete the wording related to obesity treatment in the indications.

Annexe 3-20

It must be pointed out that drugs indicated in the management of obesity should comply with the CPMP Guideline on drugs used in weight control (CPMP/EWP/281/96).

3. METABOLIC PATHWAYS

Benfluorex is rapidly absorbed by the gastrointestinal tract and only 0,5% is found in faeces.. Within the first 24 hours, 90% of the administered dose is eliminated in urine as metabolites.

Benfluorex is extensively metabolised in man so that the parent compound cannot be detected in body fluids. In humans (fig. 1), benfluorex is totally and rapidly hydrolysed by plasma esterases to the corresponding alcohol (S422). The alcohol deriving by complete hydrolysis of the ester is partially transformed to norfenfluramine (S585) that is an active metabolite of fenfluramine.

The percentage of norfenfluramine detected in urine is only 2%, but this percentage could not account for the real amount of norfenfluramine that is generated in the body. This is because norfenfluramine is metabolised to trifluoromethylketone that is further transformed into other demolition and/or conjugation compounds.

In fact, after the administration of d-fenfluramine in man, only 6-10% of the dose is excreted as d-fenfluramine, and 5.8-8.8% of dose is excreted as norfenfluramine (1).

For this reason, the data obtained in urine analysis are not relevant to know the exact kinetic of norfenfluramine (1).

The results of the detection of plasma concentration of norfenfluramine in man after repeated doses administration of benfluorex is much more significant.

This level is of about 50 ng/ml (fig.2) and it is in the same magnitude order observed in plasma of patients receiving normal doses of fenfluramine.

4. PUBLISHED LITERATURE ON FENFLURAMINE PHARMACOKINETICS

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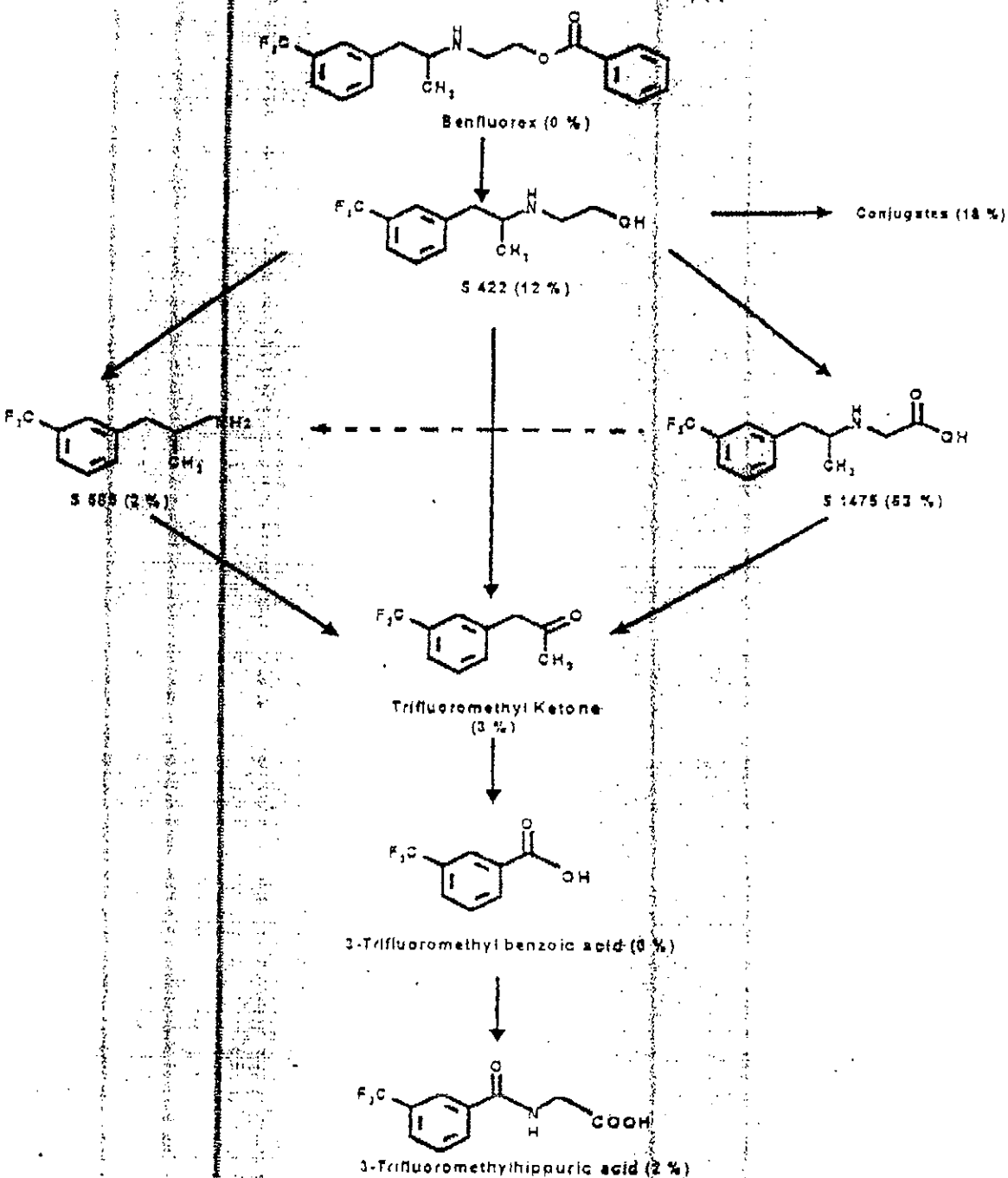
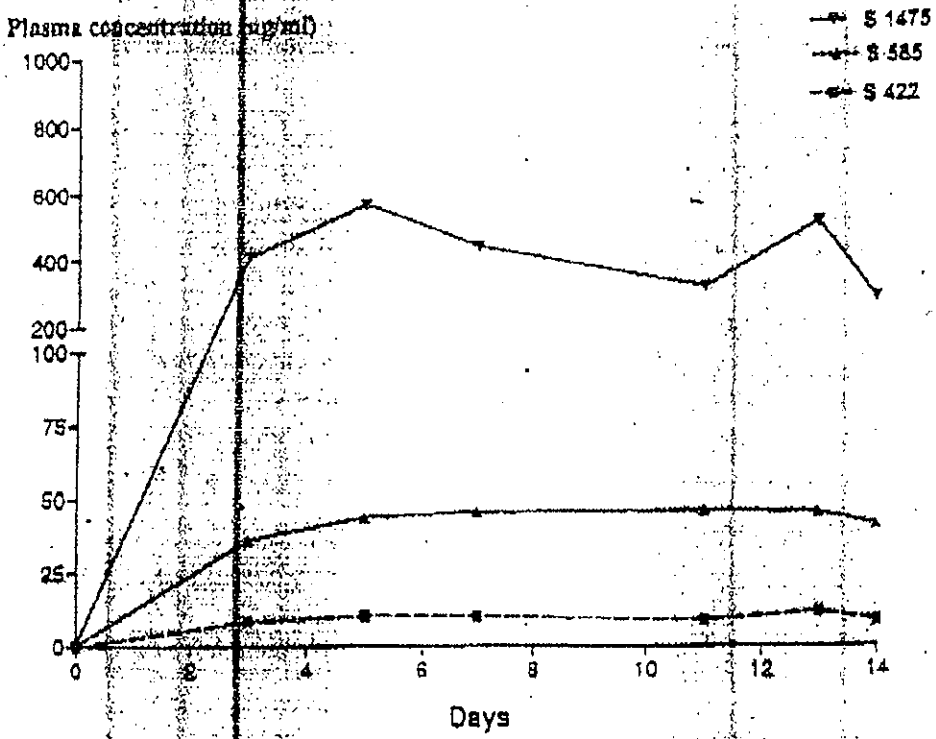
Metabolic pathways suggested for benfluorex in humans
(% of the dose eliminated between 0 and 24 hours) (1)



Annexe 3-20

Mean plasma concentrations of metabolites of benfluorex after the administration of 3 x 150 mg of benfluorex tablets over a period of 14 days (n = 6)



Annexe 3-20

After the administration of 20 mg of fenfluramine thrice in day, plasma levels of fenfluramine varying in the 40-120 ng/ml range have been described (2).

Another study (3), carried out in 41 subjects, describes plasma levels of fenfluramine and norfenfluramine after repeated doses of fenfluramine. Daily dose was decreased or increased to a maximum of 160 mg/day according to individual response. The mean fenfluramine intake was 142 ± 29 (23-107) mg/day. The mean of mean plasma fenfluramine was 158 ± 70 (35-299) ng/ml and the mean of mean plasma norfenfluramine was 72± 29 (22-144) ng/ml. In 13/41 subjects with a mean fenfluramine intake of 135 ± 33 mg/day the values of the above mentioned parameters were 78 ± 22 ng/ml for fenfluramine and 44 ± 17 for norfenfluramine.

5. TOXICOLOGICAL DATA FOR NORFENFLURAMINE

Fenfluramine and norfenfluramine are both neurotoxic in experiment animals, causing reduction in the serotonin axonal markers (4). Doses of fenfluramine found to be effective in this respect are in the same order of those utilised to achieve the anorectic effect in man, if corrected for body mass and pharmacokinetic differences (5).

Furthermore, the neurotoxic potential of norfenfluramine seems to be higher than for the parent compound (4).

6. PHARMACOVIGILANCE DATA

The PSURs covering the period since 1st of January 1992 to 15th December 1998, the assessment and case narratives from French Authorities were considered.

Nervous system and cerebral circulation in the PSUR.

Two cases of cerebrovascular accident have been described:

Company ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
123 F41	France	39	F	450	3m	**Cerebrovascular accident, cerebellar infarction**

C2S1

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124B09	France	72	F	450	2y	**Cerebrovascular accident, ischemia of internal capsula.**

After analysis of complete case narratives provided by Agence du Medicament it must be pointed out that the causality assessment is complicated by the concomitant therapies and by the pre-existing conditions. In the case of the 39 years old patient, spironolactone was the drug indicated as suspected by the reporter and there is no clear indication of concomitant pathologies.

For the 72 years old patient case, there were underlying diabetes and unstable hypertension.

The following reports from the Company can be related to nervous system toxicity too:

(after analysis of French case narratives the following confounding factors have been added into brackets)

Company ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
540J08	France	68	M	450	1m	**Polyneuropathy** (pre-existing diabetes)
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541173	France	45	F	300	8d	**Hallucination, aggressiveness** (no complete case narrative available)
120M52	France	60	M	150	2d	**Somnolence, personality disorder** (no complete case narrative

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						available)
120M85	France	70	M	300	11d	**Amnesia, confusion** (no complete case narrative available)

Cases of nervous system reactions from Agence du Medicament:

Considered as likely related from French assessors:

ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
MA8900523	France	50	F	1cp		**Nervousness.** Onset 1 -2 h after the first dose
10010345	France	80	F		13 D	**Obnubilation, disorientation.** Positive rechallenge
123S98	France	27	M	1350	6 M	**Drug abuse, headache, manic reaction, mydriasis on withdrawal**

Considered as possibly related from French assessors

ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
NC9700094	France	74	F		6 D	**Aggressiveness.** Recovered on suspension of treatment.
NC9300347	France	39	M		11 M	**Irritability.** Recovered on suspension of treatment
NC9300349	France	50	M		9 M	**Depression.** Recovered on suspension of treatment
MA9100069	France	40	M	4 cp	1D	**Palpitation, anguish.** Onset 2h after the first dose

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CF90001 37	France	79	F			Disorientation. Recovery on suspension o benfluorex and of other concomitant drugs.

16 Further cases of psychiatric reactions not included in the PSUR and classified as doubtful by French assessors have been reported, including one further case of delirium, one of stupor and one of withdrawal symptoms.

In France **20 cases of impaired balance** have been reported, and in six of such cases, patients recovered on suspension of benfluorex therapy.

Moreover, two cases of **convulsions** have been reported to French Authorities but no complete case narratives are available.

Cardiovascular system

No cases of primary pulmonary hypertension has been included in the PSUR by the Company.

French Authorities have provided 11 cases of pulmonary hypertension, but the patients also assumed fenfluramine or dexfenfluramine and/or other anorectic agents. Three cases of arterial hypertension have been described, one of which considered related by Agence du Medicament experts. Also one case of tachycardia and one case of atrial fibrillation were considered likely related.

One case of aortic insufficiency has been reported to French Authorities but the patient had previous myocardial infarction and mitral insufficiency.

It must be pointed out that norfenfluramine inhibits serotonin re-uptake and all serotonergic agents, including ergotamine and methysergide can cause valve lesions (Wong et al. *Cleveland Journal of Medicine* 1998 65 (1):35-41).

Furthermore, one case of syncope with respiratory insufficiency, one case of shock with ventricular tachycardia and one of torsade de pointes in a patient with no predisposing factors, have been included in the PSUR but no complete case reports are available.

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Haemopoietic system

Three cases of agranulocytosis, 5 of thrombocytopenia, 2 of leucopenia, 2 of lymphopenia 3 of neutropenia plus thrombocytopenia have been described in France. No complete case reports available.

Allergic reactions

Several cases of allergic reactions and six cases of anaphylactic shock have been reported. The Company proposes to add the allergic reactions in the undesirable effects section of the SPC.

Liver and biliary tract

23 cases of hepatitis have been provided from French Authorities, with 7 cases probably related and a possibly related one.

Respiratory system

Two cases of interstitial pneumonitis have been reported in France, but French assessors have pointed out several confounding factors.

7. Patient exposure

The Company has provided the following estimates of patients-months based on a mean daily dosage of 2,4 tablets, for a month of 30.4 days.

COUNTRY	N. patients-months OCT 96 - SEP 98
France	4,657,495
Luxembourg	2,130
Portugal	24,619
Greece	1,502

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Italy	235.612	
Spain		10.215
TOTAL		4,931,573

8. DISCUSSION

The first element to be considered in the overall safety evaluation of benfluorex is that it cannot be ruled out that norfenfluramine is responsible for the nervous system and cardiovascular adverse reactions reported in patients assuming benfluorex. It must be pointed out that these reactions have been described also for fenfluramine. It's well known that norfenfluramine is neurotoxic in animals and it's very likely it is also in humans.

Furthermore, adverse reactions such as psychiatric disorders, blood dyschrasias, anaphylactic shock, hepatitis and cardiovascular effects have been reported several times and are not included in the Summary of Product Characteristics.

CONCLUSION

We agree with French Colleagues that on the basis of the data deriving from spontaneous monitoring there is no definitive evidence of neurotoxicity and cardiotoxicity of benfluorex in humans, but there are elements of suspicion to require that precautions are adopted to further monitor this issue, especially to prevent long term adverse effects.

The following actions are possible:

- Referral of benfluorex to CPMP by Italy and France;
- Request the Company to provide preclinical and clinical studies on cardiovascular effects of repeated doses of benfluorex and toxicological studies about its neurotoxicity, further elements for cerebrovascular, nervous, pulmonary and cardiac adverse reactions if available, confidence limits of norfenfluramine plasma levels after repeated doses of benfluorex, further data on long-term efficacy of benfluorex therapy.

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- Reduction of indications of benfluorex containing medicinal products, updating of adverse effects, contraindications and special warnings sections of SPC, with particular regard to cardiac function monitoring, possibly by echocardiography for long term use and contraindication in case of pre-existing hypertension or cardiovascular and/or cerebrovascular diseases.

Rome, 06 May 1999

Dr. Renato Bertini Malgarini

Dr. Giuseppe Pimpinella

Annexe 3-21

AGENCE

Direction de l'Evaluation
Unité de Pharmacovigilance

FAX

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
AFSSAPS

DATE : 27 MAI 1999

Pages (incl. cover) :

TO :

Fax N° :

Italy : Dr Giuseppe PLUCHINO 39-6-5994.3554
..... 39-6-5994.3456
..... 39-6-5994.3365

SUBJECT / OBJET : Benfluorex / comments on revised assessment report

Dear colleague,

Our French expert (Pr Bechtel) has globally endorsed your revised assessment report. However we would like to remind you that the French spontaneous case reports do not allow an accurate evaluation of the neurotoxicity and cardiotoxicity.

Please note that :

- Page 6 : the ref. N° of the first case of nervous system reaction considered as likely related is NC9500171 instead of MA8900523.

- Page 7 : in the case of atrial fibrillation and the case of syncope with respiratory insufficiency, the patients were treated concomitantly by amfepramone.

In addition, we consider that it should be appropriate to ask the company to perform a pharmacokinetic study on benfluorex and its metabolites, especially norfenfluramine after a single dose and after several days of treatment.

Best regards.

Le Chef de l'unité de Pharmacovigilance

Dr Anne CASTOT

B.6 Vigabatrin: Risk/benefit balance, visual field defects – Article 12 Referral (FI & UK) ❑

The PhVWP was informed that the CPMP discussed vigabatrin in February 1999 and adopted a List of Questions and a draft Summary of Product Characteristics to be sent to the marketing authorisation holders. The CPMP included the risk-benefit of vigabatrin in pregnancy and lactation as an item of the List of Questions. The Oral Explanation will take place at the CPMP in March 1999 and the Opinion is scheduled for April 1999.

B.7 Benfluorex: Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) (IT) ❑

The Italian Member presented their Assessment Report. Marketing authorisations for benfluorex containing medicinal products exist in France, Greece, Italy, Luxembourg, Portugal and Spain, with highest consumption in France where the authorised indication is hyperlipidaemia. The PhVWP agreed that there was no major benefit-risk concern for benfluorex containing medicinal products. Italy is considering to withdraw the indication of obesity and to update the section on undesirable effects in their Summary of Product Characteristics with regard to potential cardiotoxicity. For June 1999, the Italian Member, in co-operation with the French colleagues, will circulate a revised Assessment Report taking into account the individual case safety reports submitted to the French authorities.

B.8 Selective serotonin reuptake inhibitors (SSRIs): Withdrawal reactions, dependency and long-term use ✣ ❑

The German Member circulated their comments on the Assessment Report prepared by the UK on the issues raised by C Medawar in his note "SSRIs, EMEA and the CPMP". The UK will prepare a draft response letter to the European Commission and recommendations on wordings for the Summaries of Product Characteristics (SPCs) for discussion and agreement by the PhVWP in April 1999. The agreed draft letter and the recommendations on SPC wordings will be forwarded to the CPMP in April 1999.

C. ENQUIRIES ON REQUEST OF NATIONAL AUTHORITIES

C.1 Alendronate sodium (FOSAMAX®): Oesophageal and upper gastrointestinal safety (UK) ❑

For discussion in April 1999, the UK will circulate an Assessment Report on results from a clinical trial, an epidemiological study performed in the US and from a Prescription Event Monitoring (PEM) study which were submitted by the marketing authorisation holder. The marketing authorisation authorisation holder was also requested to provide proposals for the Summary of Product Characteristics (SPC) and a report on possible reformulation.

In addition, Member States sent their SPCs and Package Leaflets to the UK for investigation of instructions for use. The results of this investigation will also be presented in April 1999.

Germany contacted their marketing authorisation holder with regard to concerns over reporting compliance. The response of the marketing authorisation holder will be circulated to the PhVWP.

Annexe 3-22

MODULARIO
Serie 8

MOD. 3 U.G.

Ministero della Sanità

F8006/F5/5271 31 MAG 1999

TO: DR. PRIYA BAHRI
PHARMACOVIGILANCE
EUROPEAN AGENCY FOR THE EVALUATION
OF MEDICINAL PRODUCTS
7 WESTFERRY CIRCUS
CANARY WHARF
LONDON
FAX 0044 171 418 8551

FROM: ITALIAN MINISTRY OF HEALTH
DRUG EVALUATION AND PHARMACOVIGILANCE DEPARTMENT
V.LE DELLA CIVILTA' ROMANA, 7
ROMA FAX + 39 6 5994 3554

SUBJECT: ASSESSMENT REPORT ON BENFLUOREX

DEAR PRIYA,

PLEASE FIND ENCLOSED THE REVISED ASSESSMENT REPORT CONCERNING BENFLUOREX TO BE DISCUSSED IN 10-11 JUNE 1999 PARMACOVIGILANCE WORKING PARTY MEETING.
I WOULD BE VERY GRATEFUL IF YOU CAN CIRCULATE IT TO ALL MEMBERS.
KIND REGARDS.

HEAD OF UNIT
DOTT. GIUSEPPE PLUCHINO

REVISED ASSESSMENT REPORT

RELEVANCE OF METABOLIC PATHWAYS OF BENFLUOREX TO NORFENFLURAMINE

Medicinal product: Mediaxal®

Manufacturing Authorisation Holder: Laboratoires Servier

Active constituent: benfluorex

Originating Member States: Italy, France

Assessors: Dr. Giuseppe Pimpinella, Dr. Renato Bertini Malgarini

Contact point: Italian Ministry of Health

Pharmacovigilance Unit

TEL: 0039 06 5994 3212

FAX: 0039 06 5994 3554

1. INTRODUCTION

This is the revised version of the assessment report on benfluorex following the discussion at the Pharmacovigilance Working Party held on 3-4 March 1999 and the analysis of complete case reports provided by Agence du Medicament.

Benfluorex is indicated in the treatment of hyperlipidaemias that cannot be adequately controlled by diet alone and for adjuvant therapy in obesity associated to disorders of glyco-lipidic metabolism.

The hypolipemic action is currently attributed to impairment of intestinal absorption of triglycerides due to inhibition of pancreatic lipase activity. It reduces hepatic synthesis of cholesterol and triglycerides in the liver and increases cellular uptake and utilisation of glucose. It is unknown if benfluorex is effective in long-term prevention of atherosclerotic processes.

The matter of concern is that the pharmacological activities of benfluorex might depend on the metabolic biotransformation to norfenfluramine leading to an anorectic effect of the drug. Based on this hypothesis, and considering the actual referral of fenfluramine under art. 15a procedure, Prof. Garattini sent a letter to EMEA to consider the referral of benfluorex to CPMP according to art. 12 procedure.

2. REGULATORY HISTORY

Benfluorex is currently marketed in the following EU Countries through national procedures: FRANCE, LUXEMBOURG, PORTUGAL, SPAIN, GREECE, ITALY. It is authorised in other non EU countries including SWITZERLAND.

Proposals from MAH

In the PSUR, the Company proposes to delete the wording related to obesity treatment in the indications.

It must be pointed out that drugs indicated in the management of obesity should comply with the CPMP Guideline on drugs used in weight control (CPMP/EWP/281/96).

3. METABOLIC PATHWAYS

Benfluorex is rapidly absorbed by the gastrointestinal tract and only 0,5% is found in faeces. Within the first 24 hours, 90% of the administered dose is eliminated in urine as metabolites.

Benfluorex is extensively metabolised in man so that the parent compound cannot be detected in body fluids. In humans (fig. 1), benfluorex is totally and rapidly hydrolysed by plasma esterases to the corresponding alcohol (S422). The alcohol deriving by complete hydrolysis of the ester is partially transformed to norfenfluramine (S585) that is an active metabolite of fenfluramine.

The percentage of norfenfluramine detected in urine is only 2%, but this percentage could not account for the real amount of norfenfluramine that is generated in the body. This is because norfenfluramine is metabolised to trifluoromethylketone that is further transformed into other demolition and/or conjugation compounds.

In fact, after the administration of d-fenfluramine in man, only 6-10% of the dose is excreted as d-fenfluramine, and 5.8-8.8% of dose is excreted as norfenfluramine (1).

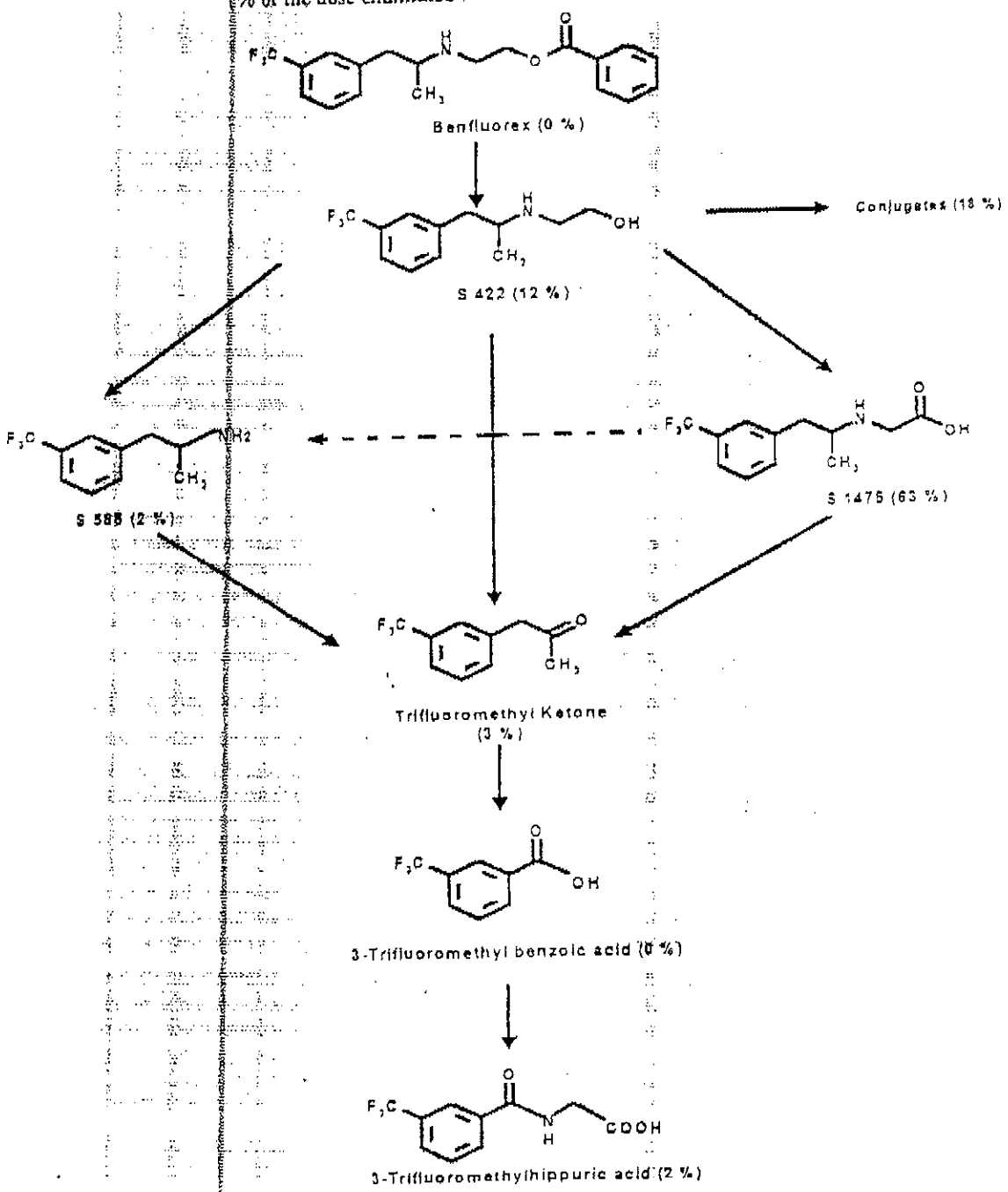
For this reason, the data obtained in urine analysis are not relevant to know the exact kinetic of norfenfluramine (1).

The results of the detection of plasma concentration of norfenfluramine in man after repeated doses administration of benfluorex is much more significant.

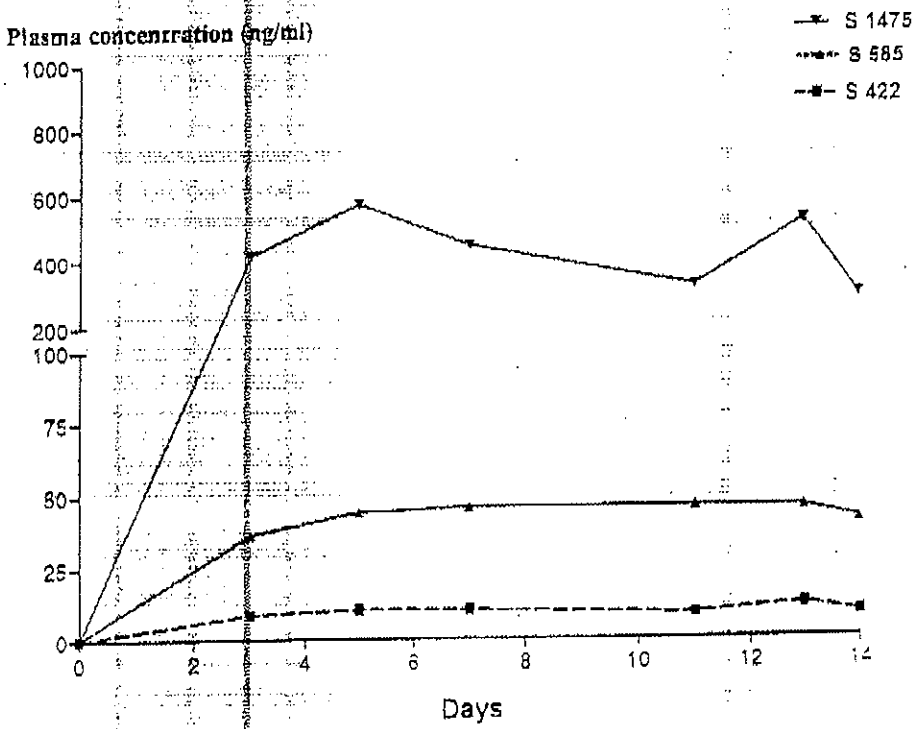
This level is of about 50 ng/ml (fig.2) and it is in the same magnitude order observed in plasma of patients receiving normal doses of fenfluramine.

4. PUBLISHED LITERATURE ON FENFLURAMINE PHARMACOKINETICS

Metabolic pathways suggested for benfluorex in humans
(% of the dose eliminated between 0 and 24 hours) (1)



Mean plasma concentrations of metabolites of benfluorex after the administration of 3 x 150 mg of benfluorex tablets over a period of 14 days (n = 6)



After the administration of 20 mg of fenfluramine thrice in day, plasma levels of fenfluramine varying in the 40-120 ng/ml range have been described (2).

Another study (3), carried out in 41 subjects, describes plasma levels of fenfluramine and norfenfluramine after repeated doses of fenfluramine. Daily dose was decreased or increased to a maximum of 160 mg/day according to individual response. The mean fenfluramine intake was 142 ± 29 (23-107) mg/day. The mean of mean plasma fenfluramine was 158 ± 70 (35-299) ng/ml and the mean of mean plasma norfenfluramine was 72± 29 (22-144) ng/ml. In 13/41 subjects with a mean fenfluramine intake of 135 ± 33 mg/day the values of the above mentioned parameters were 78 ± 22 ng/ml for fenfluramine and 44 ± 17 for norfenfluramine.

5. TOXICOLOGICAL DATA FOR NORFENFLURAMINE

Fenfluramine and norfenfluramine are both neurotoxic in experiment animals, causing reduction in the serotonin axonal markers (4). Doses of fenfluramine found to be effective in this respect are in the same order of those utilised to achieve the anorectic effect in man, if corrected for body mass and pharmacokinetic differences (5).

Furthermore, the neurotoxic potential of norfenfluramine seems to be higher than for the parent compound (4).

6. PHARMACOVIGILANCE DATA

The PSURs covering the period since 1st of January 1992 to 15th December 1998, the assessment and case narratives from French Authorities were considered.

Nervous system and cerebral circulation in the PSUR.

Two cases of cerebrovascular accident have been described:

Company ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
123 F41	France	39	F	450	3m	**Cerebrovascular accident, cerebellar infarction**

124B09	France	72	F	450	2y	**Cerebrovascular accident, ischemia of internal capsula.**

After analysis of complete case narratives provided by Agence du Medicament it must be pointed out that the causality assessment is complicated by the concomitant therapies and by the pre-existing conditions. In the case of the 39 years old patient, spironolactone was the drug indicated as suspected by the reporter and there is no clear indication of concomitant pathologies.

For the 72 years old patient case, there were underlying diabetes and unstable hypertension.

The following reports from the Company can be related to nervous system toxicity too:

(after analysis of French case narratives the following confounding factors have been added into brackets)

Company ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
540J08	France	68	M	450	1m	**Polyneuropathy** (pre-existing diabetes)
540V17	France	59	F	450	2m	**Delirium, agitation, disorientation** (Concomitant amfepramone)
541173	France	45	F	300	8d	**Hallucination, aggressiveness** (no complete case narrative available)
120M52	France	60	M	150	2d	**Somnolence, personality disorder** (no complete case narrative

						available)
120M85	France	70	M	300	11d	**Amnesia, confusion** (no complete case narrative available)

Cases of nervous system reactions from Agence du Medicament:

Considered as likely related from French assessors:

ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
NC95001 71	France	50	F	1cp		**Nervousness.** Onset 1 -2 h after the first dose
10010345	France	80	F		13 D	**Obnubilation, disorientation.** Positive rechallenge
123S98	France	27	M	1350	6 M	**Drug abuse, headache, manic reaction, mydriasis on withdrawal**

Considered as possibly related from French assessors

ref. No	Country	Age	Sex	Dose (mg/day)	treatment duration	reaction
NC97000 94	France	74	F		6 D	**Aggressiveness.** Recovered on suspension of treatment.
NC93003 47	France	39	M		11 M	**Irritability.** Recovered on suspension of treatment
NC93003 49	France	50	M		9 M	**Depression.** Recovered on suspension of treatment
MA9100 069	France	40	M	4 cp	1D	**Palpitation, anguish.** Onset 2h after the first dose

CF90001 37	France	79	F			**Disorientation**. Recovery on suspension o benfluorex and of other concomitant drugs.

16 Further cases of psychiatric reactions not included in the PSUR and classified as doubtful by French assessors have been reported, including one further case of delirium, one of stupor and one of withdrawal symptoms.

In France **20 cases of impaired balance** have been reported, and in six of such cases, patients recovered on suspension of benfluorex therapy.

Moreover, two cases of **convulsions** have been reported to French Authorities but no complete case narratives are available.

Cardiovascular system

No cases of primary pulmonary hypertension has been included in the PSUR by the Company.

French Authorities have provided 11 cases of pulmonary hypertension, but the patients also assumed fenfluramine or dexfenfluramine and/or other anorectic agents. Three cases of arterial hypertension have been described, one of which considered related by Agence du Medicament experts. Also one case of tachycardia and one case of atrial fibrillation were considered likely related.

One case of aortic insufficiency has been reported to French Authorities but the patient had previous myocardial infarction and mitral insufficiency.

It must be pointed out that norfenfluramine inhibits serotonin re-uptake and all serotonergic agents, including ergotamine and methysergide can cause valve lesions (Wong et al. *Cleveland Journal of Medicine* 1998 65 (1):35-41).

One case of syncope with respiratory insufficiency has been reported but there was concomitant amfepramone.

Furthermore, one case of shock with ventricular tachycardia and one of torsade de pointes in a patient with no predisposing factors, have been included in the PSUR but no complete case reports are available.

Haemopoietic system

Three cases of agranulocytosis, 5 of thrombocytopenia, 2 of leucopenia, 2 of lymphopenia 3 of neutropenia plus thrombocytopenia have been described in France. No complete case reports available.

Allergic reactions

Several cases of allergic reactions and six cases of anaphylactic shock have been reported. The Company proposes to add the allergic reactions in the undesirable effects section of the SPC.

Liver and biliary tract

23 cases of hepatitis have been provided from French Authorities, with 7 cases probably related and a possibly related one.

Respiratory system

Two cases of interstitial pneumonitis have been reported in France, but French assessors have pointed out several confounding factors.

7. Patient exposure

The Company has provided the following estimates of patients-months based on a mean daily dosage of 2,4 tablets, for a month of 30.4 days.

COUNTRY	N. patients-months OCT 96 - SEP 98
France	4,657,495

Luxembourg	2,130
Portugal	24,619
Greece	1,502
Italy	235,612
Spain	10,215
TOTAL	4,931,573

8. DISCUSSION

The first element to be considered in the overall safety evaluation of benfluorex is that it cannot be ruled out that norfenfluramine is responsible for the nervous system and cardiovascular adverse reactions reported in patients assuming benfluorex. It must be pointed out that these reactions have been described also for fenfluramine. It's well known that norfenfluramine is neurotoxic in animals and it's very likely it is also in humans.

Furthermore, adverse reactions such as psychiatric disorders, blood dyschrasias, anaphylactic shock, hepatitis and cardiovascular effects have been reported several times and are not included in the Summary of Product Characteristics.

CONCLUSION

We agree with French Colleagues that on the basis of the data deriving from spontaneous monitoring there is no definitive evidence of neurotoxicity and cardiotoxicity of benfluorex in humans, but there are elements of suspicion to require that precautions are adopted to further monitor the issue, especially to prevent long term adverse effects.

The following actions are possible:

- Referral of benfluorex to CPMP by Italy and France;
- Request the Company to provide preclinical and clinical studies on cardiovascular effects of repeated doses of benfluorex and toxicological studies about its neurotoxicity, further elements for cerebrovascular, nervous, pulmonary and cardiac adverse reactions if available, confidence limits of

norfenfluramine plasma levels after repeated doses of benfluorex, further data on long-term efficacy of benfluorex therapy.

- Ask the Company to perform, as suggested by French Colleagues, a pharmacokinetic study on benfluorex and its metabolites, especially norfenfluramine after a single dose and after several days of treatment.
- Reduction of indications of benfluorex containing medicinal products, updating of adverse effects, contraindications and special warnings sections of SPC, with particular regard to cardiac function monitoring, possibly by echocardiography for long term use and contraindication in case of pre-existing hypertension or cardiovascular and/or cerebrovascular diseases.

Rome, 31 May 1999

Dr. Renato Bertini Malgarini

Dr. Giuseppe Pimpinella

REFERENCES

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4. Johnson MP, Nichols DE. Comparative serotonin neurotoxicity of the stereoisomers of fenfluramine and norfenfluramine. *Pharmacol Biochem Behav* 1990 36(1):105-109

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Investigation of possible safety issue (i.e. toxicity similar to fenfluramine which is subject to Article 15a Procedure) (IT)

From: IT
Sender:
Date: 10/06/1999

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

The Assessment Report prepared by Italy had been circulated to the PhVWP on 2 June 1999, and during the meeting the Italian Member informed the PhVWP that, as suggested by the French colleagues, pharmacokinetic studies on benfluorex and its metabolites will be requested from the marketing authorisation holder. The Italian and French Members will prepare an updated Assessment Report for discussion by the PhVWP in September 1999.

Proposed Issues for Discussion

PhVWP
Primary pulmonary hypertension, cardiac valve disorders

From: IT
Sender:
Date: 30/09/1999

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

Italy informed the PhVWP that further data from the marketing authorisation holders will be requested by means of a list of questions prepared by France and Italy. Italy will evaluate the response in co-operation with France and this issue will be discussed in November 1999 or January 2000

Proposed Issues for Discussion

Annexe 3-24

INFOFAX
PHARMACOVIGILANCE

FROM/EXPEDITEUR : Dr Anne CASTOT
Head of Pharmacovigilance Unit
French Agency for the Safety of Health Products

DATE : 18 JUIN 1999

Pages (incl. cover) : 2

TO : **Fax N° :**

Austria :	Ms Eva HOFBAUER	43-1-712.08.23
Belgium :	Dr Xavier KURZ	32-2-227.55.28
Denmark :	Dr Doris STENVER	45-4-491.73.73
Finland :	Dr Tapio KUITUNEN	358-9-47-33.42.97
France :	Prof. Christian RICHE	33-2-98.01.64.66
Germany :	Dr Jürgen BECKMANN	49-30-4548.3515
	Dr Brigitte KELLER-STANISLAWSKI	49-6103-77.12.63
Greece :	Ms Antonia PANDOUVAKI	30-1-654.95.85
	Dr Georgia ATHANASIOU	30-1-654.95.85
Ireland :	Dr Mary TEELING	353-1-676.78.36
Italy :	Dr Giuseppe PLUCHINO	39-6-5994.3554
		39-6-5994.3456
		39-6-5994.3365
Luxembourg :	Mrs Jacqueline GENOUX-HAMES	352.22.44.58
		352.29.99.13
Netherlands,:	Dr Arthur MEINERS	31-70-356.75.15
Portugal :	Dr Antonio Nuncio FARIA VAZ	351-1-795.91.16
Spain :	Dr Carmen ALVAREZ-FRAILE	34-91-596.14.55
Sweden :	Dr Orjan MORTIMER	46-18-54.85.66
United Kingdom :	Dr Patrick WALLER	44-171-273.02.05
	Dr Ennis H. Lee	44-171-273-0675
EMEA :	Mr Noel WATHION	44-171-418.85.51
Chair CPMP :	Prof. ALEXANDRE	33-1-55.87.32.72
European Commission :	Dr EMER COOKE	32-2-296.15.20

SUBJECT / OBJET : **Benfluorex (MEDIATOR®)**

Annexe 3-24

MESSAGE :

A case of pulmonary hypertension (PH) in a woman treated with benfluorex has recently been reported to the French pharmacovigilance system.
This case is currently under review. The patient was treated with benfluorex alone for 4 years (treatment dates unknown). In December 1998, the patient experienced dyspnea. In March 1999, the worsening of symptoms led to diagnose a primary pulmonary hypertension (PAPS = 91 mmHg). A chronic thromboembolic process has been excluded by pulmonary scintigraphy.

Up to now, except this new case, 11 cases of PH have been reported with benfluorex. In 10 cases, benfluorex was concomitantly used with dexfenfluramine and in 1 case with amfepramone and clobenzorex.
Hence, this new case is the first case of PH reported with benfluorex used in monotherapy.

As agreed at the June Pharmacovigilance Working-Party, Italy and France proposed to send a list of questions to the MAH and to revise the SPCs of benfluorex. This issue should be discussed in September.
This new case raises a great concern.
Therefore, we are proposing the following actions :

1 - The French Agency will ask the MAH to submit before the end of June :
- an update on safety data,
- all pharmacological and pharmacokinetic data available on benfluorex and its metabolites and a comparison of these data to those known with fenfluramine / dexfenfluramine and its metabolites.

2 - This issue will be reviewed by our experts at the beginning of July. You will be informed of any recommended action.

Le Chef de l'unité de Pharmacovigilance

Dr Anne CASTOT

Nom : PHARMACOVIGILANCE Numéro : 3554 Date : 15mai99 18:30

Date/Heure	6 18:15
Liste de diffusion	3
Durée totale	18''
Nb. pages du document	2

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AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

RÉPUBLIQUE FRANÇAISE

1

INFOFAX
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Chair CPMP :	Prof. ALEXANDRE	33-1-55.87.32.72
European Commission :	Dr EMER COOKE	32-2-296.15.20

SUBJECT / OBJET : Benfluorex (MEDIATOR®)

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE
Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance
3159

RÉPUBLIQUE FRANÇAISE

Saint-Denis, le 21 OCT. 1999

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 22 Juin 1999)

Etaient présents

M. RICHE : Président
Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. BLAYAC, Mme BROCH (représentant le CRPV de Brest), M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. ESCHALIER, Mme SGRO (suppléante de M. ESCOUSSE), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme KREFT-JAIS, Mme GINISTY (représentant le CRPV de Paris - F. Widal), Mme LAINE-CESSAC, M. LAROUSSE, M. MALLARET, M. MERLE, Mme LAPEYRE-MESTRE (suppléante de M. MONTASTRUC), M. MOULIN, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE). M. TRENQUE, M. VANDEL, M. VIAL.
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant de M. le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle GOEBEL
M. JACQUET
M. LANG
Mme LEREBOURS
Melle MAUREL
M. MASSET
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Melle ROBINE
M. ROPERS
Mme ROMIEE
Mme SCHLOSSER
Mme WECHSLER

Assistaient à la réunion :

DEV :

Mme CALLENS
Mme COSTAGLIOLA

CRPV :

M. CLEMENT
M. COQUEREL
Mme PICAUD

VI - POINT SUR LA PHARMACOVIGILANCE EUROPEENNE.

Compte-rendu du groupe de travail européen de pharmacovigilance des 10 et 11 juin 1999.

- Inhibiteurs de la protéase / lipodystrophies :
Un groupe d'experts comprenant des membres du Comité des Spécialités Pharmaceutiques (CSP), des membres du groupe de travail de pharmacovigilance (Suède, Espagne et Belgique) et des experts cliniciens a été mis en place pour évaluer le risque des lipodystrophies et ses conséquences. Une première réunion a eu lieu le 28 mai 1999. La réunion suivante est programmée le 29 juin 1999. Les recommandations finales de ce groupe sont attendues pour septembre 1999.

- Association de lamivudine et zidovudine : atteintes mitochondriales et complications cérébrales chez l'enfant :
Les Etats membres ont été informés des conclusions de la réunion d'experts organisée en France le 31 mai 1999. La France doit proposer les principaux éléments d'une lettre d'information aux prescripteurs lors du groupe du travail de juillet 1999 pour adoption par le CSP de manière à ce qu'une information commune soit diffusée en Europe.

- Rituximab (MABTHERA®) :
Cet anticorps monoclonal indiqué dans les lymphomes de stade IV fait l'objet d'une surveillance renforcée depuis la survenue de plusieurs cas de réactions liées à la perfusion de rituximab (signes pulmonaires). Les données concernant les autopsies des patients décédés n'apportent aucun élément nouveau. Un protocole d'étude clinique sera discuté durant l'été.
Par ailleurs, 6 observations de réactions cutanées graves (syndrome de Lyell, pemphigoïde bulleuse) ont été rapportées. Une demande de variation de type II (demande de modification de l'information médicale) relative à ces observations est en cours d'évaluation.

- Sildénafil (VIAGRA®) :
Le protocole de l'étude de surveillance post-commercialisation doit être prochainement rediscuté avec les laboratoires PFIZER.
A la suite de plusieurs notifications d'atteintes hépatiques survenues en dehors de l'Union européenne, les effets indésirables hépatiques font également l'objet d'une surveillance.
L'ajout d'une interaction médicamenteuse concernant le ritonavir et le saquinavir a été adopté par le CSP.

- Anorexigènes (article 15 de la Directive 75/319/CEE):
La plupart des laboratoires ont fait appel à l'opinion du CSP rendue en avril 99. De nouveaux pays rapporteurs et co-rapporteurs ont été nommés :
- Angleterre et Pays-Bas pour la fenfluramine, dexfenfluramine,
- Italie et Espagne pour la phentermine, amfépramone,
- Belgique et Portugal pour les autres anorexigènes.

L'opinion définitive du CSP est attendue pour fin juillet 1999.

- **Sertindole (article 15 de la Directive 75/319/CEE) / morts subites :**
Les rapporteurs concluent à un rapport bénéfice-risque négatif.
L'opinion du CSP est attendue pour fin juin 1999.

- **Vigabatrin (article 12 de la Directive 75/319/CEE) / restrictions du champ visuel :**
A la suite de l'opinion du CSP (mai 1999) modifiant les indications et les mises en garde du vigabatrin, les laboratoires ont préparé un nouveau RCP, une lettre d'information aux prescripteurs et un projet d'études cliniques.

- **Inhibiteurs sélectifs de recapture de la sérotonine / syndrome de sevrage et dépendance :**
Les éléments suivants apparaîtront dans la section "Effets indésirables" des RCP des produits de la classe :
- des syndromes de sevrage peuvent survenir à l'arrêt du traitement,
- liste de symptômes associés au syndrome de sevrage,
- une diminution progressive de la dose est recommandée pour tous les traitements excepté pour la fluoxétine (car longue demi-vie). Les RCP de la venlafaxine et de la paroxétine devront être plus détaillés quant aux modalités de diminution de la dose en fin de traitement car des syndromes de sevrage ont été rapportés plus souvent avec ces deux médicaments.
- il n'y a pas de données cliniques permettant d'exclure un risque de pharmacodépendance.

- **Benfluorex / métabolisation en norfenfluramine :**
le rapport rédigé par l'Italie en collaboration avec la France a été distribué aux Etats membres.
Les données disponibles ne permettant pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex, le groupe de travail a souhaité que les pays rapporteurs (France et Italie) proposent des modifications de RCP et adressent une liste de questions au laboratoire en demandant une mise à jour des données de tolérance et la réalisation d'une étude de pharmacocinétique du benfluorex et de ses métabolites.

Par ailleurs, mi-juin 1999, un cas d'HTAP d'allure primitive a été rapporté chez une femme de 51 ans traitée par benfluorex depuis 4 à 5 ans. Il s'agit du premier cas d'HTAP rapporté avec le benfluorex utilisé sans association de médicament anorexigène. 11 cas avaient auparavant été rapportés lors d'un traitement associant le benfluorex à de la dexfenfluramine dans 10 cas et à de l'amfépramone et du ciobenzorex dans 1 cas.

Compte-tenu de ce nouveau cas, l'Agence a adressé un courrier aux laboratoires SERVIER leur demandant de verser, avant le 28 juin 1999, une mise à jour des données de tolérance ainsi que les données de pharmacologie et pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines. Un infofax a par ailleurs été envoyé à tous les Etats membres.

- **Thiomersal / sensibilisation :**
Un groupe de travail a été mis en place par le CSP pour étudier l'éventuelle toxicité de cet excipient présent dans certains vaccins, collutoires, collyres et gouttes nasales. L'OMS soulève le risque de neurotoxicité et néphrotoxicité du thiomersal, notamment chez l'enfant.

WPR

Ministero della Sanità

F8006|FS|8606

TO: Dr. A. CASTOT/Dr. C. FOSSET
PHARMACOVIGILANCE UNIT
AGENCE DU MEDICAMENT
FAX 0033 1 55 87 35 32

FROM: ITALIAN MINISTRY OF HEALTH
DRUG EVALUATION AND PHARMACOVIGILANCE DEPARTMENT
V.LE DELLA CIVILTA' ROMANA, 7
ROMA
FAX + 39 6 5994 3554

SUBJECT: ASSESSMENT REPORT FOR BENFLUOREX.

Dear Dr. Castot and Dr. Fosset,

We agree with your comments. It's preferable to leave the discussion on indications and pharmacodynamics to national level and eventually discuss it later.
Would you be so kind to send the letter to the Company. We are available to examine the answer and prepare a joint assessment report.
We enclose also a revised version of the assessment report that if you agree we could circulate.
Thank you for the collaboration.
Best regards.

HEAD OF UNIT

Dott. Berlin Melazzini

Annexe 3-26

Ministero della Sanità

REVISED ASSESSMENT REPORT

RELEVANCE OF METABOLIC PATHWAYS OF BENFLUOREX TO NORFENFLURAMINE

Medicinal product: Mediaxal®

Manufacturing Authorisation Holder: Laboratoires Servier

Active constituent: benfluorex

Originating Member States: Italy, France

Assessors: Dr. Giuseppe Pimpinella, Dr. Renato Bertini Malgarini

Contact point: Italian Ministry of Health

Pharmacovigilance Unit

TEL: 0039 06 5994 3212

FAX: 0039 06 5994 3554

Confidential

1. BACKGROUND

Following the report of a case of pulmonary hypertension occurred in France, the Colleagues of Agence du Medicament asked the Laboratoires Servier to provide further documentation for safety, efficacy and pharmacokinetic profile of benfluorex compared to those of fenfluramine and dexfenfluramine.

The French experts have also provided to Italian Ministry of Health the Documentation from the Laboratoires Servier and a joint assessment has been carried out.

2. DATA ANALYSIS

Pharmacokinetic parameters after 14 days treatment.

		AUC 24	Cmin (24h)	Cmax
			(ng ml-1)	(ng ml-1)
Benfluorex 3x 150 mg	dl-norfenfluramine	1149 ± 286	43 ± 8	59 ± 15
Dexfenfluramine 2x 15 mg	d-fenfluramine	1060 ± 316	34 ± 7	70 ± 15
	d-norfenfluramine	527 ± 281	18 ± 10	26 ± 13
Fenfluramine 60 mg	d-fenfluramine	1014 ± 445	33 ± 12	65 ± 26
	l-fenfluramine	1581 ± 778	54 ± 24	97 ± 47
	d-norfenfluramine	377 ± 136	14 ± 5	21 ± 8
	l-norfenfluramine	586 ± 210	21 ± 9	32 ± 13

From the data in the table, we can derive that an exposition to 450 mg/day of benfluorex (only metabolised to norfenfluramine) leads to a norfenfluramine level that is in the same magnitude order of that observed after a 60 mg/day dose of fenfluramine (the contribution of dl-fenfluramine and dl-norfenfluramine has been taken into account).

Annexe 3-26

2.1 Clinical trial

Only one long term (29 weeks) trial in obese patients with type II diabetes has been carried out. In this study benfluorex was compared to placebo and to metformin. The considered parameters were weight loss and glycosylated haemoglobin.

Weight loss was not significant among the three groups.

Glycosylated haemoglobin showed a significant decrease in benfluorex treated patients with respect to placebo (HbA1c -0,6% and +0,5% respectively).

However, benfluorex was less effective of metformin (-0,6 % and -1% respectively).

It must be pointed out that this study is an unpublished internal report and confidence intervals were not available.

Concerning the indication in hyperlipidaemia, there are no data for therapy duration longer than 1 month and numerous therapeutic alternatives are available.

Furthermore, for these short term studies no quantitative data for serum lipids reduction are provided have been provided by the Company.

3. Pharmacovigilance data.

A part from the case of pulmonary hypertension that is still under evaluation, no new significant data have been submitted.

5. Conclusions

As previously concluded, there are suspicions that patients treated with benfluorex are exposed to a potentially toxic level of norfenfluramine. The drug is less effective than metformin in the management of obese patients with type II diabetes. No data on safety and efficacy of the drug for therapy periods longer than six months have been provided.

Psychiatric reactions (confusion), anaphylactic shock, hepatitis, blood disorders and cardiovascular adverse effects are not listed in the SPC.

Annexe 3-26

The final proposal has been decided together with French Colleagues that will address them to Servier:

- The following questions will be addressed to the Company:
  - What are the values of pharmacokinetic parameters in animals and in humans after long term (more than six months) administration of benfluorex?
  - Have the cardiovascular and neurological effects of benfluorex in animals and in humans been assessed after long-term (more than six months) exposure to benfluorex?
  - Has long term efficacy in lowering serum lipids assessed in controlled studies and compared to currently available therapeutic alternatives (fibrates, statins, etc.)?
  - Has long term efficacy in controlling glycaemic parameters assessed in controlled studies?

- If the above data are not available, the Company should carry out a long term study (more than one year) with periodic echocardiographic, glycaemic, serum lipids level controls and measurement of pharmacokinetic parameters.
- SPC revision as follows:

No data supporting the indication hypetriglyceridaemia were included. This indication as the others are currently under review by National French Authorities. We suggest to wait for the conclusion of such review and to discuss the efficacy and pharmacodynamics issues at national level if deemed necessary.

Section 4.3 Contraindications

...Hypersensitivity to the drug or to any other component of the formulation.

Chronic pancreatitis...

Section 4.4 Special warnings

... In case of hepatic enzymes elevations the treatment should be discontinued.

Use with caution in case of pre-existing hepatic disorders and cardiovascular disease.

Annexe 3-26

The clinical [illegible] after such a period the continuation of the treatment should be re-evaluate (in the French SPC a similar statement is already present in special warnings section)....

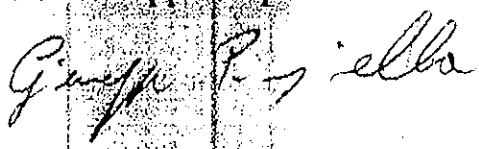
Section 4.8 **Adverse effects**

...Cases of hepatitis, allergic reactions including anaphylactic shock, blood disorders, hypertension, palpitations and confusion have been reported...

Rome, 12 October 1999

Dr. Renato Bertini Malgarini

Dr. Giuseppe Pimpinella



Annexe 3-27

Carole FOSSET MARTINETTI (poste 3553)
Pharmacovigilance

COMPTE-RENDU TELEPHONIQUE

Communication reçue / ~~demandée~~ Date : 22/09/99

Avec : Pr BECHTEL 10H30

Téléphone :

Objet : Mediator®

Commentaires sur le "revised AR" des Italiens

Compte-tenu des données disponibles, il est difficile de démontrer qu'il n'y a pas de risque surtout si l'on regarde les paramètres cinétiques (AUC) de Benfluorex, DeF et Fenfluramine.

Le Propositions des Italiens concernant étude clinique au long cours est satisfaisante. Il paraît difficile de faire autrement. (L'étude de cinétique évoquée précédemment ne serait pas utile compte-tenu des AUC disponibles).

Le fait de demander cette étude au long cours permettra au labo de se positionner : peut-être préférera-t-il retirer le produit plutôt que de mettre en place l'étude ?

Destinataires :

AGENCE
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTE

**DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET
DES PRODUITS BIOLOGIQUES**

3597

Saint-Denis, le 2 2 NOV 1999

**Monsieur le Pharmacien Responsable
Laboratoires SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE**

Objet : MEDIATOR® (benfluorex)

Monsieur,

En septembre 1998, les autorités de santé italiennes ont demandé au Comité des Spécialités Pharmaceutiques (CSP) de réévaluer le profil de sécurité d'emploi du benfluorex, considérant que l'un de ses métabolites, la norfenfluramine, pouvait être à l'origine de la survenue d'hypertension artérielle pulmonaire ou d'atteinte des valves cardiaques.
Le CSP a chargé le groupe de travail de pharmacovigilance de cette réévaluation qui est conduite par l'Italie et la France.

Les données de pharmacovigilance analysées en commun soulèvent un certain nombre de questions auxquelles nous vous remercions de bien vouloir répondre.

- Quels sont les paramètres pharmacocinétiques chez l'animal et chez l'homme après administration de benfluorex au long cours (plus de 6 mois) ?
- Les effets cardio-vasculaires et neurologiques du benfluorex ont-ils été évalués chez l'animal et chez l'homme après administration au long cours (plus de 6 mois) ?
- L'efficacité au long cours du benfluorex sur la diminution des lipides sériques a-t-elle été évaluée par des essais cliniques contrôlés et a-t-elle été comparée aux traitements actuellement disponibles (fibrates, statines...)?
- L'efficacité au long cours du benfluorex dans le contrôle de la glycémie a-t-elle été évaluée par des essais cliniques contrôlés ?

En l'absence de données au long cours, envisagez-vous de mettre en place une étude clinique de plus de 12 mois avec contrôle périodique de la glycémie et des lipides sériques, échocardiographies et mesure des paramètres pharmacocinétiques ?

Il paraît, par ailleurs, souhaitable de soumettre dans les plus brefs délais, une demande de modification de l'information dans les pays de l'Union Européenne où le benfluorex est autorisé, afin de compléter et d'harmoniser le Résumé des Caractéristiques du produit.
Ces modifications concernent les rubriques 4.3 « contre-indications », 4.4 « mises en garde et précautions d'emploi » et 4.8 « effets indésirables » :

- *4.3 Contre-indications* :
  ajout de « Hypersensibilité au benfluorex ou à l'un des constituants ».
- *4.4 Mises en garde et précautions d'emploi* :
  Ajout de « Le traitement devra être interrompu en cas d'élévation des enzymes hépatiques » et « le benfluorex devra être utilisé avec précautions en cas d'atteintes hépatiques ou de maladies cardio-vasculaires pré-existantes. ».
- *4.8 Effets indésirables* :
  Ajout de « atteintes hépatiques, réactions allergiques incluant des cas de choc anaphylactique, atteintes hématologiques, hypertension, palpitations et confusions ».

Nous sommes à votre disposition si vous souhaitez de plus amples informations.

Nous vous prions d'agréer, Monsieur, l'assurance de notre considération distinguée.

Dr. Eric ABADIE
Directeur du Département Pharmaco Toxico Clinique
des Médicaments

Annexe 3-29

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AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

RÉPUBLIQUE FRANÇAISE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 22 FEV. 2000

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 07 Décembre 1999)

Etaient présents

M. RICHE : Président
M. KLOVZ (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme BAVOUX, M. BIOUR, M. BLAYAC, M. CARON, Mme CHICHMANIAN, M. COQUEREL, Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme JOLLIET, Mme DAVID-LAROCHE (suppléante de M. KANTELIP), Mme LILLO LE LOUET (représentant le CRPV de Paris-Broussais), Mme THOMAS (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, M. MERLE, Mme BAGHERI (suppléante de M. MONTASTRUC), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant de CRPV de Brest), Mme SGRO, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL, M. VIAL
Mme CHOMA (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme CHOULIKA
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle FRADET
Melle GOEBEL
M. JACQUET
Mme JOLIMOY
Mme JOUSSELIN-PAUTROT
M. LANG
Mme LEREBOURS
M. MASSET
Mme MESSINA-GOURLOT
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Melle ROBINE
M.ROPERS
Mme SCHLOSSER

Assistaient à la réunion :

DEMEB :

Mme ALLUE
M. BURY
Mme CHAUVENET
Mme GUENANECHE
Mme JAGER
M. MEYER
Mme MIGNON
Mme PELLANNE
Mme PHAM-BA
Mme REIDIBOYM
Mme WECHSLER

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

XI -POINT SUR LA PHARMACOVIGILANGE EUROPENNE (GROUPE DE TRAVAIL DES 23 ET 24 NOVEMBRE 1999).

- Antiprotéases / rhabdomyolyse :

La possibilité d'une interaction entre les antiprotéases et les inhibiteurs de la HMG-COA réductase avec apparition d'une rhabdomyolyse est toujours en discussion.
En janvier 2000, le groupe de travail européen de pharmacovigilance fera le point pour déterminer si cet effet indésirable est plutôt « un effet de classe » ou bien s'il apparaît uniquement avec certaines statines.

- Halothane / arythmies cardiaques graves et fatales chez des enfants :

Une étude randomisée publiée dans le Lancet a montré que l'incidence de survenue d'arythmie cardiaque est six fois plus élevée avec l'halothane qu'avec le sévofurane chez des enfants ayant subi une anesthésie en chirurgie dentaire.
A la suite de cet article, le Royaume-Uni a décidé de contre-indiquer l'utilisation extra-hospitalière de l'halothane en chirurgie dentaire chez les patients âgés de moins de dix-huit ans.

- Phosphénytoïne (PRODILANTIN®) / effets cardio-vasculaires :

Ce médicament est autorisé selon une procédure de reconnaissance mutuelle et commercialisé en France depuis mai 1995. Le pays rapporteur (le Royaume-Uni) a rapporté 3 décès et 52 effets cardiovasculaires. Devant la gravité de ces cas, le Royaume-Uni a demandé au laboratoire de fournir une revue analytique des effets cardiaques au plan international pour le 23 décembre 1999. Le problème évoqué serait un débit de perfusion trop rapide. L'adaptation posologique s'avère également difficile.
Un essai clinique est en cours en France, incluant en particulier des enfants de moins de cinq ans. Une lettre d'information aux investigateurs a été finalisée au plan national. Ce courrier insiste sur la nécessité d'effectuer un monitoring cardio-respiratoire et sur le respect du débit de perfusion. (cf. annexe 2)

- Ropinirole / accès de sommeil d'apparition soudaine :

Depuis l'envoi d'une lettre d'information aux prescripteurs et aux pharmaciens par la firme entre le 10 et le 15 novembre 1999 relatant la possibilité de survenue d'accès de sommeil d'apparition soudaine sous Requip®, des nouveaux cas ont été notifiés notamment en Allemagne et en France. (1 cas en [illegible])
Un rectificatif d'AMM a été effectué le 9 novembre 1999 mentionnant les nouvelles mises en garde insistant sur la nécessité de ne pas conduire.
Pour mise en conformité avec l'AMM, de nouvelles notices vont être délivrées aux pharmacies [illegible] décembre 1999. De même, des stickers reproduisant le pictogramme obligatoire (une voiture dans un triangle rouge) devront être apposés sur le conditionnement.

- Benfluorex / hypertension pulmonaire primitive et valvulopathie :

Il a été demandé à la firme de réaliser une synthèse sur les données d'efficacité du médicament et sur la tolérance préclinique et clinique à long-terme et de déposer une demande de modification de l'information dans tous les pays où le produit est autorisé.

- Vigabatrin / restrictions du champ visuel :

Les mesures obligatoires de suivi des patients sous VIGABATRIN® ont été rediscutées (fiches d'observation recueillant les résultats de périmétrie). Les modalités d'application seront définies nationalement du fait d'une trop grande variabilité du nombre de patients traités par cette spécialité en fonction des pays européens (ex : 12 000 en France et 400 en Finlande).

CENTRE DE PHARMACOVIGILANCE DE MARSEILLE

COMITE TECHNIQUE DU : 7 décembre 1999

N° des cas	Date de survenue	Sexe /Age	Médicaments suspects	Effets observés	Evol.	Imput	G	N	E	Commentaires *Interaction*
Ma99 1079 1181	 Oct 99 Nov99	 F62 M31	IDARAC	malaise bronchospasm urticaire bronchospas	 A A	 I2 I2	 O N	 N N	 N N	Qu'en est il au labo? Médecins s'étonnent du maintien du produit
			Préparation amaigrissante à base de: Phenylpropanolamine 60 mg x3fois /j ephedrine 10 mgx3fois/j pendant 3 mois + laxatif ou diurétiques							Question posée par un médecin conseil de la SS sur les risques? Poso et durée non conformes. Pas d'indication dans l'obésité . (plus de 50 ordonn.)
			Norlevo	Pilule demandée dans un but contraceptif avant le rapport à risque . pas de préservatif !						Information sur le bon usage auprès des populations concernées (et les MST ?)
			Mediator	Mesusage : 50% augm des ventes en pharma souvent hors AMM						Chiffres de vente à surveiller.

36

PhVWP

1403 Annexe 3.30

Primary pulmonary hypertension, cardiac valve disorders (IT) – Oral update

From: IT
Sender:
Date: 24/01/2000

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

Italy informed the PhVWP that the response requested from the marketing authorisation holder to a List of Questions regarding efficacy and safety in drug use longer than 6 months is awaited and will be assessed for discussion in May 2000 as agreed in November 1999. Also in May 2000, France will report upon their efficacy review. An oral update will be provided in February 2000.

Proposed Issues for Discussion

Annexe 3-31 UU

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ
Direction de l'Evaluation du Médicament et des Produits Biologiques
143 - 147 Boulevard Anatole France
93200 SAINT-DENIS

Neuilly-sur-Seine, le 18 février 2000

JNA ACom ET CC LD CRQ

EA copie →

A l'attention de Monsieur de Docteur ABADIE
Département de l'Evaluation Pharmaco
Toxico Clinique des Médicaments

N. Réf. : IT/kh/00.0173
☎ 01 55 72 65 34
Fax 01 55 72 33 02
Mme THUILLIER

Objet : **MEDIATOR®**
Dossier VNL 10008

Monsieur,

J'ai bien reçu votre lettre en date du 22 novembre 1999 relative à la pharmacovigilance de notre spécialité MEDIATOR® et elle a, bien sûr, retenu toute mon attention.

La démonstration de l'efficacité antidiabétique et hypotriglycéridémiante de MEDIATOR® a été effectuée dans des études cliniques contrôlées versus placebo ou produits comparateurs.

L'indication de la spécialité dans le domaine des hypertriglycéridémies a été validée en 1987, et renouvelée sans aucune question à plusieurs reprises.

Le programme d'études à réaliser en vue de la validation de la spécialité dans l'indication diabète avait fait l'objet d'une concertation avec vous-même (votre courrier en date du 26 Janvier 1996). Le rapport de l'étude 6 mois démontrant l'efficacité de MEDIATOR® versus placebo et metformine chez le diabétique de type 2 mal contrôlé par le régime seul a bien été soumis en décembre 1997 puis en mai 1998 à l'Agence pour permettre d'obtenir la validation de la spécialité dans cette indication.

tel Pr Abadie

.../...

SERVIER

Nous serions tout à fait d'accord pour vous rencontrer afin de discuter des objectifs, des caractéristiques et des paramètres à inclure dans une future étude long terme qui pourrait permettre de conforter les données de pharmacocinétique, d'efficacité et d'acceptabilité de MEDIATOR®.

Il convient de souligner que les données de pharmacovigilance accumulées depuis 25 ans d'utilisation du médicament (plus de 25 millions de mois de traitement), apportent des données irremplaçables notamment pour la détection d'évènements indésirables sévères, en particulier ceux dont l'incidence dans la population générale est très faible.

Par ailleurs, la réévaluation du profil de sécurité d'emploi de MEDIATOR® est le sujet d'une enquête officielle de pharmacovigilance depuis le 11 mai 1998, confiée au Centre Régional de Pharmacovigilance de Besançon (Pr. P. Bechtel). Au cours de l'année 1998, nous avons mis à la disposition du rapporteur les informations demandées, et en particulier la totalité des observations d'effets indésirables collectées en France par notre laboratoire depuis 1976, année de mise à disposition de MEDIATOR® aux prescripteurs. Ces observations ainsi que celles recueillies par les Centres Régionaux de Pharmacovigilance ont été analysées par le rapporteur de l'enquête. Cependant, nous ne sommes pas informés des conclusions de l'enquête et nous ignorons si la Commission Nationale de Pharmacovigilance a évalué les données disponibles.

Les conclusions de cette Commission (ainsi que les données de pharmacovigilance « analysées en commun » dont vous faites mention) pourraient permettre d'argumenter d'éventuelles modifications du Résumé des Caractéristiques du Produit. Nous nous tenons à votre disposition pour revoir ces données avec vous.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Alain LE RIDANT
Pharmacien Responsable

AGENCE
PRODUITS SANTÉ

**DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET
DES PRODUITS BIOLOGIQUES**
Unité de Pharmacovigilance
583

Saint-Denis, le 17 MAR. 2000

Monsieur le Pharmacien Responsable
Laboratoires SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Objet : MEDIATOR® (benfluorex) / votre courrier en date du 18 février 2000

Monsieur,

Pour faire suite à votre courrier en date du 18 février 2000, nous vous informons que le rapport d'évaluation relatif aux données de pharmacovigilance du benfluorex, présenté au groupe de travail de pharmacovigilance européen, a été rédigé par l'Italie.
En conséquence, si vous souhaitez obtenir de plus amples informations sur ce rapport d'évaluation en vue d'argumenter votre demande de modification du RCP, vous pouvez contacter l'unité de pharmacovigilance du Ministère de la Santé Italien. La personne chargée du dossier est Monsieur le Dr Giuseppe PIMPINELLA.

Nous vous prions d'agréer, Monsieur, l'assurance de notre considération distinguée.

Le Chef d'Unité de Pharmacovigilance

Carmen KREFT-JAIS

PhVWP
Primary pulmonary hypertension, cardiac valve disorders (IT)

Annexe 3-32

From: IT
Sender:
Date: 19/07/2000

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

M-T Tebano provided an update on this issue informing the PhVWP that Italy will send the draft study protocol from the marketing authorisation holder to France for comments and report on this to the PhVWP in October 2000. A Castot further informed the PhVWP that in France the indications are under review and a report on this review will be circulated for October 2000. D Montero explained that a re-evaluation of the benefit-risk has been initiated in Spain with an urgency to decide upon the necessity to take action, following a doubling of consumption since April 2000.

Proposed Issues for Discussion

Annexe 3-32

Primary pulmonary hypertension, cardiac valve disorders, draft study protocol (IT) – Update

From: IT
Sender:
Date: 11/10/2000

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

Following the update in provided in July 2000, M-T Tebano informed the PhVWP that the assessment of the data and of the draft study protocol submitted by the marketing authorisation holder has not yet been completed. It was agreed that Italy and France will contact the marketing authorisation holder to hold a meeting in the margins of the PhVWP in November 2000 to discuss outstanding issues and that they will report to the PhVWP in November 2000. D Montero informed the PhVWP about the concerns on use of magistral preparations in Spain as their consumption has remarkably increased over the last months.

Proposed Issues for Discussion

Annexe 3-33

Direction de l'Evaluation
des Médicaments et
des Produits Biologiques
Unité de Pharmacovigilance

FAX

FROM :

Carole FOSSET MARTINETTI
AFSSAPS
Fax N° 33(0).1.55.87.35.32

DATE : 25 OCT. 2000

Pages (incl. cover) : 2

TO :

		Fax N° :
Italy :	Dr Giuseppe PIMPINELLA	39-6-5994.3554
E.M.E.A. :	Mrs Priya Bahri	00-44-207-418-8668

SUBJECT : Benfluorex

Dear colleagues,

Please find enclosed the letter sent to Servier concerning the meeting of the 30 November 2000.

Best regards.

Carole Fosset Martinetti

Annexe 3-33

Date/Heure	25-10 10:12
Numéro composé	0004420741886680 95=EMEA
Correspondant	
Durée	0'37''
Mode	NORMAL
Pages	2
Résultat	Correct

RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

Direction de l'Evaluation des Médicaments et des Produits Biologiques

Unité de Pharmacovigilance

FAX

FROM :

Carole FOSSET MARTINETTI
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Fax N° 33(0)1.55.87.35.32

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TO :

		Fax N° :
Italy :	Dr Giuseppe PIMPINELLA	39-6-5994.3554
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SUBJECT : Benfluorex

Dear colleagues,

Please find enclosed the letter sent to Servier concerning the meeting of the 30 November 2000.

Best regards.

Carole Fosset Martinetti

Annexe 3-33

Date/Heure	25-10 10:11
Numéro composé	000390659943554 888=ITALY/PLUCHINO
Correspondant	+0659943554
Durée	0'49"
Mode	NORMAL
Pages	2
Résultat	Correct

RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

Direction de l'Evaluation des Médicaments et des Produits Biologiques

Unité de Pharmacovigilance

FAX

FROM :

Carole FOSSET MARTINETTI
AFSSAPS
Fax N° 33(0).1.55.87.35.32

DATE : 25 OCT. 2000

Pages (incl. cover) : 2

TO :

		Fax N° :
Italy :	Dr Giuseppe PIMPINELLA	39-6-5994.3554
E.M.E.A. :	Mrs Priya Bahri	00-44-207-418-8668

SUBJECT : Benfluorex

Dear colleagues,

Please find enclosed the letter sent to Servier concerning the meeting of the 30 November 2000.

Best regards.

Carole Fosset Martinetti

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

Annexe 3-33

DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET
DES PRODUITS BIOLOGIQUES
Unité de Pharmacovigilance

4 UK

Saint-Denis, le

Monsieur le Pharmacien Responsable
Laboratoires SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Objet : MEDIATOR® (benfluorex)

Monsieur,

A la demande du Comité des Spécialités Pharmaceutiques, le benfluorex fait l'objet d'une réévaluation par le groupe de travail de pharmacovigilance européen depuis septembre 1998. Cette réévaluation est conduite par l'Italie (pays rapporteur) et la France (pays co-rapporteur).

A la suite d'une première évaluation des données de pharmacovigilance, nous vous avons adressé, le 22 novembre 1999, un courrier soulevant un certain nombre de questions auxquelles nous aurions souhaité obtenir des réponses.

Devant l'absence de réponse, le groupe de travail de pharmacovigilance européen a proposé de faire le point sur ces questions à l'Agence Européenne du Médicament, en présence du titulaire de l'autorisation de mise sur le marché (AMM) du benfluorex et des rapporteurs italiens et français. L'objectif de cette réunion est de redéterminer les questions pour lesquelles les rapporteurs attendent une réponse du titulaire de l'AMM. Il ne s'agit en aucun cas d'une discussion scientifique du dossier.

Cette réunion se tiendra le :

Jeudi 30 novembre 2000 à 10 heures,

E.M.E.A. (European Agency for the Evaluation of Medicinal Products)
7 Westferry Circus, Canary Wharf
LONDON E14 4HB
UK

Nous vous prions d'agréer, Monsieur, l'assurance de notre considération distinguée.

C.C. Mme Priya Baluri / EMEA
M. Giuseppe Pimpinella / Italie

Annexe 3-34

DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET DES
PRODUITS BIOLOGIQUES
Unité de Pharmacovigilance
C. FOSSET MARTINETTI

Saint-Denis, le 31/01/00

Benfluorex

Compte-rendu de la réunion du 28 novembre 2000 en présence de M. Wagniart (laboratoires Servier), Mme Castot et Mme Fosset Martinetti

But de la réunion : faire le point sur l'état d'avancement du dossier en prévision de la réunion organisée à l'EMEA le 30 novembre 2000, en présence des laboratoires Servier et des rapporteurs italiens et français.

Le benfluorex est autorisé et commercialisé dans 6 pays de l'Union Européenne, la France représentant environ 85% des parts de marché. La grande majorité des observations de pharmacovigilance concerne la France.

En septembre 1998, les autorités de santé italiennes ont demandé au CSP de réévaluer le profil de sécurité d'emploi du benfluorex. Cette réévaluation est conduite par l'Italie et la France.

Après analyse des données de pharmacovigilance, un courrier a été adressé aux laboratoires Servier le 22 novembre 1999. Dans ce courrier, il était notamment demandé aux laboratoires :

« En l'absence de données au long cours, envisagez-vous de mettre en place une étude clinique de plus de 12 mois avec contrôle périodique de la glycémie et des lipides sériques, échocardiographies et mesure des paramètres pharmacocinétiques ?

Il paraît, par ailleurs, souhaitable de soumettre dans les plus brefs délais, une demande de modification de l'information dans les pays de l'Union Européenne où le benfluorex est autorisé, afin de compléter et d'harmoniser le Résumé des Caractéristiques du produit.
Ces modifications concernent les rubriques 4.3 « contre-indications », 4.4 « mises en garde et précautions d'emploi » et 4.8 « effets indésirables » :

- *4.3 Contre-indications :*
  ajout de « Hypersensibilité au benfluorex ou à l'un des constituants ».
- *4.4 Mises en garde et précautions d'emploi :*
  Ajout de « Le traitement devra être interrompu en cas d'élévation des enzymes hépatiques » et « le benfluorex devra être utilisé avec précautions en cas d'atteintes hépatiques ou de maladies cardio-vasculaires pré-existantes. ».
- *4.8 Effets indésirables :*
  Ajout de « atteintes hépatiques, réactions allergiques incluant des cas de choc anaphylactique, atteintes hématologiques, hypertension, palpitations et confusions ».

En mars 2000, une demande de modification de l'information relative aux réactions allergiques a été déposée en France et dans les autres pays de l'Union Européenne.

Annexe 3-34

M. Wagniart a rencontré récemment les autorités italiennes qui maintiennent leur souhait de mentionner dans le RCP les réactions allergiques, les atteintes hépatiques et les confusions.
En conséquences, les laboratoires Servier envisagent de déposer rapidement un complément à la demande de modification de mars 2000 en proposant l'ajout de « augmentation des enzymes hépatiques, très rares cas d'hépatites » et « confusion ».

Concernant l'étude clinique au long cours, les laboratoires Servier présenteront un projet d'étude lors de la réunion du 30 novembre à l'EMEA dont les principales caractéristiques sont les suivantes :

Etude comparative versus acarbose sur 12 mois, multicentrique (plusieurs pays : France, Italie et éventuellement Espagne). Association des deux traitements chez certains patients.
Sujets diabétiques avec surcharge pondérale : nouveaux diabétiques ou diabétiques sans traitement depuis plus de 12 mois.
Au cours de cette étude : plan de cinétique du benfluorex et de ses métabolites.
Les laboratoires Servier envisage d'utiliser les résultats de cette étude pour la réévaluation de l'ASMR prévue en France dans 3 ans.

En ce qui concerne l'échocardiographie, compte-tenu des critères d'inclusion et d'exclusion (BMI, echogénicité…), une seconde étude serait proposée : étude contrôlée sur 12 mois.

Les autorités espagnoles s'inquiètent depuis quelques mois de l'utilisation croissante de préparations magistrales à base de benfluorex. Il ne s'agirait pas de déconditionnement de la spécialité. La Commission de Pharmacovigilance espagnole se réunissait à ce sujet le 23 novembre.
Les laboratoires Servier sont prêts à proposer une DDL à l'attention des prescripteurs espagnols leur rappelant les indications du benfluorex.

Toutes ces propositions seront de nouveau exposées lors de la réunion du 30 novembre à l'EMEA.

Primary pulmonary hypertension, cardiac valve disorders, draft study protocol

From: IT
Sender:
Date: 29/11/2000

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

G Pimpinella, C Fosset-Martinetti and A Castot hold a meeting with the marketing authorisation holder Servier on 30 November 2000 to discuss outstanding issues on this topic. G Pimpinella reported to the PhVWP that the marketing authorisation holder will submit in January 2001 to Italy and France the draft protocol on a study on efficacy in type II-diabetes in which periodic echocardiography will be foreseen to detect cardiotoxic effects. Italy and France will circulate this to Member States together with a preliminary Assessment Report for consideration, and discussion will take place at the PhVWP in March 2001. G Pimpinella further informed the PhVWP that the marketing authorisation holder intends to submit a Variation Application to change the Summary of Product Characteristics with regard to anaphylactic reactions, hepatotoxicity and confusion.

Proposed Issues for Discussion

BENFLUOREX - Therapeutic indications

France :

Since 1987 (validation of the marketing authorization) :

« - Adjuvant to adequate diet in hypertriglyceridemia. The follow-up of the diet is always requested.
- Adjuvant to diet in asymptomatic diabetes with overweight.
***Note* : the efficacy in primary and secondary prevention of the complications of atherosclerosis has not been proved. »**

In May 1998, the MAH asked an extention of therapeutic indication in type II diabetes.

In December 1999, the opinion of the French advisory board was unfavourable. After appeal procedure, the French advisory board of September 2000* maintains the unfavourable opinion :

« Considering the methodologic flaws of the clinical trial, no conclusion can be made on the hypoglycemic effect of benfluorex versus placebo and benfluorex versus metformin.
The therapeutic indication proposed is :
« - Adjuvant to adequate diet in hypertriglyceridemia.
- Adjuvant to diet in diabetes with overweight.
***Note* : the efficacy in primary and secondary prevention of the complications of atherosclerosis has not been proved. »»»**

****adoption of this draft opinion on 16 November 2000***

BENFLUOREX - Therapeutic indications

Luxembourg :

- **Adjuvant to adequate diet in hypertriglyceridemia. The follow-up of the diet is always requested.**
- **Adjuvant to diet in the symptomatic dibetes with overweight.**

Portugal :

- **In association to diet in the asymptomatic diabetes with overweight.**
- **Isolated or associated endogenous hypercholesterolemia and hypertriglyceridemia in adult.**

Spain :

- **Benfluorex has activity on several factors related to the atherogenic risk.**

1. **Action on the lipidic metabolism :**
   Hypertriglyceridemia, adult hypercholesterolemia, isolated or associated, when cannot be exclusively controlled with dietary measures.
2. **Action on the glucidic metabolism : coadjuvant of the diet in the asymptomatic diabetes with overweight.**
3. **As a complementary action, benfluorex in obese hyperuricemic patients, exerts a decrease in the uricemic levels.**

Italy :

Hyperlipidemia not repondent to the diet only. Adjuvant in the obesity associated with glyco-lipid metabolism modifications.

BENFLUOREX - Patient exposure (Patient-months)

Estimation based on a mean daily dosage of 2.4 tablets per day-Months of 30.4 days

	France	Luxemburg	Portugal	Spain	Italy
Market introduction - Sept 99	27 721 118	30 889	322 658	328 901	3 429 566
Oct 99	226 201	119	627	255	9 813
Nov 99	244 717	49	960	241	9 639
Dec 99	240 211	62	846	227	11 616
Jan 2000	170 009	33	701	260	7 336
Feb 2000	191 371	99	745	245	8 895
Mar 2000	243 258	16	894	448	12 468
Apr 2000	229 631	16	852	778	9 554
May 2000	274 868	115	835	727	12 522
Jun 2000	247 510	62	1 045	950	13 308
Jul 2000	238 342	45	1 055	1 314	24 677
Aug 2000	198 882	66	827	285	648
Sept 2000	254 950	99	991	676	6 131
Total Oct 99 – Sept 2000	2 759 949	781	10 379	6 406	126 606

Annexe 3-36

DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET DES
PRODUITS BIOLOGIQUES
Unité de Pharmacovigilance
C. FOSSET MARTINETTI

Saint-Denis, le 14 décembre 2000

Minutes of the meeting on benfluorex
EMEA – 30 November 2000

Participants : France : Mrs A. CASTOT (vice-chairperson of the PhVWP)
Mrs C. FOSSET MARTINETTI

Italy : Mr G. PIMPINELLA

MAH : Servier : Mrs BESSAC
Mr WAGNIART

Conclusions :

- ***Draft protocol study :***

The MAH has agreed to submit before the end of January 2001, two draft protocols :

- a 12 months multi-center randomized controled study on benfluorex versus acarbose (with probably two groups of 300 patients).
The main criteria of efficacy will be glycosylated hemoglobin. The secondary criteria will be glycemia and serum lipids. In addition, the pharmacokinetic parameters of benfluorex and its main metabolites will be measured.
A measurement of hepatic parameters seems appropriate in both groups because of the risk of hepatotoxicity of acarbose and benfluorex.

- a 12 months study on benfluorex with periodic echocardiographic control (same number of patients as above, anyway, the same patients may be enrolled in both protocols).

These two protocols will be sent to French and Italian rapporteurs and first assessed at national level, before discussion within the PhVWP.

Following the results of the study, Italy intends to review the indications.

- ***Type II variation :***

The MAH has agreed to submit as soon as possible a variation type II in member states where benfluorex is marketed to add in the section 4.8. hepatic disorders, confusion and allergic reactions.

Annexe 3-36

DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET DES
PRODUITS BIOLOGIQUES
Unité de Pharmacovigilance

Saint-Denis, le 2 /07 /01

Study protocol on benfluorex :
« a one-year, multicentre, international, randomised, double-blind comparison of benfluorex and acarbose administered orally for the treatment of type 2 diabetic patients »
ASSESSMENT REPORT

Assessors :
Pr. P. BECHTEL
Dr. J. CARON

I- INTRODUCTION

The therapeutic indications of benfluorex are :
- adjuvant to adequate diet in hypertriglyceridemia,
- adjuvant to diet in diabetes with overweight.

In European Union, benfluorex is currently marketed in France, Luxembourg, Portugal, Spain, Italy and Greece (national procedures).

In September 1998, Italy requested to the CPMP an assessment on safety of benfluorex considering that the pharmacological activities of benfluorex might depend on the metabolic biotransformation to norfenfluramine (active metabolite of fenfluramine).

In November 1999, considering the lack of data, after long term administration (more than 6 months), on efficacy, pharmacokinetic parameters, cardiovascular and neurological effects of benfluorex, Italy (rapporteur) and France (co-rapporteur) requested to the MAH to carry out a long term study with periodic echocardiographic, glycaemic, serum lipids level controls and measurements of pharmacokinetic parameters.

Following a meeting dated 30th November 2000 at the EMEA, the MAH submitted in February 2001 a draft phase III study protocol.

II- PROTOCOL ANALYSIS

3 points are discussed in the introduction :
- risk of hypoglycaemia with sulfonylurea and lactic acidosis with metformin,
- benfluorex and alpha-glucosidase inhibitors have been safely used in clinical practice over several years,
- lack of long term data on the anti-hyperglycaemic efficacy and safety of benfluorex.

II.1- Objectives

The objectives of this phase III study are :

- to investigate the long term efficacy (1 year) of benfluorex versus acarbose in a multicentre, international double blind study. The primary efficacy variable is the evolution from inclusion to the end of the treatment period of glycated haemoglobin level (HbA1c), centrally measured by HPLC. The secondary efficacy variables are fasting plasma glucose levels, fasting serum insulin levels, fasting lipids levels.
- The safety of benfluorex and acarbose will be assessed throughout the 1-year double blind period.
- Population pharmacokinetics will be assessed.

II.2- Study plan

II.2.1- Baseline period (14 days) :

The patient will continue his usual anti-diabetic treatment (if any) until the inclusion visit.
Evaluation of the patient eligibility :
- physical examination and vital signs measurement,
- ECG,
- echocardiography,
- ophtalmologic examination,
- biological examination,
- general records.

II.2.2- Titration period (70 days) :

At D0 : all the patients receive the first randomised treatment.
Dose level 1 : benfluorex : daily dose of 150 mg
acarbose : daily dose of 50 mg

At D14 : all the patients receive dose level 2 : benfluorex : daily dose of 300 mg
acarbose : daily dose of 100 mg

At D28 : the dose level of benfluorex is increased to dose level 3 if fasting plasma glucose level is ≥7.8 mmol/L. All patients in the acarbose group will receive dose level 3.
Dose level 3 : benfluorex : daily dose of 450 mg
acarbose : daily dose of 150 mg

At D70 : the dose level is increased if HbA1c ≥ 6.5% :
dose level 4 : benfluorex : daily dose of 450 mg
acarbose : daily dose of 300 mg.

II.2.3- maintenance period (from D70 to M12) :

4 visits will be performed : M4, M6, M9 et M12.
If the HbA1c value is ≥ 6.5%, the dose level will be increased by one dose level (if the patient is not already receiving dose level 4).

In case of adverse events and/or repeated hypoglycaemic episodes, the dose level can be decreased.
From visit M6, if the patient is already receiving dose level 4 and HbA1c value is > 8%, an antidiabetic drug with a different mode of action can be added (to be discussed by Servier).

II.3- Study population

Type 2 diabetic patients aged ≥ 35 years inclusive, suboptimally controlled with diet or low to moderate doses of an oral hypoglycaemic agent in monotherapy. The dietary advice and the oral hypoglycaemic agent dosage should be unchanged since at least 2 months.

The non inclusion criteria and the inclusion criteria are detailed and seem complete. They allow to define an homogeneous patient group with exclusion of well known selection biais.

The criteria for premature discontinuation of treatment are well defined too.

II.4- Efficacy and safety criteria

II.4.1- efficacy :

All the measurements will be analysed by a central laboratory :
HbA1c,
fasting plasma glucose,
fasting serum insuline,
fasting C peptide,
fastmg serum lipids.

II.4.2- acceptability :

Adverse events will be recorded at each visit and must be subject to medical follow-up and suitably documented.
A full physical examination will be performed at baseline, M4 and M12.
An ECG and an echocardiography will be performed at baseline, M6 and M12.
Laboratory examination will be performed at baseline, D70, M6 and M12.

II.4.3- Pharmacokinetic parameters of benfluorex and metabolites (S422, S1475 and S585):

Measurement of plasma concentration of benfluorex and metabolites will be performed two times during the afternoon (14 :00 and 18 :00) at D28, D70, M4, M6, M9 and M12.
Moreover, two alternatives are proposed :
- a pharmacokinetic assessment performed over 24 hours at M6 in a subgroup of forty patients recruited in two to four centers,
or
- 24 hour pharmacokinetic assessment performed in a specific open label study carried out in parrallel in twenty patients treated with benfluorex.

A population pharmacokinetic analysis will be performed using the NONMEM software version 5.1.

II.5- Sample size

297 subjects per group are necessary to show a non-inferiority between groups if the real difference is null with a 90% power. Taking into account the number of tretaments groups and the rate of drope-out patients, the total sample size required for the study is 684 patients.

The total number has been set at 700 patients (two groups of 350 patients).

II.6- Appendices

The draft protocol encloses 5 appendices :
- diagnosis and classification of diabetes mellitus,
- chronic heart failure classification,
- concomitant treatments allowed and not allowed,
- Cockroft and Gault formula,
- echocardiography procedure.

III- ASSESSORS COMMENTS AND CONCLUSION

The assessors are agree with the MAH proposal. This protocol will probably help to answer to the following points :
- long term efficacy,
- long term security,
- pharmacokinetic parameters.

However, assessors have some comments :
- The pharmacokinetic study performed over 24 hours must be done two times (M6 and M12 for example) in the subgroup of forty patients included in the study. Such a study could allow to discover a link between adverse reactions reported and pharmacokinetic of benfluorex and metabolites. A specific open label pharmacokinetic study in parallel would be less informative.
- The three echocardiographic evaluation (baseline, M6 and M12) should be performed, for each patient, in a same center and, if possible, by a same evaluator. This point must be mentioned in the protocol study.

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Madame le Docteur Anne CASTOT
Agence Française de Sécurité
Sanitaire des Produits de Santé
143-147 Boulevard Anatole France
93200 SAINT DENIS

Neuilly-sur-Seine, le 1er février 2001

Direction de l'Evaluation du Médicament
et des Produits Biologiques
Département des Vigilances

N/Réf. : IT/dst/01.0105
☎ 01 55 72 65 34
Fax 01 55 72 33 02

Objet : **MEDIATOR® 150 mg, comprimé enrobé**
Dossier VNL 10008

Madame,

Comme convenu lors de la réunion de pharmacovigilance à l'EMEA en date du 30 novembre 2000, nous vous adressons, ci-joint, pour notre spécialité **MEDIATOR® 150 mg**, comprimé enrobé, le synopsis du protocole d'étude intitulé :

« A one-year, multicentre, international, randomised, double-blind comparison of Benfluorex (150mg to 450mg daily) and Acarbose (150mg to 300mg daily) administered orally for the treatment of type 2 diabetic patients »

Ce synopsis de protocole d'étude d'efficacité de Benfluorex versus Acarbose sur 12 mois inclut également l'étude écho-cardiographique souhaitée.

Nous vous prions de croire, Madame, à l'expression de nos salutations distinguées.

Pierre MONTES
Directeur des Affaires Pharmaceutiques France
Pharmacien Responsable Intérimaire

Mme Carole FOSSET-MARTINETTI
Unité de Pharmacovigilance

Annexe 3-37

S 780
(benfluorex)

STUDY PROTOCOL

Protocol N°:

A ONE-YEAR, MULTICENTRE, *INTERNATIONAL*, RANDOMISED, DOUBLE-BLIND COMPARISON OF BENFLUOREX (150 TO 450 MG DAILY) AND ACARBOSE (150 MG TO 300 MG DAILY) ADMINISTERED ORALLY FOR THE TREATMENT OF TYPE 2 DIABETIC PATIENTS

DRAFT

Coordinator	:	*Prof.*
Director of the Therapeutic Research Department	:	*Dr L. BESSAC*

CONFIDENTIAL

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3. INTRODUCTION

Type 2 diabetes mellitus is characterised by abnormalities of insulin secretion and reduced response to insulin in its target tissues.[1] The early pathogenetic events are still poorly understood. Several studies have however indicated that insulin resistance plays a role in impaired glucose tolerance and type 2 diabetes mellitus.[2-4] Therefore, a treatment that improves insulin action is part of a rationale therapy of type 2 diabetes, when dietary measures and exercise are not sufficient to provide adequate blood glucose control.

One of the major concerns in the treatment of diabetes is the risk of hypoglycaemia while attempting to control plasma glucose. This is particularly true in the elderly population: the main causes of drug-induced mortality in patients with diabetes mellitus are insulin- and/or sulfonylurea- induced hypoglycaemia,[5-6] and metformin associated lactic acidosis.[7]

Drugs which are not associated with hypoglycaemia and/or lactic acidosis, and which have been safely used in clinical practice over several years, are benfluorex and alpha-glucosidase inhibitors:

- Benfluorex is an agent that possesses both anti-hyperglycaemic and hypolipidaemic properties. Its main action in diabetic patients is to improve insulin sensitivity, as demonstrated in 3 double-blind, placebo-controlled studies using the euglycaemic [8,9] or the isoglycaemic [10] clamp technique. Its mode of action is different from that of metformin or thiazolidinediones. It encompasses a direct effect on the liver (decrease in the activity and gene expression of key enzymes involved in the hepatic metabolism of glucose and free fatty acids) and an indirect effect on the muscle through a decrease in triglycerides influx.[11-18]

- Alpha-glucosidase inhibitors (e.g. acarbose, miglitol) reduce or delay carbohydrate digestion by competitive enzyme inhibition at the ciliate border of the small intestine. Because of their mechanism of action, these drugs act mainly on the post-prandial hyperglycaemia and they do not induce hypoglycaemia. The most common adverse effect of these drugs is abdominal discomfort associated with flatulence and diarrhoea which occurs in approximately 50% of patients, but tend to recede over time.[19]

We currently lack long-term data on the anti-hyperglycaemic efficacy of benfluorex. Most data originate from double-blind placebo-controlled trials of 3-month duration in various populations of type 2 diabetic patients: as single oral antidiabetic therapy in newly-diagnosed patients,[20] and as combination therapy in patients poorly controlled with sulphonylurea or metformine alone [21-22] or with insulin.[23-25] A 6-month study was carried out in 722 type 2 diabetic patients still suboptimally controlled after 2 months of diet under the supervision of a dietician (benfluorex vs metformin vs placebo). It showed a significant decrease in HbA1c with benfluorex and metformin, whereas blood glucose control deteriorated in the placebo group. However, this study, which began in 1996, did not follow the recent recommendations for the treatment of type 2 diabetes, i.e. drug treatment when HbA1c is over 6.5%, and a part of the population was below this limit. Furthermore, it did not include elderly patients nor patients with impaired renal function, due to precautions regarding the use of metformin. Therefore, it is difficult to extend its conclusion to the general diabetic population.

The data should therefore be confirmed in a large population of type 2 diabetic patients over 1 year. The primary objective of the present phase III study is to investigate the **long-term efficacy** of benfluorex in a population of type 2 diabetic patients suboptimally controlled with diet alone or low to

moderate doses of oral hypoglycaemic agents, in comparison to acarbose. The current therapeutic recommendations for type 2 diabetes will be closely followed.

Another objective is to assess the **long term safety** of benfluorex. The other agents acting on the peripheral action of insulin have quite extensive precautions for use:

- Metformin is contra-indicated in situations associated with a risk of hypoxia (*e.g.* cardiac or respiratory insufficiency, recent myocardial infarction) and in patients with altered renal function (creatinine level ≥ 135 µmol/L in men and ≥ 110 µmol/L in women, or less in case of reduced muscle mass), both situations rather frequent in type 2 diabetic patients, notably in the elderly, who represent 35 to 50% of diabetic patients.[26, 27] They are linked to an increased risk of lactic acidosis.

- Thiazolidinediones are contraindicated in patients with any degree of cardiac failure or history of cardiac failure (NYHA stages I to IV) and in patients with hepatic impairment. They can cause fluid retention which may exacerbate or precipitate heart failure; this has been reported more frequently in patients with a history of heart failure, in elderly patients, and in patients with mild or moderate renal failure, and the risk of oedema is increased with concomitant administration of NSAID. Thiazolidinediones are also associated with a reduction of haemoglobin levels, with an increased risk of anaemia in patients with low haemoglobin levels. Finally, they are contraindicated in patients with hepatic impairment; there have been rare reports of hepatocellular dysfunction with the more recent thiazolidinediones.

Benfluorex has no contra-indication other than chronic pancreatitis. No specific safety concern has been raised in the clinical trials to date, nor in the periodic safety reports (since its market introduction, benfluorex has been used over more than 25 million patient-months). The aim of this study is to assess the long term safety of benfluorex in the context of a clinical trial, in a population representative of type 2 diabetic patients, including elderly patients and patients with altered renal function. A full assessment of the safety profile of benfluorex will be carried out, including echocardiography, in order to have a comprehensive dossier in a setting close to the reality of clinical practice.

Finally, population kinetics will be assessed in this population that should include patients of various age and degree of renal function, and with various patterns of concomitant treatment.

4. OBJECTIVES

The primary objective is to **assess the efficacy of benfluorex compared to acarbose**, both medications being administered in optimal dosages for the treatment of type 2 diabetic patients.
The secondary objective is to assess the safety of benfluorex compared to acarbose

- The primary efficacy variable is the evolution **from inclusion to the end of the treatment period of glycated haemoglobin level (HbA1c), centrally measured by HPLC.**

- Secondary efficacy variables are:
  1. fasting plasma glucose levels,
  2. fasting serum insulin levels,
  3. fasting lipids (total cholesterol, HDL- and calculated LDL-cholesterol, triglycerides) levels.

- The safety of benfluorex will be assessed in comparison with acarbose throughout the 1-year double blind period.

- Population pharmacokinetics will also be assessed.

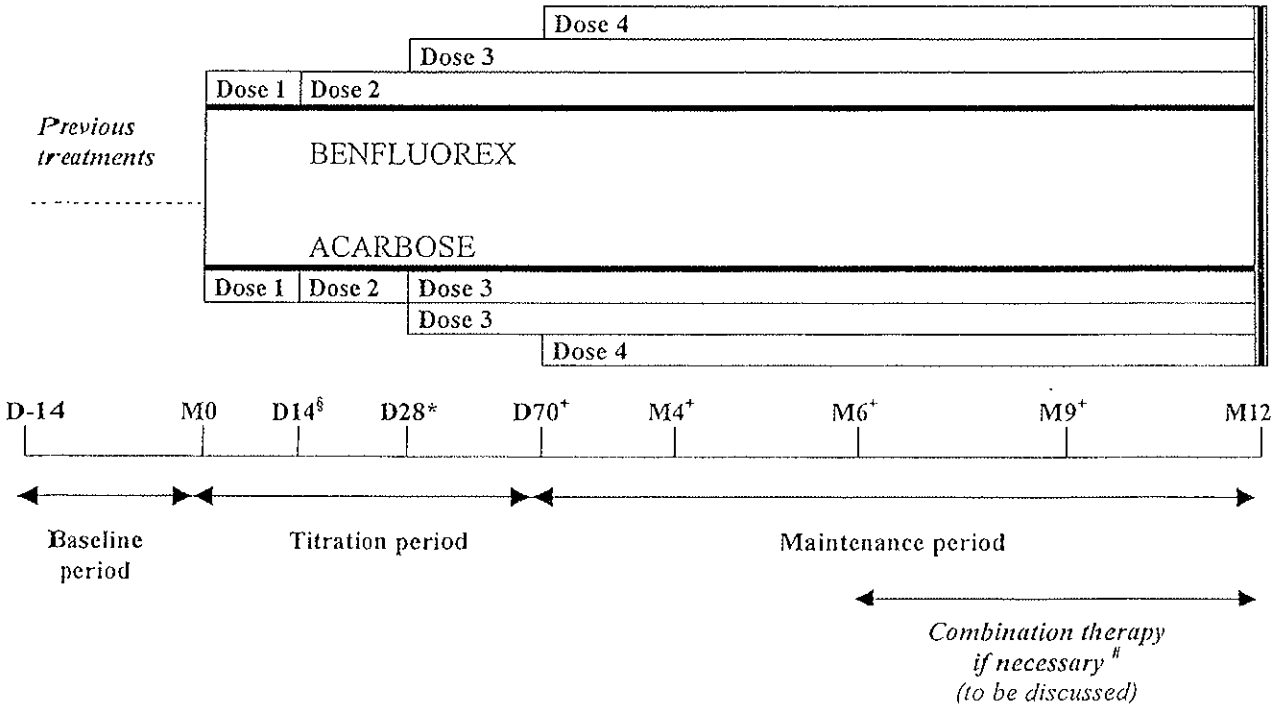
5. STUDY PLAN

5.1 Description of study plan

The study plan is shown in figure 1.

Figure 1: Study plan

Time unit: D =Day, M = Month.



§ dose level increase for all patients at D14.

* dose level increase by one step if FPG is ≥ 7,8 mmol/L at D28, all patients in the acarbose group will actually receive dose 3 whatever the FPG level (in a blinded manner: doses will not be identified on the treatment boxes).

\+ dose level increase by one step if HbA1c ≥ 6.5% from D70 (from M4: if the patient is not already receiving dose level 4).

\# *(from M6, possibility to add another agent if HbA1c > 8% and the study drug has been given at maximal dosage since at least 2 months : TO BE DISCUSSED)*

This is a prospective, multinational, multicentre, randomised, double blind comparative clinical phase III study with therapeutic benefit.

The study will be performed in **700 type 2 diabetic out patients** (350 patients in each group).

The following treatments will be given :

- **benfluorex** at the daily doses of 150 mg (dose level 1), 300 mg (dose level 2) and 450 mg (dose levels 3 and 4);
- **acarbose** at daily doses of 50 mg (dose level 1), 100 mg (dose level 2), 150 mg (dose level 3), and 300 mg (dose level 4).

If the eligibility is confirmed (inclusion = M0), the patient will start a **12-month double blind period** including a **70 day titration period** during which the doses of benfluorex and acarbose will be up-titrated to optimal dosage according to the fasting plasma glucose value value (at day 28) and the HbA1c level (starting from day 70). **The first titration step (from dose level 1 to dose level 2) will be carried out in all patients at day 14.**

A total of 8 clinical visits will be carried out for each patient during the study. The study will proceed as follows (see table 2 for the details of examinations):

- **the selection visit (D-14)** performed within 2 weeks (4 weeks as a maximum) prior to inclusion to inform the patient about the study (written informed consent to be signed) and evaluate his/her eligibility **before prescribing or performing** the examinations required for the study.
  - physical examination and vital signs measurement,
  - ECG 12-lead,
  - echocardiography,
  - ophthalmologic examination (if not performed within 1 year)
  - biological examination: including standard biology, HbA1c, fasting plasma glucose, fasting insulin, fasting lipids (triglycerides, total cholesterol, HDL-cholesterol, calculated LDL), creatinine level (clearance calculated with the Cockroft and Gault formula).
  - general records (demography, life style, medical history, concomitant medications).

  The patient will continue his/her usual anti-diabetic treatment (if any) until the inclusion visit.

- **the inclusion visit (M0)** to confirm the eligibility of the patients by checking all the clinical and biological data prescribed at the selection visit as well as the use of concomitant medications. The eligible patient will then have a baseline clinical assessment (physical examination, vital signs measurement). **All the patients will receive the first randomised treatment (dose level 1)** instead of their usual OHA (if any), concomitantly to reinforced advice on diet and physical exercise.

During the **titration period** 2 visits will be performed:

- **visit D28** will be performed 28 days after M0 [acceptable margin of days (-5; +8)]
- **visit D70** will be performed 70 days after M0 [acceptable margin of days (-7; +10)]

During the **maintenance period** 4 visits will be performed:

- **visit M4** will be performed 4 months after M0 [acceptable margin of days (-10; +14)]
- **visit M6** will be performed 6 months after M0 [acceptable margin of days (-14; +21)]
- **visit M9** will be performed 3 months after M6 [acceptable margin of days (-21; +21)]
- **visit M12** will be performed 6 months after M6 [acceptable margin of days (-21; +21)]

5.2 Definition of the study population

5.2.1 Selection criteria

Some of the examinations such as centrally analysed metabolic parameters, standard biology, echocardiography and the 12-lead ECG (and the ophthalmologic examination -if not performed within 1 year) will be prescribed at the selection visit. The results of these examinations must be available at the **inclusion visit in order to determine the eligibility of patients.**

The eligible patients will be **type 2 diabetic patients suboptimally controlled with diet or low to moderate doses of an oral hypoglycaemic agent.** The population will be stratified on the triglycerides level at baseline (≤ or > 2.3 mmol/L).

5.2.1.1 Demographic and ethnic characteristics

- patients **aged ≥ 35 years** inclusive,

5.2.1.2 Characteristics of type 2 diabetes

- Type 2 diabetes diagnosed as published by the WHO in 1999 (see appendix 1),
- Patients currently treated with either: **diet alone or OHA in monotherapy at low or moderate doses**, the dietary advice and the OHA dosage being unchanged since at least 2 months,
- Patients previously treated by the following daily OHA doses will be eligible in the study:

Previous treatment	Maximal admitted daily dosage at inclusion
Gliclazide	160 mg
Glibenclamide	10 mg
Glimepiride	4 mg
Glipizide	10 mg
Glipizide GITS	10 mg
Repaglinide	6 mg
Metformin	1000 mg

(thiazolidinediones and nateglinide will be added if become available before the start of the study)

Patients previously treated by alpha-glucosidase inhibitors or benfluorex at non-maximal dosage can be included:

Previous treatment	Maximal admitted daily dosage at inclusion
Acarbose	150 mg
Benfluorex	300 mg
Miglitol	150 mg

- with no severe diabetic complications (see non selection criteria).

5.2.1.3 Clinical examination

- in relative good health,
- BMI ≤ 37 kg/m^2,

5.2.1.4 Informed consent

- having freely given their written informed consent to participate in the study,
- agreeing to attend the scheduled examinations,

5.2.2 Non selection criteria

5.2.2.1 Related to diabetes

- type 1 diabetes,
- history of diabetes ketoacidosis, with or without coma,
- type 2 diabetes currently treated with more than 1 OHA or OHA at high doses,
- type 2 diabetes currently treated with insulin,
- any expected indication of chronic insulin treatment during the study,
- recent metabolic impairment due to an inter-current illness, an infection or surgery within the last 2 months.

5.2.2.2 Related to concomitant diseases

Any recent, unstable, uncontrolled concomitant pathology that could interfere with the conduct of the study or the pharmacodynamic evaluation:

- retinopathy with neo-vascularisation and/or sight-threatening macular oedema (fundus examination performed within 1 year),
- any unstable or recent macrovascular complications such as unstable angina, myocardial infarction or cerebral stroke within the last 6 months,
- any coronary re-vascularisation procedure (angioplasty, stent, bypass) within the last 6 months,
- high blood pressure levels: sitting systolic blood pressure ≥ 160 mm Hg and/or sitting diastolic blood pressure ≥ 100 mm Hg, with or without treatment. This is not a strict non selection criterion; it must be carefully checked at inclusion: if blood pressure levels are still over the limit, then the patient must not be included,
- chronic hepatic failure such as cirrhosis,
- acute or chronic conditions, apart from diabetes, that would compromise end-point evaluation into the long-term follow-up, e.g. all factors/diseases that interfere with the HbA1c analysis (serious anaemia, haemoglobinopathy, haemolysis, blood donor in the previous 12 weeks),
- any severe concurrent illness that would limit life expectancy or require prohibited treatments.

5.2.2.3 Related to the patient

- pregnancy, breastfeeding or possibility of becoming pregnant during the study without adeqaute contraception (intra-uterine device, oral contraception, barrier contraception could be acceptable if judged adequate by the investigator).
- drug and/or alcohol abuse,

- participation in another study at the same time or within 3 months prior to selection
- unlikely to cooperate in the study,

5.2.2.4 Related to benfluorex treatment

- known hypersensitivity to benfluorex or any of the excipients (the benfluorex monography will be available in the appendices),
- chronic pancreatitis,

5.2.2.5 Related to acarbose treatment

- known hypersensitivity to acarbose or any of the excipients (the acarbose monography will be available in the appendices),
- inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or patient predisposed to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption, patient who suffer from states which may deteriorate as a result of increased gas formation in the intestine, e.g. large hernias,
- creatinine clearance of <25ml/min/1.73 m^2.

5.2.2.6 Related to concomitant treatment (s)

- anticipated need of systemic treatment with corticosteroids for more than 15 days.

A list of authorised and non-authorised concomitant drugs is added in appendix 3.

5.2.2.7 Related to the echocardiography assessment

- poor echogenicity (at least 75% of the endocardial border of the left ventricle should be seen),
- severe chronic heart failure (grades III & IV of the New York Heart Association classification) (appendix 2),
- valvulopathy that may require surgical treatment during the course of the study (i.e. valve regurgitation ≥ step 3, aortic stenosis with peak gradient > 30 mm Hg or mitral stenosis with mean diastolic gradient > 8 mm Hg),
- chronic lung disease.

5.2.3 Inclusion criteria

The eligibility of the patients will be confirmed if:

- HbA1c value (analysed by the central laboratory) is as follows :

Previous treatment	HbA1c required at inclusion (HPLC method, normal range 4-6%)
Diet alone	≥ 7%
Monotherapy OHA	≤ 8.5 %

- The results of the clinical and biological investigations performed at the selection visit or during the pre-inclusion period are available to determine eligibility,

- The duration of the pre-inclusion period (between selection and inclusion) is not exceeding 1 month,

5.2.4 Non-inclusion criteria

- non-respect of the selection and non-selection criteria after the clinical and biological examinations performed since the selection visit,
- blood pressure above the upper limit (see 5.2.2.) at both the selection and the inclusion visit,
- abnormal liver function tests : serum transaminases > 3 times the upper normal laboratory value; any abnormality of other parameters such as bilirubine, γ glutamyl transferase, alkaline phosphatase could be acceptable for the study if complementary examinations do not indicate the presence of any hepatic pathology and if the abnormality is well documented and stable,
- retinopathy with neo-vascularisation and/or sight-threatening macular oedema (if fundus examination performed between selection and inclusion visit)
- related to acarbose treatment: chronic renal failure, with creatinine clearance < 25 ml/min/1.73 m^2 according to Cockroft and Gault formula (see appendix 4; upper limit value can be lowered if judged necessary by the investigator according to the physiological age of the patient and the muscular mass).

5.2.5 Premature discontinuation of treatment

5.2.5.1. Criteria for premature discontinuation of treatment

Treatment may be prematurely and definitively discontinued for a participant for one of the following reasons :

- **non medical reason** (withdrawal of consent…),
- **major deviation from protocol** (including pregnancy or lactation),
- in case of **major symptoms related to hyperglycaemia** such as rapid weight loss, polyuria – polydipsia, ketonuria, asthenia **confirmed by a fasting plasma glucose value > 15 mmol/l (2.7 g/l)** or, in the absence of symptoms, in case of FPG > 16.5 mmol/L on 2 measurements at least 2 days apart, in both cases **not explained by external factors** (intercurrent disease, modification of diet or physical activity, concomitant treatments). This will be considered as lack of efficacy if it occurs after at least 1 month of treatment at maximal dose level.
- **adverse event** or any condition incompatible with continuation of either treatment according to the investigator. This includes hyperglycaemia not qualified as lack of efficacy (see above).
- **lost to follow-up**: when the investigator has no news of the participant, he/she must make every effort to contact him/her, to establish the reason for the discontinuation of treatment, and to suggest the participant to come to an end-of-study visit. The investigator must document all the efforts made to contact the patient. If all these attempts to contact the participant fail, the investigator can declare the participant "lost to follow-up".

In cases corresponding to the above, the study treatment will be stopped and the investigator will be responsible to take all the appropriate therapeutic measures to ensure blood glucose control.

5.2.5.2. Procedure

(will be detailed in the final draft)

5.3 Study treatments

5.3.1 Treatments administered and treatment adaptation

The randomisation will be balanced (350 patients in each group) and global for all the participating countries.

Throughout the study the patients will receive one tablet 3 times a day immediately before each of the 3 main meals, with a matching placebo when necessary. The appearance of benfluorex, acarbose and placebo capsules, regardless of their contents, will be identical.

5.3.1.1 Identification of treatments administered

Benfluorex and acarbose active drug and their placebo will be given in three administrations per day: one tablet before each main meal (breakfast, lunch and dinner). During the titration period the doses will be adapted following the instructions described in the section "treatment adaptation".
For **benfluorex** the daily doses at the **4 dose levels** will be 150 mg, 300 mg and 450 mg (dose levels 3 and 4).
For **acarbose** the daily doses at the **4 dose levels** will be 50 mg, 100 mg, 150 mg. and 300 mg

Table 1 : Description of dose levels and administration schedule

	benfluorex			acarbose		
	Morning	Midday	Evening	Morning	Midday	Evening
Dose level 1	placebo	placebo	150 mg	placebo	placebo	50 mg
Dose level 2	150 mg	placebo	150 mg	50 mg	placebo	50 mg
Dose level 3	150 mg	150 mg	150 mg	50 mg	50 mg	50 mg
Dose level 4	150 mg	150 mg	150 mg	100 mg	100 mg	100 mg

5.3.1.2 Dose adaptation

The dose level will be titrated up in order to reach the optimal dosage for both medications.

The initial recommended dosage for acarbose is 50 mg tid. However, in order to avoid gastro-intestinal intolerance, this dosage can be gradually reached. In this study, the dosage of 50 mg tid of acarbose will be gradullay reached over 28 days; the dosage will then be increased to 100 mg tid according to blood glucose control after at least 6 weeks of treatment, as recommended in the monography (will be available in the appendices in the final version of the protocol).

It is recommended to begin treatment with benfluorex (the monography will be available in appendices in the final version of the protocol) at 150 mg per day at dinner, and to increase the dosage every week up to 450 mg per day, and then to decrease the dosage if necessary according to blood glucose control. The dose adaptation schedule recommended for acarbose can be applied to benfluorex, in the context of a 1-year study.

The dose level can also be decreased at any time during the study for tolerance reasons (judgement of the investigator).

- **Titration period (M0-M4)**

  All patients will start the study treatment with dose level 1.

If the overall tolerance is good (judgement of the investigator, mode of contact to be defined (TO BE DISCUSSED) at D+14, the dose level will be increased by one dose level (from dose level 1 to dose level 2).

If the **fasting plasma glucose level at visit D28 is ≥ 7,8 mmol/L**, the dose level will be increased by 1 dose level per visit (if the overall safety is good).

If the **glycated haemoglobin value is ≥ 6.5% at visit D70,** the dose level will be increased by 1 dose level per visit (if the overall safety is good).

- **Maintenance period (M4-M12)**
  If the **HbA1c value is > 6.5%** at the scheduled visits (M4, M6, M9), the dose level will be increased by one dose level (if the patient is not already receiving dose level 4). The dose level can be decreased in case of adverse events and/or repeated hypoglycaemic episodes (judgement of the investigator).
  From visit M6, if the patient is already receiving dose level 4 and HbA1c value is > 8%, an antidiabetic drug with a different mode of action (sulfonylurea?) can be added (TO BE DISCUSSED).

5.3.2 Diet and activities

All the patients will receive counselling about diabetes, nutrition and physical activity before the inclusion visit (M0). Dietary advice will also aim to avoiding as far as possible the gastro-intestinal side effects of acarbose.

5.4 Efficacy and safety criteria

5.4.1 Investigation schedule

The efficacy and safety measurements assessed during the study are described in Table 2.

Table 2: Investigation schedule

	Selection visit	Inclusion visit	Titration period			Maintenance period			
	D-14	M0	D+14	D+28	D+70	M4	M6	M9	M12
Informed consent	X								
Randomisation		X							
GENERAL RECORDS									
Demography, life style, medical history	X								
Titration: - dose level increase if good tolerance - dose level increased if FPG ≥ 7.8 mmol/L - dose level increase if HbA1c ≥ 6.5%			X	X	X	(X)	(X)	(X)	
Diet and exercise instructions		X*				X			
Concomitant medications	X	X		X	X	X	X	X	X
Compliance				X	X	X	X	X	X
ASSESSMENT OF EFFICACY (Central lab)									
HbA1c		X*			X	X	X	X	X
Fasting plasma glucose		X*			X	X	X	X	X
Fasting serum insulin		X*					X		X
Fasting C peptide :		X*							
Fasting serum lipids[°]		X*					X		X
ASSESSMENT OF PHARMACOKINETICS									
Plasma levels of benfluorex and its main metabolites[+]				X	X	X[§]	X	X	X
ASSESSMENT OF ACCEPTABILITY									
Adverse events		X		X	X	X	X	X	X
Vital signs	X	X		X	X	X	X	X	X
Physical examination	X	X°			X	X°	X	X	X°
Ophthalmologic examination		X*#							
ECG 12-leads		X*					X		X
Echocardiography		X					X		X
Creatinine clearance (Cockroft and Gault formula)		X*			X		X	X	X
Standard biology (central lab)θ		X*			X		X		X

* to be done between selection and inclusion (# if not performed within 1 year) - ° Full physical examination
(X) dose level increased by one dose level if the patient is not already receiving dose level 4.

Pharmacokinetics : + including 2 samples in the afternoon among the 6 determinations - § at M6, a subgroup of patients will be hospitalised for a 24h profile

°Lipid parameters= triglycerides, total cholesterol, HDL, calculated LDL. θ Standard biology = biochemistry (total proteins, creatinine, albumin, sodium, potassium, chloride, calcium, total bilirubin, ASAT, ALAT, γ-GT, alkaline phosphatase) & haematology with complete blood cell count.

5.4.2 Assessment of efficacy

All the efficacy laboratory measurements will be analysed by a central laboratory. Sampling must be done within 7 days prior to the visit. Sampling and shipment material will be provided by the central laboratory. The methods for sampling, handling and analysis will be specified in a separated document available prior to the start of the study. The normal laboratory values will be provided by the central laboratory prior to the start of the study and updated if needed during the study, on every laboratory report, normal laboratory ranges will be present.

5.4.3 Assessment of acceptability

At each visit, adverse events will be recorded in the CRF. They will be assessed by questioning the patient, and physical examination including vital signs (sitting systolic and diastolic blood pressure, weight and heart rate). A full physical examination will be performed at Baseline, M4 and M12.

An ECG 12-lead will be performed at Baseline, M6 and M12.

An echocardiography will be performed at Baseline, M6 and M12. The parameters to be measured are detailed in Appendix 5.

Laboratory examinations will be performed at Baseline, D70, M6 and M12.

5.4.4 Adverse events

All adverse events must be subject to medical follow-up and suitably documented.

5.4.5 Determination of plasma concentrations of the product and its major metabolites

Pharmacokinetic assessment will be performed in the patients receiving benfluorex during the titration period at D28 and D70 and during the maintenance period on M4, M6, M9 and M12. These measurements will include plasma concentration of benfluorex, S 422, S 1475 and S 585.

- Amongst the 6 visits, the patients will be asked to come at least two times during the afternoon (14:00-18:00). A single blood sample will be taken during each visit into one tube containing lithium heparin. The clock time of the four previous dosings and the sampling time will be entered into the case report form.
- In a subgroup of forty patients recruited in two to four centres (in order to have around twenty patients receiving benfluorex 2 or 3 times a day), pharmacokinetic assessment will be performed over 24 hours at M6. Patients will be asked to come to the investigation centre at 08:00, with their current therapeutic unit. They will receive their study treatment at approximately 09:00, 13:00 and 20.00. Blood samples will be collected pre-dose and at selected times up to 13 hours: 1, 2, 3, 5, 6, 7, 8, 9, 10, 12, and 13 h after the morning dose. [*An alternative – to be discussed – is to have the 24 hour pharmacokinetic assessment performed in a specific open label study carried out in parallel in twenty patients treated with benfluorex*].

In each case, plasma (2x1 ml) obtained after a 10 min centrifugation at 4°C will be stabilised by adding sodium fluoride and frozen at -20°C until shipment. Plasma samples (2 aliquots) will be sent frozen in dry ice on a regular basis from the centres to the central laboratory for storage and then to the Servier pharmacokinetic department (Servier Research and Development, Fulmer, UK) for analysis. **In order to allow bio-analyses during the study, the blind will be**

maintained by using a validated recording procedure. Methods for sampling, labelling, coding, storage and shipment of samples and assay methods will be given in more detail in an appendix of the final version of the study protocol.

PK parameters

The primary objective of the analysis is to estimate benfluorex, S 422, S 1475 and S 585 pharmacokinetic parameters in type 2 diabetic patients. A population pharmacokinetic analysis will be performed using the NONMEM software version 5.1. (Beal et al., 1992) under the responsibility of C. Laveille (IRIS).

5.5 *Determination of sample size*

The sample size is estimated on the final HbA1c value, for a non-inferiority research between benfluorex and acarbose groups. The sample size is calculated for a one-sided Student's t test at 2.5 % type I error (as an approximation of the model that will be defined in the section "statistical analysis" of the final draft).

For a 1.5 % standard deviation and a 0.4 % clinical equivalence limit, 297 subjects per group are necessary to show a non-inferiority between groups if the real difference is null with a 90% power.

For the research of superiority, the same power is obtained if the real difference is 0.4 % in favour of benfluorex.

Taking into account the number of treatment groups and the rate of dropped-out patients estimated at 15 %, the total sample size required for the study is 684 patients. As it is difficult to precisely estimate the gastro-intestinal intolerance with drugs that might induce withdrawals, the total number has been set at 700 patients.

This number is coherent with the size required to have a relevant evaluation of the safety over one year.

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APPENDICES

Annexe 3-37

Appendix 1

Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation Part 1: Diagnosis and classification of diabetes mellitus

World Health Organization
Department of Noncommunicable Disease Surveillance
Geneva
WHO/NCD/NCS/99.2

Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

	Glucose concentration, mmol l^{-1} (mg dl^{-1})		
	Whole blood		Plasma*
	Venous	Capillary	Venous
Diabetes Mellitus			
Fasting *or*	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
2-h post glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
Impaired Glucose Tolerance (IGT)			
Fasting (if measured) *and*	< 6.1 (< 110) and	< 6.1 (< 110) and	< 7.0 (< 126) and
2-h post glucose load	≥ 6.7 (≥ 120)	≥7.8 (≥ 140)	≥ 7.8 (≥ 140)
Impaired Fasting Glycaemia (IFG)			
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
and (if measured)			
2-h post glucose load	< 6.7 (< 120)	< 7.8 (< 140)	< 7.8 (< 140)

* Corresponding values for capillary plasma are: for Diabetes Mellitus, fasting ≥ 7.0 (≥ 126), 2-h ≥ 12.2 (≥ 220); for Impaired Glucose Tolerance, fasting < 7.0 (< 126) and 2-h ≥ 8.9 (≥ 160) and < 12.2 (< 220); and for Impaired Fasting Glycaemia ≥ 6.1 (≥ 110) and < 7.0 (< 126) and if measured, 2-h < 8.9 (<160).

For epidemiological or population screening purposes, the fasting or 2- value after 75 g oral glucose may be used alone. **For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms.**

Glucose concentrations should not be determined on serum unless red cells are immediately removed, otherwise glycolysis will result in an unpredictable underestimation of the true concentrations. It should be stressed that glucose preservatives do not totally prevent glucolysis. If whole blood is used, the sample should be kept at 0-4 °C or centrifuged immediately, or assayed immediately.

Appendix 2

Chronic heart failure classification (NYHA)

The American Journal of Cardiology, January 21, 1999

Class I	Patients without symptoms or only at levels that would produce symptoms in normal individuals
Class II	Patients with symptoms on ordinary exertion
Class III	Patients with symptoms on less than ordinary exertion
Class IV	Patients with symptoms at rest

Appendix 3

Concomitant treatments

DRUGS NOT ALLOWED

- *Sulfonylureas (TO BE DISCUSSED after M6)*
- Short acting insulin secretagogues (such as repaglinide)
- Biguanides
- α-glucosidase inhibitors
- Thiaziolidinediones
- Anti bacterial sulfonamides
- Insulin (chronic treatment) / see "Drugs allowed in episodic case" below
- Corticosteroid (chronic treatment) / see "Drugs allowed in episodic case" below

DRUGS ONLY ALLOWED IN CHRONIC USE

Usual concomitant medications are authorized if resulting in a well controlled and stabilized pathology. Their dosage should remain stable throughout the study as far as possible.

DRUGS ONLY ALLOWED IN EPISODIC USE

Episodic use in exceptional cases

- Insulin for short term treatment (≤ 3 weeks – TO BE DISCUSSED) if the treatment takes place more than 1 month before the evaluation visits
- Oral and injected corticosteroids for short term treatment (≤ 2 weeks – TO BE DISCUSSED) if the treatment takes place more than 1 month before the evaluation visits

Appendix 4

Creatinine clearance (Cockroft and Gault formula).

$$C(ml/mm) = \frac{140\text{-age (years)} \times \text{weight (kg)} \times K}{\text{Creatinine } (\mu mol/l)}$$

K = 1,25 for man and 1 for woman.

Appendix 5

Echocardiography

(to be adapted and finalised by the centre in charge of central reading)

Measurements will be undertaken once the patient has been rested for 10 minutes in a supine position. For the echocardiography, patients will be placed in left lateral decubitus position.

The required views for recording are:
- parasternal long axis view,
- parasternal short axis view at the level of:
  - mitral valve,
  - papillary muscle,
  - apex,
- apical four-chamber view,
- apical two-chamber view.

In parasternal long axis view, M-mode recording should be performed with maximally perpendicular cursor position. It cannot exceed 20 degrees at time base run 50 mm/s.

In the apical four-chamber view, mitral flow will be recorded using Doppler pulse wave. The sample volume should be 5 mm.

All 2D echocardiograms, M-mode and Doppler records must contain 10 heart cycles. The M-mode and Doppler recordings should be recorded initially with D image monitoring (5 cycles) with the screen divided into 1/3 and 2/3, and then the 10 heart cycles of M-mode and Doppler in full-screen mode.

- Fractional shortening (M-mode recordings): the parasternal short axis window and the papillary muscle level short axis transthoracic view will be used to obtain end-diastolic left ventricular internal dimension (LVEDd) and end systolic left ventricular dimensions (LVEDs). The fractional shortening (FS) will be calculated as:

$$FS\ \% = [(LVEDd - LVEDs) / LVEDd \times 100\%]$$

- Ejection fraction (2D echo recordings): the apical window and the long axis transthoracic views will be used to obtain LV (left ventricle) images needed for LV volume calculations. Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) will be calculated according to the modified Simpson's rule approach. Ejection fraction will be calculated as follows:

$$EF\ \% = SV / EDV \times 100\%$$

where stroke volume is $SV = EDV - ESV$

- Mitral regurgitation and aorte regurgitation will be quantified as follows:
  - Presence: color flow
  - Quantification: + to ++++

- Mitral inflow will be recorded using doppler pulse wave in the apical four-chamber view. The following parameters will be measured:
  - Maximal E wave velocity (m/s)
  - Maximal A wave velocity (m/s)
  - E/A wave velocity ratio
  - E wave deceleration time (m/s)
  - Isovolumic Relaxation Time

- Pulmonary artery pressure (PAP) will be recorded as follows:
  - Recording of tricuspid flow at the endapex
  - Calculation of PAP from regurgitant flow with the simplified Bernouilly formula:

$$PAPs = 10 + 4 \text{ TR velocity}^2 \text{ (mmHg)}$$

PhVWP

1453 Annexe 3-38

Primary pulmonary hypertension, cardiac valve disorders, draft study protocol

From: IT
Sender:
Date: 06/03/2001

Related issues

Benfluorex - MEDIAXAL, LIPOPHORAL, MEDIATOR (anorectic and hypolipidemic agents) - Investigation of possible safety issue (i.e. structure-related toxicity similar to fenfluramine which is subject to Article 15a Referral) like pulmonary hypertension, cardiac valve disorders
EPITT Reference: 20

Adpoted Minutes

Following the update provided in November 2000, G Pimpinella informed the PhVWP that the marketing authorisation holder submitted the draft study protocol only recently and that the Assessment Report will be circulated for discussion in June 2001. A Castot explained that the circulation of an Assessment Report on the indications is not considered necessary since there will be no change to the indications authorised in France.

Proposed Issues for Discussion

Annexe 3-39

Docteur Pierre BECHTEL

Professeur Emérite de Pharmacologie Clinique
Faculté de Médecine de Besançon

Besançon, le 13 05 2001,

Dr. Carmen KREFT-JAIS,
chef de l'Unité
de
Pharmacovigilance

Chère Carmen,

Ci-joint mon rapport sur le protocole Beaufour.

Je l'envoie par fax et par courrier avec la déclaration publique d'intérêts remplie.

Avec mon plus cordial souvenir et toute mon amitié.

32 rue de Dole -25000 BESANCON

Annexe 3-39

Docteur Pierre BECHTEL

Professeur Emérite de Pharmacologie Clinique
Faculté de Médecine de Besançon

RAPPORT CONCERNANT LE PROTOCOLE S 780 (*Benfluorex*)

A one year, multicentre, international, randomised, double blind comparison of *Benfluorex* (150 mg to 450 mg daily) and *acarbose* (150 mg to 300 mg daily) administered orally for the treatment of type 2 diabetic patients.

Préparé et présenté par les Laboratoires SERVIER
(Dr L. BESSAC Directeur du Département de Recherche Thérapeutique).

Documents fournis :

- un protocole (présenté comme un avant projet)
- une lettre de l'AFSSAPS du 22 novembre 1999, N° 3597, adressée au pharmacien responsable des Laboratoires SERVIER.

ANALYSE DU PROTOCOLE

A- Dans l'introduction qui est un résumé des prérequis, l'accent est mis sur 3 points :

- les risques des antidiabétiques oraux usuels (hypoglycémie, acidose lactique) dans le traitement des diabètes de type 2.
- L'intérêt que pourrait présenter dans ces cas le *Benfluorex*., avec des propriétés hypolipémiantes associées à l'action anti-hyperglycémique
- L'absence de données sur l'utilisation au long cours de *Benfluorex* (activité thérapeutique et pharmacovigilance) sur une population présentant un diabète de type 2, comprenant des sujets jeunes, d'âges moyens, des sujets âgés, des sujets ayant des modifications de la fonction rénale.

B- <u>Objectifs de la recherche</u>

B1- Evaluer l'efficacité au long cours (1 an) de *Benfluorex* comparée à celle de l'*Acarbose* dans une étude en double insu, multicentrique, internationale.
Cette efficacité sera jugée sur l'évolution, de la phase d'inclusion à la fin de l'étude, du niveau de l'hémoglobine glyquée (HbA1C) mesurée de façon centralisée par CLHP.

Seront également vérifiés :

- la glycémie à jeun
- le niveau d'insulinémie à jeun
- le bilan lipidique à jeun (cholestérol total, LDL-cholestérol, triglycérides)

B2- La pharmacovigilance de *Benfluorex* et d'*Acarbose* sera suivie tout au long de l'étude.

B3-La pharmacocinétique de ***Benfluorex*** sera déterminée en utilisant la Pharmacocinétique de Population.

C- <u>Plan de l'étude</u>

3 périodes sont prévues :

C1- Période d'inclusion et d'évaluation de l'état de base des malades : 14 jours.

Le malade continue son traitement habituel au cours de visites comprenant :

- examen physique
- anamnèse
- ECG
- échocardiographie
- visite ophtalmologique
- biologie standard

permettent en fonction de critères d'inclusion et de non inclusion pertinents, de déclarer les malades éligibles ou non.

C2 - Période de titration (J0 - J70)

La randomisation faite, les présentations de *Benfluorex* - *Acarbose* et placébo étant identiques, tous les malades lors de la visite d'inclusion reçoivent à la place de leur traitement usuel, le traitement en évaluation : **Niveau 1** : *Benfluorex* : 150 mg par jour
Acarbose : 50 mg par jour.

A J14 tous les malades passent au **Niveau 2 :** *Benfluorex* : 300 mg par jour
Acarbose : 100 mg par jour.

A J28 une première visite permet en fonction du niveau de glycémie à jeun (> 7,8 mmole/L) d'augmenter la dose de *Benfluorex* d'un niveau : **Niveau 3** : 450 mg par jour, ou de rester au niveau 2.
Pour Acarbose, quel que soit le niveau de la glycémie à jeun, il reçoit le niveau 3 soit 150 mg/jour.
<u>Note</u> : Le double insu est prévu de telle façon que cette procédure puisse être suivie sans rupture du double insu.

A J70 si HbA1C ≥ 6,5 % , passage au **Niveau 4** soit : *Benfluorex* : 450 mg/jour
Acarbose : 300 mg/jour.

C3 - Période d'entretien M4 → M12

4 visites sont prévues durant cette période : M4 - M6 - M9 - M12.
Lors de ces visites, en fonction du niveau de l'HbA1C :

si ≥ 6,5 % on augmente la posologie d'1 niveau
si ≤ 6,5 % on baisse d'un niveau
si ≥ 8 % et que le malade reçoit le niveau 4, on peut ajouter un antidiabétique oral dont le choix n'est pas établi en l'état du protocole.

Note : Devant tout effet indésirable apparaissant au cours de l'essai, l'investigateur est laissé libre, sans rupture du double insu, de modifier le niveau du traitement.

D- Population étudiée

Malades de plus de 35 ans, présentant un diabète de type 2 contrôle de façon « suboptimale » par le régime ou des doses faibles à modérées d'un antidiabétique oral, utilisé en monothérapie , stable depuis 2 mois.

Les éléments permettant d'inclure dans ou d'exclure de l'étude les malades, sont détaillés et apparaissent complets. Ils permettent de définir un groupe de malades homogène avec élimination des biais de sélection connus.

Les conditions de retraits de l'étude en cours sont également bien définis.

E- Procédures

E1- Efficacité : les mesures biologiques seront effectuées dans un seul laboratoire.
E2 - Acceptabilité : sera évaluée lors de chaque visite .
l'ECG sera réalisé à M6 et M12
l'échocardiographie à M6 et M12.
E3 - Effets indésirables : tout au long de l'étude
E4 - Pharmacocinétique de *Benfluorex et des métabolites S 422, S 1475 et S 585 :*
A J 28, J 70, M 4, M6 , M 9, M 12. : une mesure des concentrations sanguines de *Benfluorex* et des métabolites cités, sera réalisée à 14 h et 18h.
Les conditions de l'étude proprement dite de Pharmacocinétique ne sont pas encore décidées (tout au moins, au moment où le protocole a été élaboré) :

- soit un sous groupe de 40 malades recrutés dans 2 à 4 centres, sera selectionné.
- soit une étude sur 24 heures sera réalisée sur un groupe de malades traités par *Benfluorex* mais ne participant pas à l'étude.

Note : L'analyse de population sera effectuée à l'aide du logiciel NONMEM version 5.1.

F - Taille de l'échantillon

Il est calculé selon les règles. Il comportera 700 malades soit 350 par groupe, en tenant compte des éventuelles sorties d'étude ou perdus de vue .

Annexe 3-39

G - Annexes
Concernent :

- le diagnostic de diabète type 2.
- la classification des défaillances cardiaques du NYHA.
- les traitements concomitants permis et non permis.
- La formule de Cokroft et Gault.
- La procédure d'Echocardiographie.

COMMENTAIRES ET CONCLUSIONS

Malgré les quelques détails qui étaient encore en discussion lorsque ce protocole a été soumis à l'AFSSAPS, il n'y a pas de critiques majeures à apporter. La question posée est claire, les moyens pour y répondre paraissent corrects.

Dans ces conditions ce protocole sera à même de répondre aux questions suivantes posées dans la lettre du 22 novembre 1999 :

- **Efficacité au long cours de *Benfluorex* sur le contrôle de la glycémie et de HbA1C, sur le niveau des lipides sériques.**
- **Effets cardiovasculaires de *Benfluorex* administré au long cours chez l'Homme (Echocardiographie et ECG répétés).**

Par contre, ce protocole ne permettra pas de répondre aux questions suivantes :

- **Effets neurologiques de *Benfluorex* (sauf apparition d'effets indésirables caractérisés et imputables au *Benfluorex*).**
- **Comparaison de l'effet hypolipémiant de *Benfluorex* par rapport aux hypolipémiants classiques (fibrates, statines ...).**
- **Les questions concernant les expérimentations animales.**

ENFIN IL SERAIT SOUHAITABLE QUE L'ETUDE PHARMACOCINETIQUE DE BENFLUOREX ET DES METABOLITES S 422, S 1475 et S 585 SOIT EFFECTUEE SUR UN ECHANTILLON DE 40 MALADES INCLUS DANS L'ETUDE AU MOINS 2 FOIS, PAR EXEMPLE A M6 ET M12, AFIN DE POUVOIR ETABLIR D'EVENTUELLES RELATIONS ENTRE EFFETS INDESIRABLES OBSERVES ET CINETIQUE DU MEDICAMENT ET DE SES METABOLITES. L'INFORMATION DONNEE PAR UNE ETUDE PHARMACOCINETIQUE MENEE SUR UN GROUPE DE MALADES NON INCLUS DANS L'ETUDE SERAIT CERTAINEMENT MOINS INFORMATIVE PAR RAPPORT AUX QUESTIONS POSEES EN TERME DE RISQUES CARDIAQUES ET NEUROLOGIQUES DU MEDICAMENT ET / OU DE SES METABOLITES.

A Besançon, le 14 mai 2001

Annexe 3-40

Subdirección General de Seguridad de Medicamentos
División de Farmacoepidemiología y Farmacovigilancia

agencia española del medicamento

NON-URGENT INFORMATION IN PHARMACOVIGILANCE

Reference:	N° of attachments: 1	Date: 3 October, 2003
FROM: Spain		
TO: FRANCE ITALY EMEA		

SUBJECT:

Brandname(s)[1]: **MODULATOR**

International Non-proprietary Name (INN) or Class[1]: **BENFLUOREX**

Marketing Authorisation Holder: **SERVIER**

REASONS FOR *NON-URGENT INFORMATION*:

This is to inform you about a case of cardiac valvulopathy associated with the use of benfluorex that has occurred in Spain and has been published (enclosed).

In Spain, the MAHolder (Servier) has requested the revocation of the marketing authorisation of modulator, the only medicinal product with benfluorex. Therefore, since april 2003, there is no medicinal product marketed in Spain containing benfluorex.

Best regards

Dr Dolores Montero

INFORMATION REQUESTED: none

Annexe 3-40

Name of person responsible for sending message: Dr Dolores Montero

Annexe 3-41

COPIA

SERVIER

Laboratorios Servier, S.A.

AGENCIA ESPAÑOLA DEL MEDICAMENTO
REGISTRO GENERAL
20 MAR 2003
ENTRADA N.º

AGENCIA ESPAÑOLA DEL MEDICAMENTO
Subdirección General de Medicamentos de Uso Humano
C/ Huertas 75

28014 MADRID

Madrid, 20 de Marzo de 2003

ASUNTO: **MODULATOR (Benfluorex) - Nº Reg.: 54.002**
Revalidación Quinquenal.-

Estimados Srs.:

MODULATOR se autorizó en España el 30 de Junio de 1978, por lo tanto, como es sabido, a esta especialidad le corresponde efectuar su Revalidación Quinquenal en el presente mes de Marzo de 2003.

Sin embargo, Laboratorios Servier no desea proceder a realizar dicha Revalidación Quinquenal y solicita la Extinción de la Autorización de Comercialización.

Las razones que han motivado esta decisión son la siguientes:

1 – BAJO CONSUMO: La demanda por parte de los pacientes de MODULATOR en España es muy baja. De hecho, los pacientes/año tratados con este producto son sólo 1.724.

2 – BAJO RENDIMIENTO INDUSTRIAL: La escasa producción anual de este producto consume demasiados recursos industriales, traduciéndose esto en un alto coste productivo. Además, este hecho dificulta la planificación productiva de nuestra planta farmacéutica de Madrid y la racionalización de la asignación de los recursos industriales de cara a la fabricación de los nuevos productos.

Estos son los motivos por los que MODULATOR carece actualmente de interés comercial. De hecho, sus ventas tan sólo han supuesto un 0,17% de la Cifra de Negocio de Laboratorios Servier en 2002.

En base a lo anteriormente expuesto y a la ausencia de laguna terapéutica por la existencia en el mercado de otras alternativas terapéuticas, como ya hemos explicado solicitamos la **no renovación y extinción de la Autorización de Comercialización** de MODULATOR.

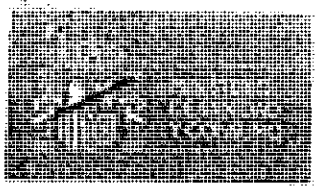
Quedamos a la espera de sus noticias,

Muy atentamente,

Fdo.: PIERRE FARALDO
Director General

DOMICILIO SOCIAL Y LABORATORIO: Avda. de los Madroños, 33 - 28043 Madrid - Telf.: 91 748 96 30* - Fax: 91 300 39 52
FÁBRICA DE PRODUCTOS QUÍMICOS: Calle Jarama, 21 - 45007 Toledo - Telf.: 925 23 12 16 - Fax: 925 23 21 66

Annexe 3-41



agencia española del medicamento

DIRECCIÓN DE LA AGENCIA ESPAÑOLA DEL MEDICAMENTO

07 ABR. 2003

REF.: MUH/GEST/PGL

AGENCIA ESPAÑOLA DEL MEDICAMENTO
SECRETARIA GENERAL
03. ABR 2003
SALIDA Nº 9541

SR. REPRESENTANTE LEGAL DE LABORATORIOS SERVIER, S.A.
...Avda. de los Madroños 33, 28043 Madrid

Fecha: 28/03/03

RESOLUCION POR LA QUE AUTORIZA LA ANULACION DE LA AUTORIZACION DE COMERCIALIZACION DE LA ESPECIALIDAD FARMACEUTICA MODULATOR, nº 54.002

EL DIRECTOR DE LA AGENCIA ESPAÑOLA DEL MEDICAMENTO

Estudiada la solicitud de anulación de autorización de comercialización de la especialidad farmacéutica MODULATOR, nº 54.002

Vistos los preceptos de la Ley 30/1992, de 26 de noviembre, de Régimen Jurídico de las Administraciones Públicas y del Procedimiento Administrativo Común, modificada por la Ley 4/1999, de 13 de enero; la Ley 25/1990, de 20 de diciembre, del Medicamento; el Real Decreto 767/1993, de 21 de mayo, por el que se regula la evaluación, autorización, registro y condiciones de dispensación de especialidades farmacéuticas y otros medicamentos de uso humano fabricados industrialmente; el Real Decreto 520/1999, de 26 de marzo, por el que se aprueba el Estatuto de la Agencia Española del Medicamento, y demás normas aplicables.

RESUELVE:

PRIMERA.- Conceder la anulación de la autorización de comercialización de la especialidad farmacéutica MODULATOR, nº 54.002, solicitada por el Laboratorio LABORATORIOS SERVIER, S.A., de conformidad con lo previsto en el apartado 1º del artículo 90 de la Ley 30/1992, de 26 de noviembre, de Régimen Jurídico de las Administraciones Públicas y del Procedimiento Administrativo Común

CORREO ELECTRÓNICO
sdaem@agemed.es

C/ HUERTAS, 75
28014 MADRID
TEL: 91 596 16 34
FAX: 91 596 44 91

Annexe 3-41

Contra esta Resolución que pone fin a la vía administrativa, puede interponerse potestativamente Recurso de Reposición ante el Director de la Agencia Española del Medicamento en el plazo de un mes, conforme a lo dispuesto en el artículo 116 de la Ley 30/1992, de 26 de noviembre, de Régimen Jurídico de las Administraciones públicas y del Procedimiento Administrativo Común, o interponerse Recurso Contencioso-Administrativo ante el Juzgado Central de lo Contencioso-Administrativo, en el plazo de dos meses a contar desde el día siguiente a la notificación de la presente Resolución, conforme a lo dispuesto en la Ley Reguladora de la Jurisdicción Contencioso-Administrativa de 13 de julio de 1998, sin perjuicio de cualquier otro recurso que pudiera interponerse.

Agencia española del medicamento

Fdo.: Fernando García Alonso

MINISTERIO
DE SANIDAD
Y CONSUMO
Agencia española del
medicamento

Annexe 3-41

Documento consegnato con DG n.1467 del 3 dicembre 2010

dl 03/12

Ministero della Salute

MOD 1-U-C

Ufficio Accettazione e Spedizione della corrispondenza

SERVIER ITALIA S.p.A
Via Luca Passi, 85 – 00166 ROMA

Oggetto dichiarato: **Specialità medicinale MEDIAXAL – 30 confetti 150 mg – AIC n. 23356025**
Domanda di revoca su rinuncia

Alla cortese attenzione Ufficio di Farmacovigilanza – c.a. Dr.ssa V. ~~SABATINI~~

TIMBRO

Ministero della Salute

MOD 1-U-C

Ufficio Accettazione e Spedizione della corrispondenza

SERVIER ITALIA S.p.A
Via Luca Passi, 85 – 00166 ROMA

Oggetto dichiarato: **Specialità medicinale MEDIAXAL – 30 confetti 150 mg – AIC n. 23356025**
Domanda di revoca su rinuncia

Alla cortese attenzione Ufficio V

TIMBRO

Annexe 3-41

SERVIER

CREATIVITÀ NELLA RICERCA

Spett.le
MINISTERO della SALUTE
Direzione Generale della Valutazione dei Medicinali e della Farmacovigilanza
Viale della Civiltà Romana, 7
Roma

Roma, 14 maggio 2003

Alla c.a. Ufficio V

e p.c. Ufficio di Farmacovigilanza

Oggetto: **Specialità medicinale MEDIAXAL – 30 confetti 150 mg – AIC n. 23356025**
Domanda di revoca su rinuncia

La *Servier Italia S.p.A.* con sede in Roma, Via Luca Passi, 85- Codice Fiscale 00701480584 / Partita Iva 00924251002, in persona del Direttore Generale Bernard MILLET, a nome e per conto di *Les Laboratoires Servier* – Neuilly sur Seine (Francia), titolare AIC della specialità medicinale in oggetto, registrata in data 13/12/1980

CHIEDE

la revoca su rinuncia della autorizzazione all'immissione in commercio della specialità medicinale MEDIAXAL 30 confetti 150 mg.
Tale richiesta scaturisce da motivazioni economiche e commerciali.

La scrivente chiede altresì un periodo di 120 giorni per lo smaltimento delle scorte dalla data di pubblicazione del relativo decreto nella G.U.

Con Osservanza.

il Direttore Generale
Dr Bernard MILLET

Annexe 3-41

SERVIER

CREATIVITÀ NELLA RICERCA

AUTOCERTIFICAZIONE

SPECIALITA' MEDICINALE: **MEDIAXAL (benfluorex) – 30 confetti 150 mg – AIC n. 23356025**

TITOLARE AIC: LES LABORATOIRES SERVIER - codice SIS: 0049

La *Servier Italia S.p.A.* con sede in Roma, Via Luca Passi, 85 – Codice Fiscale 00701480584/Partita Iva 00924251002, in persona del procuratore Maria Carla CURIS, a nome e per conto di *Les Laboratoires Servier* (Francia), titolare dell'AIC della specialità medicinale MEDIAXAL

DICHIARA

che la situazione riportata nella "Variazione 3" relativa alla specialità medicinale suddetta, corrisponde esattamente alla situazione autorizzata alla data della presentazione della documentazione.

Roma, 14 maggio 2003

Un Procuratore
Dr.ssa M.Carla CURIS

Annexe 3-41

SCHEDA IDENTIFICAZIONE RICHIESTA VARIAZIONI TIPO II - PRODOTTI MEDICINALI

Medicinal Product - Type II Variation - Identification Form

Azienda titolare o futura titolare A.I.C. - M.A. Holder or Future M.A. Holder Company

LES LABORATOIRES SERVIER

Eventuale Codice SIS
Possible SIS Code
49

Denominazione Commerciale Proposta o Autorizzata - Trade Name of the Medicinal Product

MEDIAXAL

Eventuale Codice AIC Specialità
Possible AIC Code
024256

Confezione - Presentation

MEDIAXAL 30 CONFETTI

Eventuale Codice Confezione
Possible Presentation AIC Code
012

VARIAZIONI TIPO II

B1 - NUOVA CONFEZIONE Modifica Quantità prodotto per Confezione	B2 - NUOVA CONFEZIONE Modifica Accessori Associati al Medicinale	B3 - NUOVA CONFEZIONE Aggiunta/Eliminazione Accessori Associati al Medicinale	B4 - ESTENSIONE AIC Aggiunta Indicazione in una Stessa Area Terapeutica	B14 Nuova Confezione Punti Precedenti in Sostituzione Confezione EsistenteCodice Confezione
B5 - NUOVA CONFEZIONE Modifica Confezionamento Primario (Non di Tipo I)	B6 - ESTENSIONE AIC Modifica Indicazione in una Stessa Area Terapeutica	B7 Modifica Stampati su Richiesta Data	B8 Modifica Regime di Classificazione S.S.N. - Legge 537/93	
B9 Modifica Regime di Fornitura D.L. 539/92 (escluso OTC)	B10 Passaggio ad Automedicazione (OTC)	B11 Riduzione Periodo di Validità	B12 Modifica Stampati su Richiesta Amministrazione	B13 ALTRO

Autorizzato - Present		Modifica Proposta - Proposed Variation	
Modifica Parte I del Dossier Change to Part I Dossier	Volume _____ Pagina _____		
Modifica Parte II del Dossier Change to Part II Dossier	Volume _____ Pagina _____	Aggiornamento Expert Report Expert Report Update	Aggiunta Expert Report Addendum Expert Report
Modifica Parte III del Dossier Change to Part III Dossier	Volume _____ Pagina _____	Aggiornamento Expert Report Expert Report Update	Aggiunta Expert Report Addendum Expert Report
Modifica Parte IV del Dossier Change to Part IV Dossier	Volume _____ Pagina _____	Aggiornamento Expert Report Expert Report Update	Aggiunta Expert Report Addendum Expert Report

RICHIESTA URGENTE - MODIFICA PER MOTIVI SANITARI - Urgent Safety Restriction — SI / NO

Firma di Conferma
Confirmation Sign _____

Altri Tipi Modifiche Proposte

MODIFICA RICHIESTA PER TUTTE LE CONFEZIONI? SI NO

D1 Modifica Titolarità A.I.C. (Vendita)	D2 Modifica Titolarità A.I.C. (Fusione-Incorporazione)	D3 Modifica Titolarità A.I.C. (Scorporo)	D4 Modifica Importatore in Italia (Solo Dato Estero)	D5 Modifica Rappresentante Legale in Italia	D6 Revoca su Rinuncia di A.I.C.	D7 Richiesta Modifica Classificazione ATC
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CODICI CASELLE BARRATE D6

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SPAZIO RISERVATO ALL'UFFICIO

For National Authority

MODULO ACQUISIZIONE DATI TECNICI

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Annexe 3-42

Centre Régional de Pharmacovigilance et d'Information sur le Médicament - Bretagne Occidentale

Centre Hospitalier Régional Universitaire
Bd Tanguy Prigent – 29609 Brest Cedex

Centre Régional de Pharmacovigilance
Service de Pharmacologie

Professeur C. Riché
Directeur du centre

Brest, le 02 janvier 2011

Note concernant le déroulement chronologique des différents comités techniques, commissions et autres évènements en relation avec le MEDIATOR®

Ma présidence a commencé en juillet 1998 pour se terminer en juillet 2001.

Document A-1
Le benfluorex faisait déjà l'objet d'un suivi intensif puisqu'au comité technique de pharmacovigilance du 30 avril 1998, il est rapporté dans le compte-rendu qu'il n'y a pas d'effet de type valvulopathie ou hypertension artérielle pulmonaire, imputable au seul Médiator®, mais compte tenu de la suspicion de détournement d'usage et de la formation, lors de la métabolisation, de norfenfluramine, le comité technique du 30 avril propose la mise en place d'une enquête officielle de pharmacovigilance.
Cette enquête est confiée au CRPV de Besançon et l'Observatoire de la prescription sera consulté, concernant l'usage du benfluorex.

Document A-2 – page 14
Comité technique de pharmacovigilance du 10 septembre 1998 :

Lors de ce comité technique, un point sur le benfluorex Médiator® est présenté par le Centre Régional de Pharmacovigilance de Besançon. Lors de cette présentation, deux aspects sont abordés :
- d'une part, l'évolution des chiffres de vente, avec toujours la suspicion de mésusage
- le problème de la métabolisation du benfluorex (un document en annexe à ce comité technique retrace le métabolisme du benfluorex tel que le laboratoire le décrit). Ce métabolisme fait apparaître la formation de norfenfluramine mais le commentaire (qui est fait à cette époque) est que la présentation ne permet pas d'avoir une idée correcte de ce métabolisme.

Bien que ce point n'apparaisse pas dans le compte rendu, rappelons qu'à cette période, il n'y a toujours pas d'effet indésirable de type valvulopathie ou hypertension artérielle pulmonaire imputable au seul benfluorex décrit.

Document D- 1
Lettre sans date d'émission mais du 21 septembre 1998 en réception, de l'Union Régionale des Caisses d'Assurance-Maladie de l'URCAM de Bourgogne :

Dans cette lettre, l'URCAM de Bourgogne attire l'attention du directeur de l'Agence sur le mésusage du Médiator®.

Document D- 2
Document émanant de la Direction des Etudes et de l'Information pharma-économique : note à l'attention de Jean-Michel Alexandre, Direction de l'Evaluation, concernant les prescriptions de Médiator®, courrier en date du 17 septembre 1998, avec une date de réception du 05 octobre 1998 :

Note : Bien que la date de ce document soit antérieure à celle du précédent il peut être considéré comme une réponse...
Ce document signé par le directeur des études de l'information pharmaco-économique (cf. Document A- 1) dit qu'en conclusion, « il apparaît que le détournement d'usage du Médiator®, s'il existe, ne pourrait être réévalué qu'à l'aide de données beaucoup plus fines et qui font actuellement défaut sur la prescription de ce médicament ».
La teneur globale du rapport tend à démontrer qu'il n'y a pas eu de report sur le Médiator® de la disparition du marché des anorexigènes

Document A-3 – page 19
Comité technique de pharmacovigilance du 22 octobre 1998 :

Ce document est important.

Page 19 : dans la rubrique « point sur la pharmacovigilance européenne » (qui est le compte rendu du groupe de travail de pharmacovigilance de l'Agence européenne des 07 et 08 octobre 1998), il est rapporté que dans le cadre d'un article 15-A, concernant les anorexigènes, l'objectif est la réévaluation du rapport bénéfice / risque d'un certain nombre d'anorexigènes de type amphétaminique. Il est signalé que l'Italie pose le problème du Médiator®, en raison de l'analogie structurale avec la fenfluramine et (l'Italie) craint la survenue de valvulopathie associée à l'utilisation de ce médicament. Ce problème sera discuté au prochain groupe de travail (de pharmacovigilance de l'Agence européenne) des 24 et 25 novembre 1998.

Document A- 4 – page 6
Comité technique de pharmacovigilance du 17 décembre 1998 :

Il est fait un compte-rendu du rapport concernant l'enquête officielle Médiator® présentée par le CRPV de Besançon : bilan des effets indésirables. Il n'est pas fait mention d'effet indésirable de type valvulopathie ou hypertension artérielle pulmonaire.
Concernant le métabolisme, on retrouve les données présentées dans le point fait au comité technique du 10 septembre 1998. Dans ce compte-rendu apparaît le fait que l'Italie propose que le benfluorex soit inclus dans l'article 15-A européen, relatif au fenfluramine, et il apparaît que l'Italie a en charge une enquête sur cette molécule. Le CRPV de Besançon doit d'ailleurs adresser une copie de son rapport à l'Agence italienne qui prépare un rapport pour le groupe de travail de pharmacovigilance européen de février 1999.
Dans le point « pharmacovigilance européenne » de ce même comité technique, il n'est pas fait mention de ce qui a été potentiellement discuté les 24 et 25 novembre 1998, au groupe de travail de pharmacovigilance européenne, tel que c'était annoncé dans le compte-rendu du comité technique du 22 octobre 1998.

Document A- 5 – page 3
Comité technique de pharmacovigilance du 23 février 1999 :

Sous la rubrique « tour de table des cas marquants », le CRPV de Marseille présente un cas d'insuffisance aortique découverte chez un homme de 43 ans, traité par benfluorex depuis six ans (aucune prise

d'anorexigène ou d'amphétamine). Un commentaire est ajouté disant que le « benfluorex qui se métabolise en norfenfluramine fait l'objet d'une discussion au groupe de travail de pharmacovigilance européen. L'Italie qui envisage de saisir le CSP, en vertu de l'article 12, rédige un rapport sur le métabolisme et les données de sécurité de ce produit en collaboration avec la France. Cette notion de prise en charge par l'Europe du problème du Médiator est confirmée par le type de présentation synthétique que l'on rencontre dans la fiche page 22 sous le numéro 99-176 à la date de survenue d'octobre 1988, apparaît pour le Médiator® un effet à type d'insuffisance aortique. Le commentaire, dernière colonne, mentionne : problème Europe - 1er cas.

Document A- 6 – pages 2 – 3 – 13
Comité technique de pharmacovigilance du 12 mai 1999 :

Dans le compte-rendu, présenté le 06 juillet 1999, Monsieur Riché est inscrit absent à la page 2. Il n'y a pas, sur la première page, le nom du président.
Page 3 – 1ère ligne : « la séance a été exceptionnellement présidée par Monsieur le Professeur Claude Larousse ; le professeur Riché était hospitalisé ce jour » (Réanimation cardiologique à Lariboisière pour infarctus).
Page 13, sous la rubrique « point sur la pharmacovigilance européenne » rapportant les travaux du groupe de travail européen de pharmacovigilance des 15 et 16 avril 1999, il existe un paragraphe « anorexigènes et atteinte des valves cardiaques - Article 15 de la Directive 75-319 CE ». Sous ce paragraphe, on rappelle que « l'opinion du CSP concernant les anorexigènes est attendue pour le 20 avril 1999 ». Ceci veut dire que la décision concernant les anorexigènes n'est toujours pas prise par l'Europe.
« Pour la fenfluramine dexfenfluramine, l'opinion sera probablement en faveur d'un retrait définitif des AMM de ces produits. » Il est également dit que « le CSP devrait considérer que les anorexigènes amphétaminiques dont les effets indésirables sont par ailleurs bien connus doivent être retirés du marché ».
Il n'est pas fait mention dans ce compte-rendu, de façon explicite du benfluorex.

Document A- 7 – pages 10 – 11
Comité technique de pharmacovigilance du 22 juin 1999 :

Sous l'intitulé « point sur la pharmacovigilance européenne », est rapporté un compte-rendu du groupe de travail européen de pharmacovigilance des 10 et 11 juin 1999.
Page 10, sous l'intitulé « anorexigènes, article 15 de la Directive 75/319/CEE », il est dit que « des laboratoires ont fait appel à l'opinion du CSP rendue en avril 1999. De ce fait, de nouveaux pays rapporteurs et co-rapporteurs ont été nommés et l'opinion définitive du CSP est attendue pour fin juillet 1999 ». En juin 1999, le problème du retrait définitif des AMM des anorexigènes amphétaminiques n'est toujours pas réglé.
Page 11, dans un paragraphe différent, est abordé le « benfluorex/métabolisation en norfenfluramine. Il est dit que le rapport rédigé par l'Italie, en collaboration avec la France, a été distribué aux Etats » (cette procédure est utilisée pour que les états puissent faire des remarques et apporter des améliorations, modifications au rapport initial).
Une idée est déjà donnée du contenu du rapport : « les données disponibles ne permettant pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex, le groupe de travail a souhaité que les pays rapporteurs (France et Italie) proposent des modifications de RCP et adressent une liste de questions aux laboratoires en demandant une mise à jour des données de tolérance et la réalisation d'une étude de pharmacocinétique du benfluorex et de ses métabolites.
Il est également indiqué qu'un cas d'HTAP, chez une femme de 51 ans, traitée par benfluorex, a été rapporté et qu'il s'agit du premier cas d'HTAP portée avec le benfluorex. (Il existait auparavant d'autres cas, mais toujours en association avec un anorexigène identifié).
Toujours dans le cadre de ce paragraphe relatif aux travaux de l'Agence européenne : il est dit que l'Agence (européenne) a adressé un courrier au Laboratoire Servier, leur demandant de verser avant le 28 juin 1999, une mise à jour des données de tolérance ainsi que les données de pharmacologie et de pharmacocinétique du benfluorex et de ses métabolites.

Document B- 1 – pages 18
Commission nationale de pharmacovigilance du mercredi 07 juillet 1999 : document B - 1 :

Sous la rubrique « questions diverses » sont abordés différents points organisationnels et également des points étudiés au groupe de travail européen.
Un paragraphe est consacré au benfluorex Médiator®. Il est rappelé que le benfluorex a fait l'objet d'une enquête officieuse dès 1995, devenue officielle en 1998 (la différence entre les deux : l'officieuse est un travail purement expertal fait par un Centre Régional de Pharmacovigilance à partir des données à la disposition de l'Agence du médicament ; une enquête officielle implique le laboratoire et impose un échange en respectant des procédures de transparence entre les données détenues par le laboratoire et les données que peut avoir connaissance l'Agence du médicament).
Après ce rappel, il est mentionné que « depuis septembre 1998, à la demande des autorités sanitaires italiennes, le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen ». La raison qui est rappelée c'est « la parenté supposée » encore à cette époque et qui sera démontrée justement dans le rapport italien et « entre le métabolisme du benfluorex et le métabolisme des autres fenfluramines ». Il est rappelé qu'au jour de cette commission, 07 juillet 1999, « les données disponibles issues de l'enquête officielle, ne permettent pas de conclure sur une possibilité de neurotoxicité ou de cardiotoxicité ». Il faut rappeler qu'à cette époque, il n'y a que l'observation de Marseille, de valvulopathie et l'observation d'hypertension artérielle pulmonaire qui vient juste d'être notifiée. Ce cas d'HTAP est d'ailleurs mentionné dans le compte-rendu. Le cas de valvulopathie n'est pas mentionné.
Enfin, en conclusion, il est rappelé que le dossier benfluorex doit être « discuté au groupe de travail européen de pharmacovigilance des 12 et 13 juillet 1999 ».

Commentaires : il faut rappeler que dès cette époque, l'opinion européenne et les actions européennes sont prépondérantes et qu'à partir du moment où un problème est saisi par l'Europe, c'est l'Europe qui pilote ce problème.
Bien que les informations de l'Europe soient partiellement retournées au niveau national, on peut considérer que l'Europe gère correctement ce dossier. Le rapport italien circule. Certes cette information n'est pas faite à la commission nationale mais le rapport est distribué aux états et conduira à une liste de questions, à la demande de réalisation d'un essai et en 2001 à la proposition d'un essai par les laboratoires Servier, essai qui, s'il a été réalisé ou s'il avait été réalisé, aurait vraisemblablement permis de mettre en évidence la faiblesse du bénéfice et le risque du benfluorex.

Document A- 8
Comité technique de pharmacovigilance du 07 septembre 1999 :

Ce compte-rendu est joint à la chronologie pour montrer qu'il n'y a, lors de ce comité technique, aucune information donnée sur le devenir du dossier européen.

Document B- 2
Commission nationale de pharmacovigilance du 21 septembre 1999 :

Lors de cette commission, il n'est pas fait mention, particulièrement du benfluorex mais sous la rubrique « questions diverses » qui retrace les travaux européens, une information extrêmement importante est portée à la connaissance de la commission disant que « le 31 août 1999, le CSP (Comité des Spécialités Pharmaceutiques) a considéré que le rapport bénéfice / risque de l'ensemble des médicaments anorexigènes était négatif et a recommandé leur retrait définitif du marché communautaire. Il est annoncé que cet avis devrait « conduire la commission européenne à prendre une décision de retrait d'AMM pour ces médicaments et que dans l'attente de cette décision, l'Afssaps va procéder, le 19 octobre, à une suspension des autorisations des anorexigènes amphétaminiques. »

Commentaires : si on rapproche l'avis du CSP (31 août 1999) et le délai logique entre l'avis et la décision de la commission européenne puisque c'est la commission qui décide, on voit que ce n'est que fin 1999, qu'une décision ferme est envisagée au niveau de l'Europe concernant les anorexigènes amphétaminiques.
Ceci est à rapprocher du travail effectué et présenté par les Italiens, le 12 octobre 1999, sur le benfluorex.

Dans ce contexte de retrait des anorexigènes amphétaminiques, l'ensemble des experts européens a considéré qu'il y avait lieu de s'interroger sur le bénéfice / risque de ce produit même si des suspicions lourdes pesaient puisque les Italiens apportaient la démonstration que le métabolisme du benfluorex conduisait - comme pour les fenfluraminiques – à la production de norfenfluramine en quantité équivalente. La faiblesse des signaux de pharmacovigilance, basée à cette époque uniquement sur la notification spontanée, l'incertitude sur une efficacité potentielle ont conduit les experts européens d'une part à poser des questions au Laboratoire et à lui demander de réaliser une étude de bénéfice / risque de façon à clarifier ce problème. Certes, a posteriori, on se rend compte que c'est surtout l'absence de signaux qui a retardé la prise de décision. C'est le principe même de la pharmacovigilance française et européenne basée essentiellement sur la signalisation par les praticiens de santé qui est mis en défaut. Ce n'est qu'en 2008, que l'utilisation d'une base de données et d'une interrogation à la fois par mots-clés mais surtout par reconnaissance de chaînes de caractères dans des dossiers qui permettra de faire émerger des observations.

Documents annexes E- 1 et E- 2 :

Pendant ma présidence, j'ai demandé régulièrement, que soit mis à jour un suivi des dossiers présentés en commission nationale de pharmacovigilance.

Lors de la commission nationale du 09 novembre 1999, le récapitulatif des données présentées à la commission nationale ne mentionne pas le benfluorex.

De même dans **la mise à jour du 15 mars 2000**, il n'est pas fait mention non plus du benfluorex.

Commentaires : On peut s'interroger pour savoir pourquoi le benfluorex est aussi peu évoqué dans les commissions nationales. Il est évoqué toujours dans le cadre du travail européen. Cette présentation aurait tendance à confirmer que le benfluorex était considéré comme un travail relevant de l'Europe ; le rôle de la France se limitant à recueillir des données de déclarations spontanées, système dont on peut dire, au vu des connaissances actuelles qu'il n'était pas adapté à ce type de problématique.

Document C- 1
Revised assessment report: Relevance of metabolic pathways of benfluorex to norfenfluramine - 12 octobre 1999

Ce document porte une date manuscrite du 12 octobre 1999. C'est a priori le document final du rapport italien sur le benfluorex.
Le premier point abordé est le métabolisme du benfluorex. Ce document démontre que le benfluorex est métabolisé en norfenfluramine et qu'il y a au moins autant de norfenfluramine circulante après 450 mg par jour de benfluorex qu'après 60 mg par jour de fenfluramine.
Le document rappelle également des données cliniques et que seule une diminution significative de l'hémoglobine glycosylée par rapport au placebo est observée. Les rapporteurs pointent d'ailleurs les insuffisances statistiques du dossier. Pour l'hyperlipidémie il n'y a pas de donnée pour des thérapeutiques supérieures à un mois.
En point 3, ce document parle de l'hypertension artérielle pulmonaire. Il est à faire remarquer qu'il n'est pas fait mention de la valvulopathie de Marseille (sans explication).
Dans les conclusions, les rapporteurs italiens pointent qu'il y a des suspicions que les patients traités sont exposés à un effet potentiellement toxique de norfenfluramine. Ils font remarquer que le produit est moins efficace que la metformine et que l'on manque de données.
Page 4 : il y a une série de questions. On retrouve là ce qui avait été annoncé précédemment. Cette série de questions est adressée au laboratoire.
Ailleurs, il « est demandé une étude supérieure à un an avec des échocardiographies et des suivis montrant l'activité thérapeutique et étudiant les paramètres pharmacocinétiques. De plus, est demandée une modification du RCP. Il est fait mention, dans ce rapport, que l'efficacité peut être discutée au niveau national par les états.

Commentaires sur ce rapport : ce rapport montre clairement l'existence de norfenfluramine. Il montre clairement que l'Europe gère le problème : il y a une liste de questions, les rapporteurs ne parlent pas de retrait mais demandent à la firme de modifier son RCP et surtout de réaliser une étude pour démontrer l'activité et l'innocuité cardiovasculaire du benfluorex en particulier en réalisant une étude échocardiographique.
Ce rapport n'a jamais été communiqué, ni à la commission nationale ni au comité technique.

Document A- 9
Comité technique de pharmacovigilance du 16 novembre 1999 :

Ce comité technique ne fait pas mention du devenir du benfluorex au niveau européen alors que le rapport italien a sûrement été discuté.

Document A- 10 – page 23
Comité technique de pharmacovigilance du 07 décembre 1999 :

Sous la rubrique « point sur la pharmacovigilance européenne – groupe de travail des 23 et 24 novembre 1999 », sous le chapitre « benfluorex – hypertension pulmonaire primitive et valvulopathie », est rapportée cette phrase « il a été demandé à la firme de réaliser une synthèse sur les données d'efficacité du médicament et sur la tolérance pré-clinique et clinique à long terme et de déposer une demande de modification de l'information dans tous les pays où le produit est autorisé.

Commentaires : cette phrase démontre que le problème est certes géré par l'Europe mais ce texte montre également qu'il y a un manque de communication entre la cellule Europe de l'Agence française et les personnes qui travaillent dans cette Agence au niveau national puisque les informations fondamentales contenues dans le rapport italien ne sont pas communiquées dans ce paragraphe qui retrace les travaux du groupe européen. Toutefois, on ne peut pas dire, à partir de ces textes, que ce manque de communication a des conséquences sur le travail des experts européens.

Document A- 11
Comité technique de pharmacovigilance du 19 décembre 2000 :

Ce document est mentionné dans la liste simplement pour montrer qu'à la date du 19 décembre 2000, aucune information sur le benfluorex n'est fournie, dans le paragraphe consacré à la pharmacovigilance européenne.

Document A- 12
Comité technique de pharmacovigilance du 09 janvier 2001 :

Ce document est fourni pour montrer qu'à la date du 09 janvier 2001, aucune information n'est donnée concernant l'étude du benfluorex à l'Europe.

Document C-2
Lettre du 1er février 2001 et protocole

Ce document émanant des laboratoires Servier est adressé à Madame le Docteur Anne Castot, Agence Française de Sécurité Sanitaire des Produits de Santé.
Ce document a été transmis par Madame Carole Fosset, par Madame Rey-Quinio et Monsieur Ropers.
Il est signé de Pierre Montes, directeur des affaires pharmaceutiques France, pharmacien responsable intérimaire.
Ce document est très important.
Il comprend une lettre de couverture et un protocole d'étude clinique.

Dans la lettre, on apprend qu'une réunion sur le Médiator® a eu lieu le 30 novembre 2000, à l'Agence Européenne (EMEA) vraisemblablement entre le Laboratoire Servier et les experts des différents pays européens. On peut déduire qu'était à l'ordre du jour la discussion d'un essai mais que lors de ce premier passage, les experts européens n'ont pas été satisfaits puisque le laboratoire mentionne « que ce synopsis de protocole d'étude d'efficacité du benfluorex versus acarbose inclut l'étude échocardiographique souhaitée ».
Ce document nous apprend également que cette étude est prévue pour une durée de 12 mois.
Lorsque l'on lit le protocole : il s'adresse à 700 patients ; 350 patients dans chaque bras. Il s'agit d'une étude comparative versus acarbose.

Commentaires : ce protocole pourrait être considéré comme l'aboutissement des discussions qui se sont produites à l'Europe suite à la liste de questions et à la demande italienne de réaliser une étude.
Ce protocole comporte 700 patients dont 350 sous Médiator®, certes avec des posologies variables (150 à 450 mg par jour) mais si l'on se rapporte aux données que l'on a, à partir de l'étude Regulate, ce protocole aurait sûrement permis, s'il avait été réalisé, de mettre en évidence d'une part la faible efficacité du produit et d'autre part les risques cardio-vasculaires puisqu'un volet échocardiographique était annexé à ce protocole.
Bien que le comité technique et la commission nationale de pharmacovigilance n'aient nullement été informées, de façon correcte, du déroulement des opérations d'évaluation du benfluorex à l'Europe, on peut considérer que la rédaction de ce protocole est, en février 2001, l'aboutissement des demandes des experts européens dans le but de montrer un bénéfice / risque acceptable pour ce produit. La durée de 12 mois laisse apparaître qu'en 2002 il est possible d'avoir les résultats et donc de prendre des décisions à partir de data d'essais thérapeutiques. En effet, à l'époque, il y a, en ce qui concerne la remontée spontanée des effets indésirables, une indigence importante puisqu'à ce moment-là, on ne dispose toujours que du cas de Marseille de valvulopathie et de l'hypertension artérielle pulmonaire déclarée par Saint-Antoine.

Document A- 13
Comité technique de pharmacovigilance du 13 février 2001 :

Ce document est joint à l'aspect chronologique d'une part pour montrer que sous la rubrique « pharmacovigilance européenne » il n'est pas fait mention du Médiator® alors qu'à l'Europe des discussions ont conduit à élaborer un protocole qui a été proposé le 1er février.
On retrouve par ailleurs, à ce comité du 13 février 2001, une question posée par le Centre Régional de Pharmacovigilance de Caen concernant le mésusage du Médiator® dans des préparations à visée amaigrissante, en contravention avec les décisions prises.

Commentaires : lorsque des faits de ce type (infraction à la réglementation) sont rapportés, l'administration fait une réponse. Il n'y a pas de trace de cette réponse dans les comptes-rendus, ce qui était la coutume.

Document A- 14
Comité technique de pharmacovigilance du 20 mars 2001 :

Ce document est fourni pour montrer que là non plus, sous la rubrique « pharmacovigilance européenne », il n'y a aucune mention concernant l'opinion du groupe de travail européen sur l'étude proposée par Servier.

Document A- 15
Comité technique de pharmacovigilance du 10 avril 2001 :

Ce compte rendu est mis en perspective pour montrer qu'il n'y a pas de mention de l'étude imposée par Servier.

Document A- 16
Comité technique de pharmacovigilance du 15 mai 2001 :

Dans le tour de table, mentionne le problème précédemment signalé par le CRPV de Caen. Il n'y a pas d'information européenne.

Document A- 17
Comité technique de pharmacovigilance du 05 juin 2001 :

Ce compte-rendu est mis en perspective pour montrer qu'il n'y a, là non plus, pas d'information concernant l'étude proposée par Servier.

Document B- 3
Commission Nationale de Pharmacovigilance du 29 novembre 2005 -

Point important :
En 2005, le produit n'est plus sur le marché italien et espagnol.

Ce document retrace l'historique et rappelle que le *benfluorex n'est pas classé parmi les anorexigènes*. Cependant, de façon un peu contradictoire, le benfluorex est inscrit sur la liste des substances interdites dans l'exécution de la délivrance des préparations magistrales en même temps que les anorexigènes dès le 10 mai 1995.

Rappelons que c'est lors de la réunion à l'EMEA du 30 novembre 2000 qu'avait été élaborée d'une part les modifications de RCP mais surtout (bien que nous n'ayons pas de document mais simplement la trace dans un courrier) qu'avait été vraisemblablement discuté un protocole qui est présenté aux instances européennes le 01 février 2001.

La commission nationale de pharmacovigilance du 29 novembre 2005, dans sa conclusion, demande une réévaluation du bénéfice / risque, avec une majorité relative (13 voix pour ; 10 voix contre ; 5 abstentions).

Document B- 4
Commission Nationale de Pharmacovigilance du 27 mars 2007

La conclusion de cette commission fait apparaître que des membres ont demandé que leur opinion se prononçant pour un rapport bénéfice / risque défavorable soit mentionnée.
Ce rapport, page 8, montre que la commission d'AMM a part contre maintenu l'indication « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ».
Même si elle émet des réserves, la commission d'AMM dit qu' « aucun motif de protection de la santé publique ne s'oppose à ce que l'indication telle que libellée soit maintenue. »

Documents divers Div- 1: sous cette rubrique sont mentionnés un certain nombre d'échanges par mails entre le Docteur Dominique Carlhant-Kowalski, Madame Carmen Kreft-Jaïs et Madame Aurore Tricotel expliquant la méthodologie qui a permis d'extraire de la base de Brest des observations de valvulopathie lors de prises concomitantes de benfluorex Médiator®.

Documents divers Div- 2 : Ces documents regroupent des échanges de mails avec le laboratoire Servier sur d'une part les cas écrits dans un article publié par le groupe d'Irène Frachon en collaboration avec le docteur Kowalski du Centre Régional de Pharmacovigilance de Brest et sur la méthodologie utilisée pour mettre en évidence l'existence d'observations en utilisant des codes de PMSI mais également en travaillant sur les chaînes de caractère.

A 1

Saint-Denis, le

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 30 avril 1998)

Etaient présents

M. LAROUSSE : Président
M. LE LOUET (suppléant de Mme ALBENGRES), Mme PENFORNIS (suppléante de M. ALLAIN H.), Mme LAINE CESSAC (suppléante de M. ALLAIN P), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme. ASSOULY, Mme AUTRET, Mme BAVOUX, Mme DAVID (suppléante de M. BECHTEL), M. BIOUR, M. BLAYAC, M. CARLHANT, M. CARON, Mme. CHAMBOST, Mme CHICHMANIAN, Mme GINISTY (suppléante de M. DALLY), Mme ZENUT (suppléante de M. ESCHALIER), Mme C. SGRO (suppléante de M. ESCOUSSE), M. VIAL (suppléant de M. EVREUX), M. GILLET, Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR (suppléante de Mme JOUGLARD), Mme KREFT-JAIS, M. MALLARET, M. MERLE, M. MONTASTRUC, M. LE DOZE (suppléant de M. MOULIN), M. NETTER, M. NORDMAN, M. OLLAGNIER, Mme RICHARD, M. RICHE, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. MOREL (suppléant de M. VANDEL),
Mme TUBERT-BITTER (représentant Monsieur le Directeur Général de l'INSERM),
Mme BARON (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur de l'Agence du Médicament).

Conseiller scientifique

M. LAGIER

Unité de pharmacovigilance

Melle AUGUSTE
Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme JOUSSELIN-PAUTROT
Melle JULLIAN
M. MAIGNEN
Mme PARIENTE-KHAYAT
Melle PIERRON
M. ROPERS
Mme VERROUST

Assistaient à la réunion (D.E.V.)

M. BRASSARD
Mme CALLENS-LAVELOT
Mme DUMARCET
Mme DURANTEAU
Mme DURETTE
Mme SAINT-RAYMOND

Expert

M. Le Pr NORDMAN

Dexamethazone / nouveaux-nés / ventilation assistée.
"A multicenter trial of two dexamethasone regimes in ventilator-dependent premature infants"
LU-ANN PAPILE and others
New England Journal of Medicine 1998 ; 338 (14) : 1112-1118
(CRPV de NANTES)

Dexfenfluramine / anomalies valvulaires.
"Dexfenfluramine : no increase significant valvular abnormalities".
Reactions 1998 ; 697 : 3-4.
(CRPV de BREST)

Diététique.
"Is obesity worth treating in the elderly ?"
R.M. ORTEGAN
Drugs & Aging 1998 ; 12 (2) : 97-101
(CRPV de LIMOGES)

Effets indésirables dans les études de phase I.
"Adverse events in phase I studies : a report in 1015 healthy volunteers"
M. SIBILLE et al
European Journal of Clinical Pharmacology 1998 ; 54 : 13-20
(CRPV de LIMOGES)

Effets indésirables médicamenteux.
"Adverse drug reactions remain a major cause of death"
D. BONN
Lancet 1998 ; 351 : 1183
(CRPV de REIMS)

Hypovitaminose D / facteurs de risque.
"Hypovitaminosis D in medical inpatients"
MELISSA K. THOMAS et al
New England Journal of Medicine 1998 ; 338 (12) : 777-783.
(CRPV de NANTES)

Iatrogénie.
"Iatrogénie évitable : un gisement considérable"
Les Nouvelles Pharmaceutiques 1998 ; 153 : 3-6.
(CRPV de GRENOBL

Imagerie médicale.
"Medical Progress : Imaging the Brain (First of two parts)"
S. GILMAN
New England Journal of Medicine 1998 ; 338 (12) : 812-820.
(CRPV de NANTES)

Interaction médicamenteuse / macrolides et statines / rhabdomyolyse.
"Lovostatin - induced rhabdomyolysis possibly associated with clarithromycin and azithromycin"
J.W. GRUNDEN, K.A. FISHER
Annals of pharmacotherapy 1997 ; 31 : 859-863 (signalé dans Adverse Drug Reactions and Toxicological Review 1997 ; 16 : 210-211)

Il faut noter que les concentrations sanguines de buprénorphine, lorsque les dosages ont été réalisés, semblent être dans les limites des taux thérapeutiques et surtout moins élevées que les concentrations cérébrales. Ceci confirme les données de la littérature quant à la lipophilie de la buprénorphine et pourrait contribuer à la dépression respiratoire.
L'analyse de la littérature et les cas rapportés sont en faveur d'une cause de décès par dépression respiratoire, le risque dépresseur pouvant être augmenté par l'administration intraveineuse de la buprénorphine et majoré par l'association aux benzodiazépines.
Cependant, si la co-responsabilité des benzodiazépines ne peut être écartée, il existe des cas sans benzodiazépine associée (la recherche de benzodiazépines s'est avérée négative dans 3 cas de décès sur les 23 pour lesquels cette recherche avait pu être effectuée).

En conclusion :

Les données actualisées présentées ne remettent pas en cause le profil de sécurité de la buprénorphine, cependant une meilleure évaluation du risque de décès par dépression respiratoire serait souhaitable (études expérimentales, potentialisation par les benzodiazépines...).
Le Comité Technique souligne que la dispensation fractionnée de la buprénorphine, pour des durées ne pouvant excéder 7 jours, permettrait de limiter le risque d'utilisation détournée par voie intraveineuse.

Le Comité Technique souhaite par ailleurs que le développement de la spécialité associant buprénorphine et naloxone (SUBOXONE) par voie sublinguale se poursuive.
En effet la mise à disposition d'une telle spécialité limiterait le risque de mésusage et donc le risque de décès par dépression respiratoire de même que les risques infectieux liés à la pratique de la voie intraveineuse, et sans doute le "trafic" de la buprénorphine.

Le Dr Riché (CRPV de Brest) fera une présentation à un prochain Comité technique sur le potentiel d'interactions entre buprénorphine - benzodiazépines - méthadone.

V - POINT BENFLUOREX (MEDIATOR®)

Le Centre Régional de Pharmacovigilance de Besançon a effectué une mise au point concernant les effets

indésirables observés avec le benfluorex.

Le MEDIATOR® (chlorydrate de benfluorex) est commercialisé en France (depuis 1976) dans les indications suivantes :
- adjuvant du régime adapté dans les hypertriglycéridémies.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex est inscrit depuis le 10 mai 1995, comme les anorexigènes, sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales.

Sur les 291 notifications rapportées avec le benfluorex, 152 ont été retenues au 30 avril 1998 (lors de la précédente mise au point de juillet 1995, 101 notifications avaient été rapportées).

● Les atteintes hépatiques : 16 cas
Les cas les plus souvent rapportés sont des hépatites et des perturbations de la biologie hépatique : élévation des transaminases. Ces effets ne sont pas mentionnés dans le RCP.

● Les atteintes digestives : 16 cas
Les cas les plus souvent notifiés sont les diarrhées. Cet effet indésirable est mentionné dans le RCP.

● Les atteintes hématologiques : 8 cas
Les effets les plus fréquents sont les thrombopénies. Il n'y a pas eu de nouveaux cas rapportés depuis juillet 1995.

● Les atteintes respiratoires : 8 cas
Les cas rapportés sont principalement des toux et des hypertensions pulmonaires (dans les 2 cas rapportés, il existe un traitement anorexigène associé).

● Les atteintes cardiovasculaires : 11 cas
Des cas d'hypertension artérielle, de tachycardie, d'extrasystoles ventriculaires et de syndrome de Raynaud sont le plus souvent notifiés.

● Les atteintes rénales : 9 cas
Parmi lesquelles on observe le plus souvent des dysuries, des pollakiuries.

● Les atteintes métaboliques : 3 cas
Une hyperlipémie, une hypothyroïdie et une crise de goutte ont été rapportées.

● Les atteintes cutanées : 38 cas
Des urticaires, des chocs anaphylactiques, des eczémas, des vascularires, des érythèmes ainsi que des purpuras sont les effets les plus fréquents. Ces effets indésirables ne sont mentionnés pas dans le RCP.

● Les atteintes neuro-psychiatriques : 27 cas
Des cas d'asthénie ou de somnolence sont le plus souvent notifiés ; ceux-ci sont mentionnés dans le RCP. Parmi les troubles psychiatriques, on observe principalement des cas d'agressivité, d'agitation, de nervosité, ou de délire. Les paresthésies sont les troubles neurologiques les plus fréquents.

● Les troubles de l'équilibre, vertiges : 16 cas
Dans 16 cas (sur les 152 rapportés), le benfluorex est associé avec un anorexigène.
En 1995, le nombre de boîtes de MEDIATOR® vendues a été estimé à 5 millions/an.

Le nombre d'effets indésirables observés ne semble pas plus important depuis la dernière mise au point de juillet 1995. Cependant on ne peut écarter la possibilité d'une déviation de l'utilisation du benfluorex comme anorexigène étant donné que l'indication "adjuvant de régime..." entretient une certaine ambiguïté. De plus, la métabolisation du benfluorex dans l'organisme entraîne la formation de norfenfluramine, métabolite apparenté à la fenfluramine, elle-même impliquée dans l'apparition d'hypertensions pulmonaires graves.

Compte tenu de la suspicion de détournement d'usage et de la formation lors de la métabolisation de norfenfluramine, le Comité Technique propose la mise en place d'une enquête officielle de Pharmacovigilance qui permettra, entre autres, de récupérer les chiffres de vente, afin d'infirmer ou de confirmer un éventuel mésusage, et les données précliniques.

L'enquête nationale est confiée au CRPV de Besançon et l'Observatoire de la Prescription sera consulté.

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A-2

DIRECTION DE L'EVALUATION Saint-Denis, le
Unité de Pharmacovigilance

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 10 septembre 1998)

Etaient présents

M. RICHE : Président
M. LE LOUET (suppléant de Mme ALBENGRES), Mme PENFORNIS (suppléante de M. ALLAIN H), Mme LAINE CESSAC (suppléante de M. ALLAIN P), M. ANDREJAK, Mme RADAL (suppléante de Mme AUTRET), Mme BAVOUX, Mme DAVID- LAROCHE (suppléante de M. BECHTEL), M. BIOUR, M. BLAYAC, Mme CARLHANT, M. CARON, Mme CHICHMANIAN, Melle DIORTE, Mme EFTHYMIOU, M. ESCHALIER, Mme SGRO (suppléante de M. ESCOUSSE), M. VIAL (suppléant de M. EVREUX), Mme GERMAIN, Mme GINISTY, Mme HARAMBURU, Mme HILLAIRE-BUYS, M. IMBS, Mme JEAN-PASTOR, Mme JOUGLARD, Mme KREFT-JAIS, M. LAROUSSE, Mme LAVARENNE, M. LE DOZE, M. MALLARET, M. MERLE, M. MONTASTRUC, M. MOULIN, M. GILLET (suppléant de M. NETTER), Mme NOBLET, M. OLLAGNIER, M. ROYER, Mme SOUBRIE, M. THUILLEZ, M. TRENQUE, Mme PERAULT (suppléante de M. VANDEL),
Mme TUBERT-BITTER (représentant Monsieur le Directeur Général de l'INSERM),
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme BARON (représentant Monsieur le Directeur Général de la Santé),
M. ALEXANDRE (représentant Monsieur le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance

Mme BIDAULT
Mme CASTOT
Melle DELEAU
M. DHANANI
Melle FERVAL
Mme FOSSET-MARTINETTI
M. JACQUET
Melle JULLIAN
Mme LEREBOURS
Mme MORIN
Mme PARIENTE-KHAYAT
Mme WESCHLER

Assistaient à la réunion (D.E.V.) :

Melle AUGUSTE
Mme DUMARCET
Mme DURANTEAU
Mme GRENE
Mme HOOG-LABOURET
Mme LANFRANCHI
Mme LELAN
Mme MIGNON
Mme MORER
Mme MORGENSZTEJN
Mme PICON
M. REYNIER
Mme REY-QUINIO
Mme SAINT-RAYMOND
M. SAWAYA
Mme VINAS

Etaient excusés

M. BEGAUD (Vice-Président)
M. BECHTEL
M. VANDEL

IV - POINT SUR LE BENFLUOREX (MÉDIATOR ®)

Le Centre Régional de Pharmacovigilance de Besançon a présenté, à la demande de l'Agence du Médicament, des données sur les chiffres de ventes et des données de cinétique du Benfluorex. L'Agence est en effet régulièrement interrogée par des pharmaciens inspecteurs de la santé sur la possibilité d'usage détourné de ce produit.

- Evolution des chiffres de vente

Depuis 1991, les ventes progressent régulièrement. Aucun pic n'a été observé au cours des mois qui ont suivi les mesures prises à l'encontre des anorexigènes. Il est toutefois, à noter que les ventes de ce produit sont d'environ 5 millions de boîtes, ce qui est loin d'être négligeable.

Il est en fait, difficile au vu des seuls chiffres de ventes de mettre en évidence un mésusage du produit. Il est donc indispensable pour affiner l'analyse de :

- disposer des données Dorema
- de pouvoir distinguer les nouvelles prescriptions des renouvellements
- de saisir l'observatoire des prescriptions

- Données cinétiques et de métabolisme

Les concentrations plasmatiques du Benfluorex sont atteintes en 1 à 2 heures, l'absorption est complète et le volume de distribution est faible de 0,37 l/kg. La fixation plasmatique est de 77 %. Le métabolite majeur est le 1-(3-trifluoromethylphenyl)-2N-2-(carboxymethyl)aminopropane. L'élimination est rénale avec 75 % du produit éliminé dans les 8 premières heures. Le Benfluorex est totalement métabolisé.

La norfenfluramine, métabolite du Benfluorex est retrouvée en faible quantité (2 %) dans les urines.

Il est surprenant de constater que les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60 ng/ml). En effet, la Norfenfluramine formée à partir de la Fenfluramine, n'est plus transformée et se retrouve intacte dans les urines de 24 h à l'état d'équilibre à 7,4 % de la dose administrée. Alors que la norfenfluramine formée à partir du Benfluorex, est transformée en produit désaminé et oxydé.

Il n'y a aucune explication actuellement pour cette différence.

Le Comité Technique juge que ces informations sont insuffisantes et ne permettent pas d'être entièrement rassuré. En particuliers, le rapporteur devrait pouvoir disposer d'une analyse correcte des AUC.

Enfin, une question relative à la parenté chimique du Benfluorex avec les amphétaminiques est posée. Il a été rapporté qu'un patient âgé traité par MEDIATOR® avait présenté un test urinaire positif ; cette recherche avait été faite chez ce dernier dans le cadre d'une procédure judiciaire, son fils étant toxicomane. Les CEIP pourrait être interrogés à ce sujet.

Dans 7 cas, le **délai** entre la radiothérapie et la gemcitabine n'était pas documenté mais dans 11 cas sur 18, il existait une corrélation entre le délai radiothérapie et gemcitabine et le délai gemcitabine et apparition de l'effet indésirable.

Hormis les manifestations neurologiques chez les patients ayant reçu une radiothérapie cérébrale (5 cas), la **symptomatologie** est très homogène avec des manifestations cutanées à type de dermato-polymyosite. Elle est grave dans 19 cas sur 25.

Selon l'expert radiothérapeute, un mécanisme histopathologique possible serait l'existence d'une microartériopathie oblitérante inflammatoire induite par la gemcitabine.

L'**évolution** est favorable dans 10 cas sur 25 ; dans 12 cas, la symptomatologie a persisté ou s'est aggravée (fibrose pulmonaire, épaississement cutané avec douleurs persistantes) ; dans 3 cas, l'évolution était inconnue.

❒ **Gemcitabine puis radiothérapie**

Deux cas pouvant évoquer un **phénomène de radiosensibilisation** ont été rapportés.

Le rapporteur serait d'avis de **contre-indiquer l'association concomitante de la gemcitabine et de la radiothérapie à visée curative et palliative.**

Selon l'expert radiothérapeute, l'administration successive de la radiothérapie et de la gemcitabine pourrait être raisonnablement envisagé avec un délai d'un mois entre les deux thérapeutiques.

En conclusion, le Comité technique souhaite que les résultats de l'enquête officielle sur "gemcitabine et radiothérapie" et "gemcitabine et cardiotoxicité" soient présentés à la Commission Nationale de Pharmacovigilance du 22 septembre 1998.

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A-2

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
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MEDIATOR (benfluorex)

Mise au point

Comité Technique du 10 Septembre 1998

Confidentiel

M.DAVID-LAROCHE
P.BECHTEL

1) Le métabolisme du benfluorex et de la fenfluramine a été réévalué récemment avec des méthodes plus sensibles et plus spécifiques.

2) La différence essentielle qui est ressortie de ces études est la suivante :

- la norfenfluramine est bien un produit du métabolisme de la fenfluramine et du benfluorex. Les concentrations sanguines de Norfenfluramine sont identiques pour des doses équivalentes de Fenfluramine et de Benfluorex (60ng/ml). Mais à partir de la Fenfluramine, la Norfenfluramine produite n'est plus biotransformée et se retrouve dans les urines de 24h à l'état d'équilibre à 7,4% de la dose administrée. Par contre à partir de Benfluorex, la Norfenfluramine est transformée en un produit désaminé et oxydé. Le pourcentage de la dose excrétée dans les urines de 24h à l'état d'équilibre n'est que de 2%.

Il n'y a aucune explication actuellement pour cette différence.

- on ne peut pas exclure un passage à travers la barrière hémato-cérébrale de la Norfenfluramine produite à partir de Benfluorex.

Mais les études pharmacodynamiques n'ont jamais mis en évidence un effet anorexigène de Benfluorex.

3) Le 3-trifluorométhylphényl-1-hydroxypropanone-2 n'a pas été retrouvé en quantité détectable avec les nouvelles méthodes. Il est probable qu'une erreur d'interprétation analytique est à l'origine de l'attribution de ce métabolite au métabolisme de Benfluorex.

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DEV + DEI.PE

Mr Jean-René BRUNETIERE
Directeur Général
Agence du Médicament
143 - 147 Bd Anatole France
93285 SAINT-DENIS CEDEX

Objet : Prescription de MEDIATOR.

Monsieur le Directeur Général,

L'Union Régionale des Caisses d'Assurance Maladie (URCAM) de Bourgogne a réalisé une étude[1] portant sur les modalités d'utilisation de la spécialité MEDIATOR® (Benfluorex).

Il est constaté qu'un nombre important de cas (environ 1/3) correspond à des prescriptions médicales se situant hors du champ des indications thérapeutiques prévues par l'Autorisation de Mise sur le Marché (adjuvant du régime dans les hypertriglycéridémies ou traitement du diabète asymptomatique avec surcharge pondérale), notamment dans le cadre de traitements à visée amaigrissante.

En conséquence, il nous est apparu nécessaire de vous transmettre les résultats de cette étude même si, en l'absence de données issues du codage pharmacie, ceux-ci ne peuvent être exhaustifs.

Face aux constats établis par les praticiens conseils, il nous apparaîtrait particulièrement opportun de procéder à une réévaluation de l'utilité du MEDIATOR dans la stratégie thérapeutique de la maladie diabétique et dans celle des hyperlipidémies.

D'autre part, il nous semble également utile d'alerter l'Agence du médicament sur l'utilisation non contrôlée d'un produit de structure amphétaminique, dans un but anorexigène. Il est en effet assez paradoxal de constater que la prescription de MEDIATOR est tout à fait libre tandis que celle des médicaments du groupe des amphétamines est strictement encadrée depuis mai 1995.

[1] 2 documents joints en annexe.

ARRIVÉE LE 21 SEP. 1998
N° 3470
TRANSMIS LE 21 SEP 1998
A PP

Enfin, il convient de rappeler que la présente démarche relève d'une volonté de promouvoir la qualité des soins qui s'inscrit dans le cadre des missions de santé publique dévolues aux organismes d'assurance maladie.

Nous vous prions de croire, Monsieur le Directeur Général, à l'assurance de nos sentiments distingués.

Le Médecin Conseil National de la C.N.A.M.TS.	**Le Médecin Conseil National de la C.A.N.A.M.**	**Le Médecin Conseil National de la M.S.A.**
Pr Hubert ALLEMAND	Pr Claudine BLUM-BOISGARD	Pr Patrick CHOUTET

D-2

AGENCE DU MEDICAMENT

DIRECTION DES ETUDES ET
DE L'INFORMATION PHARMACO-ECONOMIQUES

Le Directeur

N/Réf : cg\n0998JMA

NOTE

- A l'attention de Monsieur Jean-Michel ALEXANDRE -

- Direction de l'Evaluation -

Objet : Evolution de la consommation et des prescriptions de MEDIATOR®

Les données dont dispose la DEIPE sur l'évolution des consommations et des prescriptions de MEDIATOR® au cours de ces dernières années ne permettent pas de mettre en évidence un détournement d'usage de ce médicament. Si MEDIATOR® a été - et est encore - prescrit comme anorexigène et, de façon plus large, comme médicament anti-obésité, la part des prescriptions dans ces indications hors AMM est modeste et - surtout - a décru au cours de la période étudiée. Ainsi, les prescriptions de ce médicament dans le traitement de l'obésité[1] étaient, selon le DOREMA, de 9 % en 1994 mais seulement de 5,1 % au cours de l'hiver 1997-1998.

Comme le montre le tableau joint en annexe, une tendance similaire peut être dégagée en ce qui concerne la prescription de MEDIATOR® comme amaigrissant ou comme anorexigène. En tout état de cause, si l'on admet que la rubrique "effets attendus" du DOREMA est correctement renseignée, les mesures prises en 1995 pour restreindre la prescription d'anorexigènes n'ont pas entraîné de reports en faveur de MEDIATOR®. Ce médicament demeure très largement prescrit comme hypocholestérolémiant et comme antidiabétique (80,2 % des prescriptions en 1997).

Quant à l'évolution globale du nombre de prescriptions de MEDIATOR®, si elle a été positive, elle est restée néanmoins modeste : + 5,6 % entre 1994 et 1997.

[1] Effet attendu : traitement de l'obésité

Il sera seulement noté que le nombre de boîtes vendues a augmenté de 16 % entre 1994 et 1997, soit une progression plus importante que celle de l'ensemble des spécialités remboursables (+ 2,9 %). Toutefois, cette progression aurait dû être encore beaucoup plus forte si les prescriptions d'anorexigènes s'étaient reportées de façon tangible sur MEDIATOR®. En effet, les ventes (en unités) d'anorexigènes s'élevaient en 1994 à 4,4 millions et, en 1995, à 2,8 millions.

Aussi, en conclusion, apparaît-il que le détournement d'usage de MEDIATOR®, s'il existe, ne pourrait être évalué qu'à l'aide de données beaucoup plus fines, et qui font actuellement défaut, sur la prescription de ce médicament.

Le Directeur des Etudes et de
L'Information Pharmaco-Economiques

Frédéric FLEURETTE

P.J. : Tableau sur l'évolution des ventes et des prescriptions de MEDIATOR®.

EVOLUTION DES VENTES ET DES PRESCRIPTIONS DE MEDIATOR

	1994	1995	1996	1997	Hiv. 97/98
Nbre de boîtes vendues (30 comp.)	4 809 905	5 159 845	5 283 371	5 588 203	
Nbre total de prescriptions	909 000	869 000	882 000	960 000	957 000
Nbre de prescriptions "anti-obésité"*	82 000	85 000	65 000	54 000	49 000
Part des prescriptions "anti-obésité"	9,02%	9,78%	7,37%	5,63%	5,12%

* Effet attendu

Parmi les prescriptions ayant pour effet attendu "Anti-obésité" :

	1994	1995	1996	1997	Hiv. 97/98
bre de prescriptions "amaigrissement"*	59 000	52 000	43 000	20 000	17000
art des prescriptions "amaigrissement"	1,23%	1,01%	0,81%	0,36%	
e de prescriptions "anorexigènes"*		19 000		17 000	15 000
art des prescriptions "anorexigènes"		2,19%		1,77%	1,57%

Effet attendu

urces : "Taxe sur les spécialités" pour les données sur les ventes
"Doréma -EPPM" pour les données de prescriptions (automne, sauf pour hiver 97/98)

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DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 22 octobre 1998)

Etaient présents

M. RICHE : Président
M. LE LOUET (suppléant de Mme ALBENGRES), M. ESCOFIER (suppléant de M. ALLAIN H), Mme LAINE (suppléante de M. ALLAIN P), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET), Mme BAVOUX, Mme DAVID- LAROCHE (suppléante de M. BECHTEL), M. BIOUR, M. BLAYAC, Mme CARLHANT, M. CARON, Mme CHICHMANIAN, Mme DJEZZAR, M. FIALIP (suppléant de M. ESCHALIER), Mme SGRO (suppléante de M. ESCOUSSE), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR (suppléante de Mme JOUGLARD), Mme KREFT-JAIS, Mme LACOTTE, Mme LAGARCE,
M. LAROUSSE, M. MERLE, Mme LAPEYRE-MESTRE (suppléante de M. MONTASTRUC),
M. MOULIN, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme RADAL, Mme SOUBRIE, Mme TANASESCU, M. THUILLEZ, M. THOMAS, M. TRENQUE, M. VANDEL, M. VIAL,
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme BARON (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance

Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Mme JOUSSELIN-PAUTROT
Melle JULLIAN
Mme LEREBOURS
M. MAIGNEN
Mme MORIN
Mme PARIENTE-KHAYAT
Melle PIERRON
M. ROPERS
Mme WECHSLER

Assistaient à la réunion (D.E.V.) :

Mme BAUMELOU
Mme GRENE
Mme KONOPKA
Mme LORENCE

Experts :

M. CHAPLAIN
M. DONADIEU

Etaient excusés

M. BEGAUD (Vice-Président)
M. MALLARET
Monsieur le Directeur Général de l'INSERM

VIII - POINT SUR LA PHARMACOVIGILANCE EUROPÉENNE.

Compte-rendu du groupe de travail de Pharmacovigilance de l'Agence Européenne des 7 et 8 octobre 1998.

- **Terfénadine (article 12)** : les décisions de la Commission Européenne doivent être appliquées par les Etats Membres avant le 22 octobre 1998. En France, la suspension de l'AMM est effective jusqu'au 11 février 1999.

- **Anorexigènes (article 15a)** :
- fenfluramine / dexfenfluramine et amfépramone / phentermine : Les réponses aux questions adressées aux firmes sont attendues pour le 1er mars 1999 au plus tard et seront examinées par le Comité des Spécialités Pharmaceutiques (CSP) de mars 1999, en présence des firmes. L'opinion du CSP est attendue pour le mois d'avril 1999.
- Clobenzorex, fenbutrazate, fenproporex, mazindol, méfénorex, norpseudoéphédrine, phendimétrazine, propylhexédrine : initiation d'un article 15a (Autriche rapporteur, France et Allemagne co-rapporteur) afin de réévaluer le rapport bénéfice / risque de tous ces anorexigènes amphétaminiques. Le rapport d'évaluation circulera parmi les Etats Membres à partir du 30 janvier 1999 et sera discuté au CSP du mois de février 1999. L'opinion du CSP est attendue pour le mois d'avril 1999.
  L'Italie pose le problème du MEDIATOR® (benfluorex) en raison de l'analogie structurale avec la fenfluramine et craint la survenue de valvulopathies associées à l'utilisation de ce médicament. Ce problème sera discuté au prochain groupe de travail des 24 et 25 novembre 1998.

- **Sparfloxacine (ZAGAM®) (article 12, France rapporteur)** : le rapport d'évaluation de la France concernant le protocole de l'étude d'efficacité a circulé parmi les Etats Membres pour information et sera discuté lors du CSP du mois d'octobre 1998.

- **Kétorolac (TORADOL®) / risque hémorragique et augmentation de la mortalité** : le Royaume-Uni a présenté son rapport d'évaluation. Deux études italiennes et une synthèse espagnole ont été distribuées. Le Royaume-Uni analyse et prépare ses commentaires sur les trois études publiées adressées par la firme. Ce sujet sera de nouveau discuté lors du groupe de travail du mois de novembre 1998.

- **Sildénafil (VIAGRA®)** : le groupe de travail a jugé nécessaire la réalisation d'une étude post-marketing par la firme. Par ailleurs, l'infofax de l'Allemagne concernant les interactions avec les nitrates sera discuté lors du Working Party du mois de novembre 1998.

- **Inhibiteurs des protéases / lipodystrophies, hyperlipidémies, altération du métabolisme du glucose, pancréatites, complications cardio-vasculaires** : un libellé commun pour la classe des inhibiteurs des protéases a été finalisé pour adoption lors du CSP du mois d'octobre 1998 où sera choisie la procédure à appliquer (mesure de restriction urgente ou variation de type II). Les prescripteurs seront informés par le biais d'une lettre d'information où d'un bulletin national selon les Etats Membres. Il a, par ailleurs, été jugé nécessaire que les firmes ré-analysent les données cliniques et mettent en place des études de tolérance. Désormais, les produits de cette classe seront revus ensembles.

- **Analogues nucléosidiques / lipodystrophies, acidoses lactiques, stéatoses hépatiques** : la révision du libellé commun concernant les acidoses lactiques a été jugées nécessaire. La Suède adressera sa proposition de libellé commun aux Etats-Membres avant le CSP du mois d'octobre 1998. Il a par ailleurs été demandé aux firmes de revoir le problème des lipodystrophies dans le prochain rapport périodique actualisé

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DIRECTION DE L'EVALUATION Saint-Denis, le
Unité de Pharmacovigilance

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Jeudi 17 décembre 1998)

Etaient présents

M. RICHE : Président
M. BEGAUD : Vice-Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN H), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BECHTEL, M. BIOUR, Mme CARLHANT (représentant le CRPV de Brest), M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. ESCHALIER, M. ESCOUSSE, Mme GINISTY (représentant le CRPV de Paris - F. Widal), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR (suppléante de Mme JOUGLARD), Mme KREFT-JAIS, Mme LAINE-CESSAC, M. LAROUSSE, M. MERLE, M. MONTASTRUC, Mme LACOTTE (suppléante de M. MOULIN), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), Mme GERMAIN (suppléante de M. TRENQUE), M. VANDEL, M. VIAL.
Mme TUBERT-BITTER (représentant Monsieur le Directeur Général de l'INSERM),
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence du Médicament).

Conseiller Scientifique : M. LAGIER

Assistaient à la réunion (C.R.P.V.) :
Mme BAGHERI, Melle CHAUMERLIAC, Mme CHIFFOLEAU, Mme DAVID- LAROCHE, Melle FERARD, Mme GENESTE, Mme GUY, Mme LAGARCE, M. QUESTEL, Mme RADAL, Melle RICHER, Mme ZENUT.

Unité de pharmacovigilance

Melle DELEAU
Mr DHANANI
Mme FOSSET-MARTINETTI
Mme LEREBOURS
Mme MORIN
Mme PARIENTE-KHAYAT
Melle PIERRON
Melle VERSTUYFT
Mme WECHSLER

Assistaient à la réunion (D.E.V.) :

Mme DEWILDE
Mme DURANTEAU
Mme GUENANECHE
Mme PAVLOVIC
Mme PELANNE
Mme REIDIBOYM
Mme REY QUINIO

Etaient excusés

M. BLAYAC
M. MALLARET
Madame le Directeur des Hôpitaux
Monsieur le Directeur Général de la Santé

Par ailleurs, un expert pneumologue sera chargé de revoir les cas d'effet pulmonaire pour faire la part entre un bronchospasme et une crise d'asthme.
Cette enquête officielle sera présentée en Commission Nationale le 10 Février 1999.

IX - ENQUÊTE OFFICIELLE MEDIATOR® (BENFLUOREX) : CRPV de Besançon

Le CRPV de Besançon a présenté les résultats de l'enquête officielle sur le MEDIATOR® (benfluorex) ainsi que les données sur le métabolisme de la molécule.

Bilan des effets indésirables :
Les effets cutanés et / ou allergiques pourraient être rajoutés dans le RCP.

Métabolisme :
La norfenfluramine produite à partir du benfluorex est retrouvée dans les urines avec une concentration de 2 % (contre 7,4 % pour la norfenfluramine produite à partir de la fenfluramine). Il est donc peu probable que le benfluorex induise les mêmes effets que la fenfluramine.

L'Italie qui propose que le benfluorex soit inclus dans l'article 15a européen relatif aux fenfluramines, a en charge une enquête sur cette molécule. Le CRPV de Besançon adressera une copie de son rapport à l'Agence Italienne qui prépare un rapport pour le groupe de travail de pharmacovigilance européen de février 1999.

X - POINT PHARMACOVIGILANCE EUROPEENNE

- Vigabatrin / rapport bénéfice risque / atteintes du champ visuel / article 12 :
Un article 12 a été initié avec la Finlande comme pays rapporteur et le Royaume-Uni comme pays co-rapporteur.
GABITRIL® : La France, en tant qu'Etat membre de référence pour la tiagabine (GABITRIL®) a fait part de son inquiétude quant aux troubles du champ visuel rapportés dans le 4ème PSUR de cette spécialité.
A ce sujet, une réunion à eu lieu à l'Agence du Médicament, en présence du CRPV de Toulouse (responsable de l'enquête officielle) et des laboratoires SANOFI. A l'issu de cette réunion, il a été proposé d'ajouter, dans le RCP de la tiagabine, une précaution d'emploi relative aux troubles du champ visuel.

- Sertindole / morts subites / article 15 :
Alors qu'un article 15 est en cours, la plupart des Etats membres ont suspendu l'autorisation de mise sur le marché du produit. Dans les Etats où il n'est pas autorisé, l'inclusion de patients dans les essais cliniques a été également suspendue.
La France n'est pas concernée par cette procédure de reconnaissance mutuelle.

- Kétorolac (TORADOL®) / risque hémorragique et augmentation de la mortalité :
Un concensus concernant les indications et les doses recommandées a été jugé nécessaire afin que chaque Etat membre concerné effectue ces modifications au niveau national. Le Toradol® n'est pas commercialisé en France.

- Inhibiteurs de protéases (indinavir, nelfinavir, ritonavir, saquinavir) / rhabdomyolyse :
Le libellé commun concernant les rhabdomyolyses, pour la classe des inhibiteurs de protéases sera soumis pour adoption au CSP de décembre 1998.

- Inhibiteurs de la cathécol O-méthyltransférase - Tolcapone (TASMAR®) / suspension de l'AMM -

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AGENCE DU MEDICAMENT

RÉPUBLIQUE FRANÇAISE

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint Denis, le 03 DEC. 1998

Cher(e) Ami(e) et Collègue,

J'ai l'honneur de vous faire connaître que la prochaine réunion du Comité Technique de Pharmacovigilance aura lieu le :

Jeudi 17 décembre 1998 à 9 h 30
à l'Agence du Médicament - Salle de Réunions n° 1
143 -147 boulevard Anatole France
93200 SAINT DENIS
(Métro Carrefour Pleyel)

ORDRE DU JOUR

Matin

1°) Adoption des Procès-Verbaux des séances du 22 octobre 1998 et du 19 novembre 1998.

2°) Enquête officielle INNOHEP® (tinzaparine sodique) et accidents hémorragiques.

3°) Tour de table des cas marquants et de la littérature.

4°) Enquête officielle LAMICTAL® (lamotrigine).

5°) Point sur la pharmacovigilance européenne.

Après-midi

6°) Enquête officielle ZOLOFT® (sertraline).

7°) Enquête officielle sur les antigènes à visée immunostimulante : résultats préliminaires.

8°) Point sur les atteintes oesophagiennes avec les tétracyclines en comprimé.

9°) Enquête officielle ROACCUTANE® (isotrétinoïne).

10°) Enquête officielle MEDIATOR® (benfluorex).

11°) Questions diverses.

Le Chef de l'unité de Pharmacovigilance

Dr Anne CASTOT

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE
DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

RÉPUBLIQUE FRANÇAISE

A-5

1430 · Saint-Denis, le 25 MARS 1999

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 23 février 1999)

Etaient présents

M. RICHE : Président
Mme ALBENGRE, Mme POLARD (suppléante de M. ALLAIN H), M. ANDREJAK, Mme AUTRET-LECA, Mme BAVOUX, Mme DAVID-LAROCHE (suppléante de M. BECHTEL), M. BIOUR, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme LAMAISON (suppléante de M. ESCHALIER), Mme SGRO (suppléante de M. ESCOUSSE), Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme LILLO (suppléante de Mme KREFT-JAIS), Mme GINISTY (représentant le CRPV de Fernand Widal), Mme LAINE-CESSAC, M. LAROUSSE, M. MERLE, M. MONTASTRUC, M. MOULIN, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE), Mme TANASESCU (suppléante de M. THUILLEZ), M. TRENQUE, Mme FLEURANCEAU (suppléante de M. VANDEL), M. VIAL.
Madame LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Madame BARON (représentant Monsieur le Directeur Général de la Santé).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme CHAUVEAU-CHARTRIN
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
M. JACQUET
Melle JULLIAN
M. LANG
Mme PARIENTE-KHAYAT
Melle ROBINE
Melle VERSTUYFT

Assistaient à la réunion :

D.E.V. :
Mme PAVLOVIC
Mme ROSSI

C.R.P.V. :
Melle CASANOVA
Mme CHAUMERLIAC
Mme COUFFIN
Mme FERARD
M. ROUX
Mme SARAZIN
Mme VEYRAC

Etaient excusés
M. BEGAUD, Vice-Président
M. MALLARET
Monsieur le Directeur Général de l'INSERM
Monsieur le Directeur Général de l'Agence du Médicament

93205 Saint-Denis Cedex - Tél. : 01.55.87.30.00

II - TOUR DE TABLE DES CAS MARQUANTS

Seuls sont signalés les cas d'effets indésirables donnant suite à des mesures (mise en enquête, notes, ...) ou faisant l'objet d'une mise au point. La liste complète des cas est jointe en annexe 1.

- **CERVOXAN® (vinburnine), ZYLORIC® (allopurinol), ARICEPT® (donépezil) / CRPV de Nantes** : crise de porphyrie aiguë intermittente chez un homme de 86 ans.
Il n'existe aucune contre-indication pour les porphyries dans les RCP de ces spécialités.
Cette observation soulève le problème de l'absence d'une liste officielle et validée par l'Agence du Médicament, énumérant les médicaments contre-indiqués dans les porphyries.
Le problème est le même pour les médicaments contre-indiqués dans les déficits en G6PD.
→ Une note sera adressée à l'unité des Affaires Réglementaires de la Direction de l'Evaluation.

- **FRAXODI® (nadroparine calcique) / CRPV de Saint-Etienne** : hémorragie massive rétropéritonéale chez un homme de 73 ans après utilisation de FRAXODI® (0,8 ml x 2/j) au lieu de FRAXIPARINE® (0,8 ml x 2/j) initialement prescrite. Il n'existe pas d'équivalence d'activité anti-Xa entre les doses de ces deux spécialités de nadroparine calcique ce qui peut entraîner des confusions.
→ Un note sera adressée à l'attention de l'évaluateur de la classe des HBPM.

- **KETODERM crème 2% (kétoconazole) / CRPV de Caen** : eczéma aigü localisé chez une femme de 23 ans. Le libellé actuel de la rubrique "effets indésirables" du RCP est "1 cas d'eczéma de contact a été rapporté". Plusieurs cas sont rapportés dans la banque nationale ou décrits dans la littérature.
→ L'unité de pharmacovigilance adressera un courrier au laboratoire afin qu'il dépose une demande de modification de l'information.

- **LOPRIL® (captopril) / CRPV de Marseille** : augmentation de la lipase à 3,5 N (amylase normale) chez une femme de 71 ans. Cet effet est mentionné dans le RCP du captopril mais pas dans celui de l'énalapril alors que des cas sont décrits dans la littérature.
→ L'unité de pharmacovigilance adressera un courrier au laboratoire afin qu'il dépose une demande de modification de l'information.

- **MEDIATOR® (benfluorex), VASTEN® (pravastatine), ASPEGIC® (acétylsalicylate de DL lysine), TENORMINE® (aténolol) / CRPV de Marseille** : insuffisance aortique découverte chez un homme de 43 ans traité par benfluorex depuis 6 ans. Aucune prise d'anorexigènes ou d'amphétamines.
→ Le benfluorex qui se métabolise en norfenfluramine, fait l'objet d'une discussion au groupe de travail de pharmacovigilance européen. L'Italie qui envisage de saisir le CSP en vertu de l'article 12, rédige un rapport sur le métabolisme et les données de sécurité de ce produit en collaboration avec la France.

- **OESCLIM® (estradiol) / CRPV de Marseille** : eczéma chez une femme de 45 ans.
→ Cette spécialité est enregistrée selon une procédure de reconnaissance mutuelle (France Etat membre de référence). Dans le dernier RCP datant du mois d'octobre 1998, il est mentionné : "dermatite de contact allergique et démangeaisons". Cependant ce libellé n'apparaît pas au dictionnaire Vidal® 1999.

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ANNEXE I

CENTRE DE PHARMACOVIGILANCE DE MARSEILLE

COMITE TECHNIQUE DU : 23 février 1999

N° des cas	Date de survenue	Sexe /Age	Médicaments suspects	Effets observés	Evol.	Imput	G	N	E	Commentaires *Interaction*
99-121	18 12 98	M,92	LOVENOX 0,6x2/j	J9 :Anémie, Hématome	D	I2	O	N	+/-	HBPM :cf Innohep
99-176	Oct. 98	M,43	MEDIATOR 2/j 6 ans	Insuffisance aortique	F	I2	O	O	O	Pb Europe _ 1° cas
99-113	Janv 99	F,71	LOPRIL	J4 :Augmentation lipase 3,5 N Amylase Normale	A	I1 C2S1	+/-	N	N	Vidal captopril : OK Vidal enalapril : RAS or cas et pub +++enalap.
99-180	Fev 99	F,36	LYSOCLINE	Fièvre à 39° paresthésies	A	I3	+/-	N	+/-	cf minocycline
99-77	Janv 99	F,45	OESCLIM	Eczéma	A	I3	N	O	N	A inscrire au RCP

Problème des modifications de l'annexe II et des notices destinées aux patients sans que les prescripteurs et les pharmaciens en soient avertis ainsi que les CRPV ?

Problème des mises en garde et précautions d'emploi qui ne sont pas reprises dans les effets secondaires ;
cf CONTALAX et dépendance.

Réunion des Pharmaciens Sentinelles pour la Santé Publique du 22 février 1999 :

- Mésusage avec Diprosone crème : pour dépigmentation, mélangée à du lait Poupina ou Vichy.
- Boîtes identiques pour CORVASAL* 2mg et 4mg
  PROXALYOC* et SPASFON LYOC*
- Confusion de noms : TERNEURINE, TENORMINE,
  MOCLAMINE, MODAMIDE
  ZECLAR, ZEFRA
  BEVITINE, BELUSTINE
  LOGIRENE, LOGECINE
  COVERSYL, CORVASAL ....

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AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE
DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

RÉPUBLIQUE FRANÇAISE

A-6

Saint-Denis, le 06 JUIL. 1999

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mercredi 12 mai 1999)

Etaient présents

Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, Mme DAVID-LAROCHE (suppléante de M. BECHTEL),M. BIOUR, Mme. HILAIRE-BUYS (suppléante de M. BLAYAC), Mme GUEDON-MOREAU (suppléante de M. CARON), Mme CHICHMANIAN, Mme ZENUT (suppléante M. ESCHALIER), Mme SGRO (suppléante M. ESCOUSSE), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme KREFT-JAIS, Mme THOMAS (répresentant le CRPV de Paris F. VIDAL), Mme LAINE-CESSAC, M. LAROUSSE, M. NOUAILLE (représentant de M. MERLE), Mme BARAILLE (suppléante de M. MONSTASTRUC), Mme LACOTTE (suppléante de M. MOULIN), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, M. TRENQUE, M. VANDEL, M. VIAL.
Mme CASTOT (représentant de M. le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle GOEBEL
Mme JOUSSELIN-PAUTROT
M. LANG
Melle MAUREL
M. MASSET
Mme MESSAN-MURPHY
Melle ROBINE
M. ROPERS
Mme ROMIEE

EXPERTS :
Mme BONITHON
M. CHAPLAIN

Assistaient à la réunion :

DEV :
Mme BAUMELOU
Mme COSTAGLIOLA
M. FERNANDEZ
Mme ROSSI

CRPV :
Mme AOUCHICHE HASSINE
Mme CHIFFOLEAU
Mme GENESTE
Mme GERMAIN
Mme GINISTY
Mme SARAZIN

143/147 Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

Etaient excusés
M. BEGAUD
M. BECHTEL
M. MALLARET
M. RICHE
Mme SOUBRIE
M.THUILLEZ
Monsieur le Directeur des Hôpitaux
Monsieur le Directeur Général de L'INSERM
Monsieur le Directeur Général de la Santé

La séance a exceptionnellement été présidée par Monsieur le Professeur C. LAROUSSE.

I - ADOPTION DU PROCÈS-VERBAL DE LA SÉANCE DU 30 MARS 1999

Le procès-verbal de la séance du 30 mars 1999 a été adopté avec les modifications suivantes :

Page 2 : Paragraphe III - CALCIDIA®
3 ème ligne : supprimer le "s" de "gardes".

Page 3 : Paragraphe III - NALADOR®
3 ème ligne : ajouter un "i" à "utilisation".

Paragraphe III - Acétylcystéine, carbocistéine
2 ème ligne et 6 ème ligne : remplacer "syndrome" par "réaction".

Page 7 : Paragraphe V-Enquête officielle LAMICTAL® : effets indésirables
2 ème rubrique : 2 ème ligne : remplacer le "P" majuscule de "Pharmacocinétique" par un "p" minuscule.
: 2 ème ligne : ajouter "également" après "ont été"
: 4 ème ligne : remplacer "suge" par "sujet"
: 5 ème ligne ajouter après "insuffisance hépatique" : "les rubriques "Mises en garde" et "Allaitement" doivent être également modifiées".

Page 8 : Paragraphe VIII - Point fibrates : photosensibilisation
2 ème ligne : ajouter un "s" à "Résumé".

Page 9 : Paragraphe VIII - Point fibrates : photosensibilisation
5 ème ligne : remplacer "un cas de réaction croisée" par "une réaction croisée"

Page 9 : Paragraphe IX-Point INNOHEP® : Priapisme
11 ème ligne : supprimer les termes "dans l'année" après "HBPM".

Page 10 : Paragraphe XI-Questions diverses/Association d'Aide Aux Victimes des Accidents des Médicaments
2 ème ligne : remplacer "utiliser" par "utilisée".

Page 5 : Paragraphe IV - Enquête officielle vaccination anti-hépatite B : effets indésirables/maladies auto-immunes : remplacer la partie consacrée aux maladies auto-immunes par le texte joint ci après.

VI POINT SUR LA PHARMACOVIGILANCE EUROPEENNE

Compte-rendu du groupe de travail européen de pharmacovigilance des 15 et 16 avril 1999

- Inhibiteurs de la protéase / lipodystrophies :
Un groupe d'experts comprenant des membres du Comité des Spécialités Pharmaceutiques (CSP) et des experts cliniciens a été mis en place pour évaluer le risque des lipodystrophies et ses conséquences.

- Inhibiteurs de la protéase / rhabdomyolyse :
Le pays rapporteur (Suède) a considéré que l'augmentation des CPK et la survenue de rhabdomyolyses étaient à rajouter dans le RCP de l'ensemble des produits de la classe. Les laboratoires ont fait appel. La proposition finale du groupe de pharmacovigilance est de mentionner ces effets en tant "qu'effets de classe" dans les RCP sans mentionner expressement le nom de la spécialité.

- Rituximab (MABTHERA®) :
Cet anticorps monoclonal indiqué dans les lymphômes de stade IV fait l'objet d'une surveillance renforcée depuis la survenue de plusieurs cas de réactions liées à la perfusion de rituximab (signes pulmonaires).
Par ailleurs, 6 observations de réactions cutanées graves (syndrome de Lyell, pemphygoïde bulleuse) ont été rapportées. Le laboratoire va déposer une demande de variation de type II (demande de modification de l'information).

- Sildénafil (VIAGRA®) :
La Variation de type II concernant l'interaction avec les inhibiteurs de la protéase est en cours d'évaluation. Le protocole de l'étude de surveillance post-commercialisation est toujours en cours d'élaboration.
Les atteintes hépatiques doivent également faire l'objet d'une surveillance.

- Anorexigènes et atteintes des valves cardiaques (article 15 de la Directive 75/319/CEE):
L'opinion du CSP concernant les anorexigènes est attendue pour le 20 avril 1999.
- Fenfluramine / dexfenfluramine : l'opinion sera probablement en faveur d'un retrait définitif des AMM de ces produits car le rapport bénéfice/risque reste négatif en raison des effets indésirables.
- Amphétaminiques : les nouveaux textes concernant les traitements de l'obésité recommandent des effets sur la perte de poids cliniquement significatifs et prolongés. Ces effets prolongés faisant défaut aux amphétaminiques, le CSP devrait considérer que les anorexigènes amphétaminiques dont les effets indésirables sont par ailleurs bien connus, doivent être retirés du marché.

- Sertindole (article 15 de la Directive 75/319/CEE) / morts subites :
L'évaluation dans le cadre de l'article 15 se poursuit. Les laboratoires doivent fournir les résultats de deux nouvelles études cliniques comparatives. L'opinion définitive du CSP est prévue pour le mois de juin 1999. Cet antipsychotique n'est pas autorisé en France.

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AGENCE FRANÇAISE DE SECURITE SANITAIRE DES [illegible]

RÉPUBLIQUE FRANÇAISE

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Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 02 SEP. 1999

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 22 Juin 1999)

Etaient présents

M. RICHE : Président
Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), M. BIOUR, M. BLAYAC, Mme BROCH (représentant le CRPV de Brest), M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. ESCHALIER, Mme SGRO (suppléante de M. ESCOUSSE), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme KREFT-JAIS, Mme GINISTY (représentant le CRPV de Paris - F. Vidal), Mme LAINE-CESSAC, M. LAROUSSE, M. MALLARET, M. MERLE, Mme LAPEYRE-MESTRE (suppléante de M. MON$TASTRUC), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE), M. TRENQUE, M. VANDEL, M. VIAL.
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant de M. le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Melle DELEAU
M. DHANANI
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M. JACQUET
M. LANG
Mme LEREBOURS
Melle MAUREL
M. MASSET
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Melle ROBINE
M. ROPERS
Mme ROMIEE
Mme SCHLOSSER
Mme WECHSLER

Assistaient à la réunion :

DEV :

Mme CALLENS
Mme COSTAGLIOLA

CRPV :

M. CLEMENT
M. COQUEREL
Mme PICAUD

Etaient excusés :
M. BEGAUD : Vice-Président
Mme ALBENGRES
Mme BAVOUX
M. BECHTEL
Mme THUILLEZ
Monsieur le Directeur Général de l'INSERM

VI - POINT SUR LA PHARMACOVIGILANCE EUROPEENNE.

Compte-rendu du groupe de travail européen de pharmacovigilance des 10 et 11 juin 1999.

- Inhibiteurs de la protéase / lipodystrophies :
Un groupe d'experts comprenant des membres du Comité des Spécialités Pharmaceutiques (CSP), des membres du groupe de travail de pharmacovigilance (Suède, Espagne et Belgique) et des experts cliniciens a été mis en place pour évaluer le risque des lipodystrophies et ses conséquences. Une première réunion a eu lieu le 28 mai 1999. La réunion suivante est programmée le 29 juin 1999. Les recommandations finales de ce groupe sont attendues pour septembre 1999.

- Association de lamivudine et zidovudine : atteintes mitochondriales et complications cérébrales chez l'enfant :
Les Etats membres ont été informés des conclusions de la réunion d'experts organisée en France le 31 mai 1999. La France doit proposer les principaux éléments d'une lettre d'information aux prescripteurs lors du groupe du travail de juillet 1999 pour adoption par le CSP de manière à ce qu'une information commune soit diffusée en Europe.

- Rituximab (MABTHERA®) :
Cet anticorps monoclonal indiqué dans les lymphomes de stade IV fait l'objet d'une surveillance renforcée depuis la survenue de plusieurs cas de réactions liées à la perfusion de rituximab (signes pulmonaires). Les données concernant les autopsies des patients décédés n'apportent aucun élément nouveau. Un protocole d'étude clinique sera discuté durant l'été.
Par ailleurs, 6 observations de réactions cutanées graves (syndrome de Lyell, pemphigoïde bulleuse) ont été rapportées. Une demande de variation de type II (demande de modification de l'information médicale) relative à ces observations est en cours d'évaluation.

- Sildénafil (VIAGRA®) :
Le protocole de l'étude de surveillance post-commercialisation doit être prochainement rediscuté. avec les laboratoires PFIZER.
A la suite de plusieurs notifications d'atteintes hépatiques survenues en dehors de l'Union européenne, les effets indésirables hépatiques font également l'objet d'une surveillance.
L'ajout d'une interaction médicamenteuse concernant le ritonavir et le saquinavir a été adopté par le CSP.

- Anorexigènes (article 15 de la Directive 75/319/CEE):
La plupart des laboratoires ont fait appel à l'opinion du CSP rendue en avril 99. De nouveaux pays rapporteurs et co-rapporteurs ont été nommés :
- Angleterre et Pays-Bas pour la fenfluramine, dexfenfluramine,
- Italie et Espagne pour la phentermine, amfépramone,
- Belgique et Portugal pour les autres anorexigènes.

L'opinion définitive du CSP est attendue pour fin juillet 1999.

- Sertindole (article 15 de la Directive 75/319/CEE) / morts subites :
Les rapporteurs concluent à un rapport bénéfice-risque négatif.
L'opinion du CSP est attendue pour fin juin 1999.

- Vigabatrin (article 12 de la Directive 75/319/CEE) / restrictions du champ visuel :
A la suite de l'opinion du CSP (mai 1999) modifiant les indications et les mises en garde du vigabatrin, les laboratoires ont préparé un nouveau RCP, une lettre d'information aux prescripteurs et un projet d'études cliniques.

- Inhibiteurs sélectifs de recapture de la sérotonine / syndrome de sevrage et dépendance :
Les éléments suivants apparaîtront dans la section "Effets indésirables" des RCP des produits de la classe :
- des syndromes de sevrage peuvent survenir à l'arrêt du traitement,
- liste de symptômes associés au syndrome de sevrage,
- une diminution progressive de la dose est recommandée pour tous les traitements excepté pour la fluoxétine (car longue demi-vie). Les RCP de la venlafaxine et de la paroxétine devront être plus détaillés quant aux modalités de diminution de la dose en fin de traitement car des syndromes de sevrage ont été rapportés plus souvent avec ces deux médicaments.
- il n'y a pas de données cliniques permettant d'exclure un risque de pharmacodépendance.

- Benfluorex / métabolisation en norfenfluramine :
le rapport rédigé par l'Italie en collaboration avec la France a été distribué aux Etats membres.
Les données disponibles ne permettant pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex, le groupe de travail a souhaité que les pays rapporteurs (France et Italie) proposent des modifications de RCP et adressent une liste de questions au laboratoire en demandant une mise à jour des données de tolérance et la réalisation d'une étude de pharmacocinétique du benfluorex et de ses métabolites.

Par ailleurs, mi-juin 1999, un cas d'HTAP d'allure primitive a été rapporté chez une femme de 51 ans traitée par benfluorex depuis 4 à 5 ans. Il s'agit du premier cas d'HTAP rapporté avec le benfluorex utilisé sans association de médicament anorexigène. 11 cas avaient auparavant été rapportés lors d'un traitement associant le benfluorex à de la dexfenfluramine dans 10 cas et à de l'amfépramone et du clobenzorex dans 1 cas.

Compte-tenu de ce nouveau cas, l'Agence a adressé un courrier aux laboratoires SERVIER leur demandant de verser, avant le 28 juin 1999, une mise à jour des données de tolérance ainsi que les données de pharmacologie et pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines. Un infofax a par ailleurs été envoyé à tous les Etats membres.

- Thiomersal / sensibilisation :
Un groupe de travail a été mis en place par le CSP pour étudier l'éventuelle toxicité de cet excipient présent dans certains vaccins, collutoires, collyres et gouttes nasales. L'OMS soulève le risque de neurotoxicité et néphrotoxicité du thiomersal, notamment chez l'enfant.
Le groupe de travail de pharmacovigilance est chargé de rédiger une mise en garde commune pour

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RÉPUBLIQUE FRANÇAISE

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 07 OCT 1999

COMMISSION NATIONALE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mercredi 7 Juillet 1999)

Etaient présents :

M. RICHE : Président
M. BEGAUD : Vice-président
Mme HARAMBURU (suppléante du Vice-président), M. BLAYAC (suppléant de Mme ALBENGRES), M. ANDREJAK, Mme ARDOIN, Mme AUTRET-LECA, Mme BALLEREAU, M. BARDIN, Mme LAINE-CESSAC (suppléante de Mme BAVOUX), M. REVEILLAUD (suppléant de M. CARLIER), M. CARON, Mme CHIRON, M. CRETON, Mme ESCHWEGE, M. OLLAGNIER (suppléant de M. IMBS), Mme JOUAN-FLAHAULT, Mme JOUGLARD, Mme KREFT-JAIS, M. LAMBERT, M. LAROUSSE, M. LAVAUD, M. VIAL, M. PRUGNAUD, Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme GOUJARD (représentant Monsieur le Directeur Général de l'INSERM),
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
M. ALEXANDRE (représentant Monsieur le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER.

Unité de Pharmacovigilance

Mme CASTOT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle GOEBEL
M. LANG
Mme LEREBOURS
M. MASSET
Mme MESSAN-MURPHY
Melle MAUREL
Mme PARIENTE-KHAYAT
Melle ROMIEE

Assistaient à la réunion (D.E.M.E.B)

Mme BAUMELOU
Mme CALLENS
Mme DURANTEAU
Mme DUMARCET
M. FERNANDEZ
Mme PAVLOVIC
Mme SAINT-RAYMOND
Mme SAINT-SALVI
Mme TCHINOU

143/147 Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01 55 87 30 00

a présidenc
dossiers con
il était rappo

Rapporteurs : Mme AUTRET-LECA, M. BENAICHE, Mme CHIFFOLEAU, Mme LAINE-CESSAC, Mme LAPEYRE, M. RICHE, Mme SGRO.

Experts : M. BUGAT, Mme COSTAGLIOLA, Mme ELEFANT, M. REVUZ, M. VERNANT.

Etaient excusés :

M. BOULU
M. CHASSANY
Mme DEGOS
M. GHISLAIN
M. GIROUD
M. MICLEA
M. MUNERA
M. ROUGEAU
M. DUPUIS (représentant de la Commission d'AMM)

VIII - QUESTIONS DIVERSES.

- Le Dr Anne CASTOT, chef de l'Unité de pharmacovigilance de l'AFSSAPS a annoncé son prochain départ de l'Unité pour prendre en charge à partir du mois d'août 1999, au sein de la Direction de l'Evaluation des Médicaments et des Produits Biologiques (DEMEB), la coordination des vigilances. Le futur responsable de l'Unité de pharmacovigilance sera le Dr Carmen KREFT-JAÏS.

- Cisapride (PREPULSID®) :

Un point sur la demande de modification d'information de la spécialité Prépulsid® déposée le 2 juin 1999 par les laboratoires Janssen-Cilag, titulaire de l'A.M.M., a été présenté par le Dr J. Caron.

Prépulsid® (cisapride) est autorisé en France selon une procédure nationale depuis 1988 dans l'indication du traitement du reflux gastro-oesophagien, de l'oesophagite par reflux gastro-oesophagien et des troubles liés à un retard de l'évacuation gastrique (gastroparésie).

En juin 1998 : compte-tenu des effets arythmogènes du cisapride, la Food and Drug Administration (F.D.A.) a pris la décision de réserver l'utilisation du cisapride au traitement de 2ème intention du reflux gastro-oesophagien, en renforçant considérablement les rubriques "Contre-indications", "Mises en garde et précautions d'emploi" du Résumé des Caractéristiques du Produit (R.C.P.).

Parallèlement, les laboratoires Janssen-Cilag ont déposé *fin juin 1998* une demande de modification d'information dans tous les pays de l'Union européenne. Ce sujet a été abordé au Comité des Spécialités Pharmaceutiques (CSP) de l'Agence Européenne pour l'Evaluation des Médicaments (EMEA) réuni les *21 et 23 juillet 1998*. Ce dernier a exprimé la nécessité d'une réévaluation du rapport bénéfice/risque et d'une harmonisation du RCP au niveau européen.

En septembre 1998 : la France a soumis aux états membres de l'Union européenne un rapport d'évaluation relatif au risque et *en mars 1999* un rapport d'évaluation relatif à l'efficacité.

En février 1999 : les laboratoires Janssen-Cilag ont soumis les résultats d'une expertise clinique menée par des cardiologues américains sur tous les effets indésirables cardiaques rapportés depuis la mise sur le marché de Prépulsid®.

En mai 1999 : les laboratoires Janssen-Cilag ont soumis les résultats d'une étude d'interaction chez le volontaire sain qui met en évidence une augmentation de 50% de la biodisponibilité du cisapride lors de l'administration de 200 ml de jus de pamplemousse .

Le 5 mai 1999 : les laboratoires Janssen-Cilag ont informé l'AFSSAPS que le libellé du cisapride était en cours de révision au niveau de la F.D.A. afin d'introduire de nouvelles mises en garde et contre-indications notamment chez les patients ayant des antécédents familiaux connus de prolongation du QT et les patients ayant une bradycardie cliniquement significative ainsi que l'interaction avec le jus de pamplemousse. L'Unité de Pharmacovigilance de l'AFSSAPS a communiqué cette information le 26 mai 1999 à l'ensemble des états membres de l'Union européenne. Ces modifications ont donné lieu aux Etats-Unis à une lettre d'information des prescripteurs (*parue le 1er juin 1999* sur le site internet des laboratoires Janssen-Cilag/Etats-Unis et *le 10 juin 1999* sur le site de la F.D.A.).

Le *25 mai 1999*, un groupe d'experts a été réuni à l'AFSSAPS afin de réévaluer le rapport bénéfice/risque du cisapride chez l'adulte et l'enfant. Il a été proposé de renforcer les mises en garde

et précautions d'emploi et de restreindre les indications.

Le *2 juin 1999*, les laboratoires Janssen-Cilag ont déposé auprès de l'AFSSAPS et dans tous les états membres de l'Union européenne une demande de modification de l'information médicale.

Cette demande concerne les rubriques "Posologie et mode d'administration" ("ajout" du jus de pamplemousse), "Contre-indications" (renforcement de la rubrique en cas d'association avec des médicaments susceptibles d'allonger le QT, hypokaliémie, hypomagnésémie, bradycardie cliniquement significative, QT long congénital et antécédents familiaux de QT long congénital), "Mises en garde" (renforcement de la rubrique), "Interactions" (renforcement de la rubrique), "Effets indésirables", "Surdosage", "Propriétés pharmacodynamiques" et" Données de sécurité préclinique".
Ce dossier a été présenté lors du Groupe de Travail Européen de Pharmacovigilance réuni les *10 et 11 juin 1999* à Londres. Le Groupe de travail a approuvé les modifications du R.C.P. proposées par les laboratoires Janssen-Cilag.

Selon le rapporteur la demande de modification de l'information médicale est acceptable sous réserve de quelques amendements. Le libellé proposé par le rapporteur a été distribué en séance. Une lettre d'information des prescripteurs devra être envoyée par les laboratoires Janssen-Cilag.

- Métamizole / agranulocytose :

A la demande du CSP de l'Agence Européenne pour l'Evaluation des Médicaments et à la suite de l'évaluation par la Suède du risque de survenue d'agranulocytoses, la France est chargée de réévaluer le rapport bénéfice/risque du métamizole pour la réunion du CSP prévue à la fin septembre 1999.
A cet effet, un groupe *ad-hoc* de la Commission d'Autorisation de Mise sur le Marché est prévu le jeudi 9 septembre 1999 à 14h00. Ce groupe sera composé de membres de la Commission d'AMM et de membres de la Commission Nationale de Pharmacovigilance.

Une télécopie sera prochainement adressée à tous les membres de la Commission Nationale de Pharmacovigilance afin de savoir qui souhaite participer à ce groupe de travail.

- Benfluorex (MEDIATOR®) :

En France, le benfluorex a fait l'objet d'une enquête officieuse dès 1995 en raison de sa parentée structurale avec les anorexigènes amphétaminiques. Cette enquête est devenue officielle en mai 1998.

Depuis septembre 1998, à la demande des autorités sanitaires italiennes, le benfluorex fait également l'objet d'une évaluation au niveau du Groupe de Travail Européen de Pharmacovigilance (l'Italie et la France sont rapporteurs sur ce dossier). L'un des motifs de cette enquête est la métabolisation du benfluorex en 9 métabolites dont l'un des 3 principaux est la norfenfluramine qui est également le métabolite des spécialités pharmaceutiques appartenant à la classe des "fenfluramines".

Les données disponibles issues de l'enquête officielle de pharmacovigilance ne permettent pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex. Cependant, des doutes persistent concernant notamment le devenir de la norfenfluramine. La réalisation par les laboratoires SERVIER d'une étude de pharmacocinétique du benfluorex et de ses métabolites pourrait permettre de lever ces doutes.

Au courant du mois de juin 1999, un cas d'Hypertension Artérielle Pulmonaire (HTAP) d'allure primitive a été rapporté chez une femme de 51 ans traitée par benfluorex depuis 4 à 5 ans. Il s'agit du

premier cas d'HTAP rapporté avec le benfluorex utilisé sans association de médicament anorexigène. 11 cas avaient auparavant été rapportés lors d'un traitement associant le benfluorex à de la dexfenfluramine dans 10 cas et à de l'amfépramone et du clobenzorex dans 1 cas.

Cette observation est en cours de documentation et le service de Pneumologie de l'hôpital Antoine Béclère entreprend une interrogation de tous les patients ayant une HTAP à la recherche d'une prise antérieure de MEDIATOR®.

Ce dossier devrait être discuté à la prochaine réunion du Groupe de Travail Européen de Pharmacovigilance les 12 et 13 juillet 1999.

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AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

RÉPUBLIQUE FRANÇAISE

A-8

Saint-Denis, le 30 DEC. 1999

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 7 Septembre 1999)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme LOUBEYRE (suppléante de Mme BAVOUX), M. BIOUR, M. BLAYAC, M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. COQUEREL, M. ESCHALIER, Mme HARAMBURU, Mme RICHARD (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme LILLO LE LOUET (représentant le CRPV de Paris - Broussais), M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris - F. Widal), Mme LAINE-CESSAC, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), M. MALLARET, M. MERLE, M. MONTASTRUC, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, Mme PERAULT (suppléante de M. VANDEL), M. VIAL,
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
M. ALEXANDRE (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme BIDAULT
Melle DELEAU
M. DHANANI
Melle JULLIAN
Mme KREFT-JAIS
M. LANG
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Mme ROMIEE
Mme WEBER

Assistaient à la réunion :

DEMEB :

Mme CASTOT
Mme DEGUINES
Mme LEBONHEUR
Mme PELLANNE
M. SAWAYA
Mme WECHSLER

CRPV :

Mme BROCH
Mme DAVID-LAROCHE
Mme LE GAL
Mme MOSQUET
Mme RAYMOND

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

Etaient excusés :

M. BEGAUD : Vice-Président
M. ESCOUSSE
Monsieur le Directeur Général de l'INSERM
Madame le Directeur des Hôpitaux

VI - POINT SUR LA PHARMACOVIGILANCE EUROPEENNE

Compte-rendu du Groupe de travail européen de pharmacovigilance des 12 et 13 juillet 1999 :

■ Lamivudine (EPIVIR®, COMBIVIR®) et zidovudine (RETROVIR®) en combinaison thérapeutique / Atteintes mitochondriales et complications cérébrales chez l'enfant

La France a présenté la lettre aux prescripteurs diffusée sur son territoire concernant les modalités de traitement et de prévention de l'infection par le VIH pour le couple mère-enfant au vu des données actuellement disponibles et des risques potentiels de dysfonctionnement mitonchondrial. L'ensemble des états membres de l'Union européenne ont accepté les propositions françaises.

■ Pramipexole (DAQUIRAN®, MIRAPEXIN®, SIFROL®) / Attaques de sommeil

Le pramipexole est un nouvel antiparkinsonien enregistré aux Etats-Unis depuis juillet 1997 et en Europe depuis octobre 1997 selon la procédure centralisée. Dans l'Union européenne, ce médicament n'est commercialisé qu'en Allemagne, en Suède, au Danemark, en Espagne, en Finlande et aux Pays-Bas. Aux Etats-Unis, 19 cas d'attaque de sommeil ont été rapportés chez des patients traités par pramipexole. Dans 14 cas, cette attaque de sommeil est survenue pendant que le patient conduisait un véhicule ; 9 d'entre eux ont été victimes d'un accident de voiture. L'exposition au médicament est estimé à 100 000 patients-année. En Europe, une mesure de restriction urgente (modification du RCP en urgence) ainsi que l'envoi d'une lettre aux prescripteurs ont été décidées par l'Agence européenne pour l'évaluation des médicaments. Les laboratoires Pharmacia & Upjohn et Boehringer Ingelheim ont été entendus et le Groupe de travail européen de pharmacovigilance a finalisé les modifications à apporter au RCP. La France et l'Italie ont proposé que la conduite de véhicules soit contre-indiquée chez les patients traités par pramipexole. L'avis du Groupe a été transmis aux membres du Comité des spécialités pharmaceutiques (CSP) le 12 juillet 1999.

■ Sildénafil (VIAGRA®, PATREX®) / Etudes de post-marketing

Le protocole de l'étude de surveillance en post-marketing a été revu par les laboratoires PFIZER et sera finalisé lors de la réunion du Groupe de travail de pharmacovigilance en septembre 1999. Il sera ensuite transmis au CSP en octobre 1999. Des études supplémentaires ne paraissent pas nécessaires pour le moment.

■ Trovafloxacine, alatrofloxacine (TROVAN®, TURVEL®) / Evaluation du risque d'hépatotoxicité en comparaison avec les autres fluoroquinolones (ciprofloxacine, grepafloxacine, levofloxacine, norfloxacine, ofloxacine, pefloxacine, sparfloxacine, temafloxacine)

Plusieurs états membres ont en charge de rédiger un rapport contenant les cas rapportés d'hépatotoxicité et les données de consommation d'une fluoroquinolone. Ce rapport devra être adressé aux états rapporteur et co-rapporteur (Pays Bas et France) qui rédigeront un rapport comportant les données compilées de l'ensemble des fluoroquinolones afin de pouvoir comparer

leur hépatotoxicité.

■ Sertindole / Cardiotoxicité

Sertindole est un antipsychotique qui n'est pas autorisé en France mais a fait l'objet d'une procédure de reconnaissance mutuelle dans plusieurs états membres de l'Union européenne. En juin 1999, dans le cadre de la procédure d'arbitrage communautaire, le CSP a décidé de suspendre la commercialisation de cette spécialité pendant un an. Durant cette période, les résultats d'études cliniques portant sur l'efficacité et la tolérance du sertindole seront réévalués.

■ Métamizole / Agranulocytoses et anaphylaxie

Le Groupe de travail européen de pharmacovigilance a adopté les éléments d'information à apporter aux professionnels de santé et qui devraient figurer dans le RCP des spécialités concernées. Cependant, chaque état membre reste libre de l'information à délivrer. La France est chargée de réévaluer le rapport bénéfice-risque du métamizole.

■ Anti-histaminiques non sédatifs / Risques cardiovasculaires

Les laboratoires JANSSEN-CILAG ont arrêté la commercialisation au niveau international de leur spécialité HISMANAL® (astémizole). Le devenir des génériques de cette spécialité est un problème pour l'instant non résolu.
Les risques cardiovasculaires liés au traitement par féxofénadine (TELFAST®) feront l'objet d'un rapport rédigé par le Royaume-Uni qui sera diffusé en septembre 1999. Les effets indésirables gastro-intestinaux feront également l'objet d'une discussion.

■ Doxycycline / Atteintes oesophagiennes

La Suède a présenté son rapport sur les atteintes oesophagiennes liées à l'utilisation de leur spécialité Doryx® : gélule contenant des minigranules de doxycycline chlorydrate (ou hyclate). Elle envisageait de retirer du marché cette spécialité en considérant que ce sel d'hyclate était seul responsable des atteintes oesophagiennes : 8 cas ont été notifiés depuis la mise sur le marché en 1994 du Doryx® alors qu'il n'y avait aucun cas avec les autres sels de doxycycline (monohydrate ou carraghenate) depuis le retrait des comprimés et des gélules de doxycycline hyclate (Vibramycine®) en 1979 et 1983. La France considère que le problème est plus lié à la forme pharmaceutique (gélule) qu'à la présence d'hyclate dans la formulation. La Suède transmettra prochainement le texte de modification du RCP de la spécialité Doryx® renforcant l'information sur ce risque digestif.

■ Interféron α-2b / Ischémies périphériques, paralysies, atteintes pancréatiques, stéatoses hépatiques

Le Groupe de travail européen de pharmacovigilance a accepté que ces effets indésirables soient mentionnés dans le RCP des spécialités composées d'interféron alfa-2b (ALFATRONOL® et

VIRTRON®) dont la demande d'AMM selon la procédure centralisée est en cours d'évaluation. Concernant INTRONA® et VIRAFERON®, enregistrés selon la procédure de reconnaissance mutuelle, le Groupe de travail a proposé que ces modification interviennent lors du passage de ces spécialités en procédure centralisée plutôt que par le biais d'une variation de type II.

- Analgésiques contenant de la vitamine C / Décision des autorités sanitaires belges

Monsieur le docteur X. Kurz a informé le Groupe de travail européen de pharmacovigilance qu'en Belgique, l'acide ascorbique ne peut plus être intégré dans des spécialités en tant que principe actif. Cependant, son emploi est encore possible en tant qu'excipient.

- Nimésulide (NEXEN®) / Effets indésirables cutanés et hépatiques, syndromes de Reye

Le Groupe de travail européen a approuvé les propositions du Portugal datant du 8 juin 1999. Cependant, le RCP n'a pas été finalisé. La France ne souhaite pas attendre la proposition définitive pour modifier le RCP de la spécialité disponible en France dans le but d'avertir le plus rapidement possible les professionnels de santé des effets indésirables hépatiques observés avec le nimésulide.

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RÉPUBLIQUE FRANÇAISE

B-2

AGENCE
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ

3611

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le [illegible] 1999

COMMISSION NATIONALE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 21 Septembre 1999)

Etaient présents :

M. RICHE : Président
Mme ALBENGRES, M. ANDREJAK, Mme ARDOIN, Mme AUTRET-LECA, Mme BALLEREAU, M. GILLET (suppléant de M. BARDIN), Mme BAVOUX, M. BOULU, M. CARLIER, Mme CHIRON, M. CRETON, Mme ESCHWEGE, M. SARRUT (suppléant de M. GHISLAIN), M. GIROUD, M. IMBS, Mme JOUAN-FLAHAULT, Mme JOUGLARD, M. LAMBERT, M. LAROUSSE, Mme WOOD (suppléante de M. LAVAUD), M. MICLEA, M. MUNERA. M. PRUGNAUD, M. ROUJEAU, M. VIAL,
Mme GOUJARD (représentant Monsieur le Directeur Général de l'INSERM),
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'AFSSAPS).

Unité de Pharmacovigilance

Mme BIDAULT
M. DHANANI
Mme FOSSET-MARTINETTI
M. JACQUET
Mmé JOUSSELIN-PAUTROT
Mme KREFT-JAIS
Mme LEREBOURS
Mme PARIENTE-KHAYAT
Melle ROBINE
Mme ROMIEE

Assistaient à la réunion (D.E.M.E.B)

M. FERNANDEZ
Mme HEDO
Mme KAPETANOVIC
Melle LEBONHEUR
Mme MANCEL
Mme PELLANNE
Mme REIDIBOYM
Mme REY-QUINIO
M. SAWAYA

Rapporteurs : Mme ALBENGRES, M. ANDREJAK, Mme AUTRET-LECA, Mme GUY, M. OLLAGNIER, Mme PERAULT, M. VANDEL

Experts : M. COHEN, M. PERROT

Etaient excusés : M. BEGAUD, Vice-Président
M. CARON
M. CHASSANY
Mme DEGOS
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux)
M. LAGIER (Conseiller scientifique)
M. DUPUIS

VII- QUESTIONS DIVERSES

1) Anorexigènes :

Le 31 août 1999, le Comité des Spécialités Pharmaceutiques (CSP) a considéré que le rapport bénéfice-risque de l'ensemble des médicaments anorexigènes était négatif et a recommandé leur retrait définitif du marché communautaire.

Le rapport bénéfice-risque des fenfluramines est négatif en raison d'un profil de sécurité d'emploi défavorable (notamment survenue d'hypertension artérielle pulmonaire et atteinte des valves cardiaques). Ces médicaments ne sont plus commercialisés depuis septembre 1997.
Le rapport bénéfice-risque des amphétaminiques est négatif en raison d'un manque d'efficacité dans la prise en charge prolongée de l'obésité, d'autant que leur effet diminue progressivement au cours du temps et qu'ils peuvent entraîner une pharmacodépendance incompatible avec un traitement prolongé.

A la suite de l'avis du CSP, une décision concernant l'ensemble de ces médicaments sera prise prochainement par la Commission européenne.
Dans l'attente de cette décision, l'AFSSAPS va procéder, le 19 octobre prochain, à une suspension des autorisations de mise sur le marché des médicaments anorexigènes amphétaminiques disponibles en France.

2) ARAVA® (léflunomide) / procédure centralisée. Pays-Bas état rapporteur :

Cette spécialité, indiquée dans la polyarthrite rhumatoïde, a obtenu début septembre 1999 une autorisation de mise sur le marché selon une procédure européenne centralisée. Le léflunomide est autorisé aux Etats-Unis depuis 1 an. 70 000 patients ont déjà été traités et plusieurs observations de pancytopénie et de syndrome de Stevens-Johnson ont été rapportées. Ce dossier sera discuté à la prochaine réunion du CSP qui se tiendra le 23 septembre 1999.

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E1

ANNEXE 1
Suivi des dossiers au 09/11/99

RÉPUBLIQUE FRANÇAISE

A G E N C E
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

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Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 02 FEV. 2000

COMMISSION NATIONALE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 9 Novembre 1999)

Etaient présents :

M. RICHE : Président
Mme HARAMBURU (suppléante de M. BEGAUD Vice-Président)
Mme ALBENGRES, M. ANDREJAK, Mme ARDOIN, Mme AUTRET-LECA, Mme ROULEAU (suppléante de Mme BALLEREAU), Mme LAINE-CESSAC (suppléante de Mme BAVOUX), M. BOULU, M. CARLIER, M. CARON, M. CHASSANY, M. SARRUT, M. GIROUD, M. IMBS, Mme JOUAN-FLAHAULT, Mme JOUGLARD, Mme SGRO, M. HARRY (suppéant de M. LAMBERT), M. LAROUSSE, M. LAVAUD, M. MICLEA, M. MUNERA, M. PRUGNAUD, M. VIAL
Mme GOUJARD (représentant Monsieur le Directeur Général de l'INSERM),
Mme LAGARDE(représentant Monsieur le Directeur Des Hôpitaux)
Mme CHOMA (repésentant Monsieur le Directeur Général de la Santé),
Mme KREFT-JAIS (représentant Monsieur le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER.

Unité de Pharmacovigilance

Mme BIDAULT
M. DHANANI
Mme FOSSET-MARTINETTI
Melle FRADET
Melle GOEBEL
Mme JOLIMOY
Mme LEREBOURS
Mme MESSINA
Mme PARIENTE-KHAYAT
Melle ROBINE

Assistaient à la réunion (D.E.M.E.B)

Mme ALLUE
Mme CAIZERGUES
Mme HEDO
Mme JAGER
Mme LEBONHEUR
M. LENOIR
Mme MANCEL
Mme MEHEUT
Mme MIGNON
Mme PAVLOVIC
Mme PELLANNE
M. SAWAYA
Mme SAINT-SALVI

COMMISSION NATIONALE DE PHARMACOVIGILANCE DU 9 NOVEMBRE 1999

Rapporteurs : Mme AUTRET-LECA
Mme ALBENGRES
Mme BENEDETTI
Mme LE BELLER
Mme NOBLET
M. OLLAGNIER

Etaient excusés : M. BARDIN
Mme CHIRON
M. CRETON
Mme DEGOS
Mme ESCHWEGE
M. ROUJEAU

Date de la Commission Nationale de Pharmacovigilance	Sujet	Suites
07/07/98	**CLEDIAL / atteintes hépatiques**	Réévaluation du rapport bénéfice / risque : commission AMM 06/05/99 Suspension AMM le 02/07/99
	SEROPRAM / effets indésirables	Rectificatif d'AMM 09/09/99
22/09/98	**TOPALGIC / effets indésirables**	Rectificatif d'AMM 31/03/99
	GEMZAR / effets cardiaques et radiosensibilisation	Rectificatif d'AMM 21/01/99
10/11/98	**NAVELBINE / effets cardiaques**	Groupe de travail des médicaments anticancéreux (GTMAC) 09/99 Rectificatif d'AMM en cours
	Allopurinol / hypersensibilité et toxidermies	Rectificatif d'AMM le 09/04/99 Communiqué de presse le 30/03/99
	Alvérine / effets indésirables	Réévaluation du rapport bénéfice / risque : les firmes ont déposé un dossier en 09/99 : commission AMM fin 1999 ou début 2000.
22/12/98	**INNOHEP / accidents hémorragiques**	Rectificatif d'AMM en 08/99. Lettre d'information aux prescripteurs et pharmaciens en 08/99 (envoyée par le laboratoire). Révision de la classe des héparines de bas poids moléculaire (HBPM) par le groupe Thrombose en cours.
	VIAGRA / effets indésirables	Modification du RCP (Variation type II) finalisée en novembre 99
	Hydroxyéthylamidons / atteintes hématologiques et hépatiques	Communiqué de presse le 21/04/99 Réévaluation du rapport bénéfice / risque prochainement
10/02/99	**Inh. Recapture sérotonine / syndromes hémorragiques**	Cf. Commission Nationale du 07/07/99

	ZOLOFT / effets indésirables	Rectificatif d'AMM en cours (intégrant les syndromes hémorragiques)
	ATRIUM / effets indésirables	Réévaluation du rapport bénéfice / risque : commission AMM du 09/12/99
	GABITRIL / troubles visuels	Modification du RCP (Variation type II) finalisée en octobre 99
13/04/99	**Nimésulide / effets hépatiques**	Modifications du RCP examinées par le groupe de travail (GTI) du 13/09/99 : Rectificatif d'AMM en décembre 99
	LAMISIL / effets indésirables	Groupe de travail « dermatologie » adopté le 14/10/99 Rectificatif d'AMM le 04/11/99
	ROACCUTANE / effets indésirables	Groupe de travail « dermatologie » en 11/99
	Immunoglobulines IV / effets rénaux	Rectificatif d'AMM en avril 99
	Fibrates / photosensibilisation	Sept 99 : demande de modification en cours de dépôt par les laboratoires.
01/06/99	**Vinca-alcaloïdes / effets cardiaques**	Groupe de travail des médicaments anticancéreux (GTMAC) : 09/99 Rectificatif d'AMM en cours
	Vaccins contre l'hépatite B / effets indésirables	En attente suite des études.
	Inh. de la transcriptase inverse / grossesse / cytopathies mitochondriales	Communiqué de presse en juin 99
	Syndrome de Reye / Aspirine	

	NOVANTRONE / leucémies secondaires	Réévaluation du rapport bénéfice / risque : En attente dépôt du dossier par le laboratoire puis Groupe de travail des médicaments anticancéreux (GTMAC) Modification du RCP : en cours
	Noramidopyrine (métamizole) /effets indésirables	Réévaluation du rapport bénéfice / risque à la demande du Comité des Spécialités Pharmaceutiques (CSP) : réunion le 18/11/99. Réévaluation en cours.
07/07/99	**Inh. Recapture sérotonine / syndromes hémorragiques**	Rectificatifs d'AMM en cours.
	DOXIUM / agranulocytoses	Rectificatif d'AMM en cours. Réévaluation du rapport bénéfice / risque au GTT du 18/11/99 : sursis à statuer dans l'attente de la réévaluation des 7 cas d'agranulocytose espagnols.
	ROACCUTANE / grossesse	En cours
	LAMICTAL / effets indésirables	Rectificatif d'AMM en novembre 99
	Anthracyclines / leucemies secondaires	Groupe de travail des médicaments anticancéreux (GTMAC) 08/10/99 Réévaluation du rapport bénéfice / risque : En attente dépôt des dossiers par les laboratoires Rectificatifs d'AMM en cours.

Annexe National
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AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

D.E.M.E.B.
Unité de Pharmacovigilance

SUIVI DES DOSSIERS
PRESENTES EN COMMISSION NATIONALE DE PHARMACOVIGILANCE
DEPUIS LE 7 JUILLET 1998

Mise à jour du 15 mars 2000

Date de la Commission Nationale de Pharmacovigilance	Sujet	Suites
07/07/98	**CLEDIAL / atteintes hépatiques**	Réévaluation du rapport bénéfice / risque : commission AMM 06/05/99. Suspension AMM le 02/07/99.
	SEROPRAM / effets indésirables	Rectificatif d'AMM 09/09/99.
22/09/98	**TOPALGIC / effets indésirables**	Rectificatif d'AMM 31/03/99.
	GEMZAR / effets cardiaques et radiosensibilisation	Rectificatif d'AMM 21/01/99.
10/11/98	**NAVELBINE / effets cardiaques**	Groupe de travail des médicaments anticancéreux (GTMAC) 09/99 . Rectificatif d'AMM 01/02/2000.
	Allopurinol / hypersensibilité et toxidermies	Rectificatif d'AMM le 09/04/99. Communiqué de presse le 30/03/99.
	Alvérine / effets indésirables	Réévaluation du rapport bénéfice / risque : GTT 20/01/2000 : retrait du marché à envisager pour Spasmavérine et Météospasmyl, suppression de l'alvérine de la composition de Schoum et Hepatoum.
22/12/98	**INNOHEP / accidents hémorragiques**	Rectificatif d'AMM en 08/99. Lettre d'information aux prescripteurs et pharmaciens en 08/99 (envoyée par le laboratoire). Révision de la classe des héparines de bas poids moléculaire (HBPM) par le groupe Thrombose en cours.
	VIAGRA / effets indésirables	Modification du RCP (Variation type II) finalisée en novembre 99.
	Hydroxyéthylamidons / atteintes hématologiques et hépatiques	Communiqué de presse le 21/04/99. Réévaluation du rapport bénéfice / risque. Commission AMM du 27/01/2000 : révision du RCP (indications, mises en garde), nécessité d'une information des prescripteurs.

10/02/99	**Inh. Recapture sérotonine / syndromes hémorragiques**	Cf. Commission Nationale du 07/07/99.
	ZOLOFT / effets indésirables	Rectificatif d'AMM 14/01/2000 (intégrant les syndromes hémorragiques).
	ATRIUM / effets indésirables	Réévaluation du rapport bénéfice / risque : commission AMM du 09/12/99 : suspension de l'AMM. Information des prescripteurs prévue fin mars 2000 et retrait de lots prévu fin avril 2000.
	GABITRIL / troubles visuels	Modification du RCP (Variation type II) finalisée en octobre 99. Rectificatif d'AMM 30/11/99.
13/04/99	**Nimésulide / effets hépatiques**	Modifications du RCP examinées par le gronpe de travail (GTI) du 13/09/99 . Rectificatif d'AMM 06/12/99.
	LAMISIL / effets indésirables	Groupe de travail « dermatologie » adopté le 14/10/99. Rectificatif d'AMM le 04/11/99.
	ROACCUTANE / effets indésirables	Groupe de travail « dermatologie » en 11/99. Demande de modification du RCP programmée au Groupe de travail « dermatologie » du 18/04/2000.
	Immunoglobulines IV / effets rénaux	Rectificatif d'AMM en avril 99.
	Fibrates / photosensibilisation	Rectificatifs d'AMM en cours.
01/06/99	**Vinca-alcaloïdes / effets cardiaques**	Groupe de travail des médicaments anticancéreux (GTMAC) : 09/99 . Rectificatif d'AMM 01/02/2000.
	Vaccins contre l'hépatite B / effets indésirables	En attente suite des études.

	Inh. de la transcriptase inverse / grossesse / cytopathies mitochondriales	Communiqué de presse en juin 99.
	Syndrome de Reye / Aspirine	
	NOVANTRONE / leucémies secondaires	Réévaluation du rapport bénéfice / risque : En attente dépôt du dossier par le laboratoire puis Groupe de travail des médicaments anticancéreux (GTMAC). Modification du RCP : rectificatif d'AMM en février 2000.
	Noramidopyrine (métamizole) /effets indésirables	Réévaluation du rapport bénéfice / risque à la demande du Comité des Spécialités Pharmaceutiques (CSP) : réunion le 18/11/99. Réévaluation en cours.
07/07/99	**Inh. Recapture sérotonine / syndromes hémorragiques**	Rectificatifs d'AMM en cours.
	DOXIUM / agranulocytoses	Rectificatif d'AMM en cours. Réévaluation du rapport bénéfice / risque au GTT du 18/11/99 : sursis à statuer dans l'attente de la réévaluation des 7 cas d'agranulocytose espagnols.
	ROACCUTANE / grossesse	Demande de modification du RCP programmée au Groupe de travail « dermatologie » du 18/04/2000.
	LAMICTAL / effets indésirables	Rectificatif d'AMM 20/12/ 99.
	Anthracyclines / leucemies secondaires	Groupe de travail des médicaments anticancéreux (GTMAC) 08/10/99 Réévaluation du rapport bénéfice / risque : En attente dépôt des dossiers par les laboratoires. Rectificatifs d'AMM en février 2000.
21/09/99	**Traitements à visée immunostimulante / effets indésirables**	Révision des indications : les laboratoires doivent déposer des propositions en 03/2000 puis l'ensemble du dossier sera revu en groupe de travail.

	Doxycycline / Atteintes oesophagiennes	Cf. commission nationale du 09/11/99.
	DUPHASTON / effets indésirables	Groupe de travail Interne (GTI) janvier 2000. Rectificatif d'AMM en cours de rédaction.
	EXELON / troubles de la conduction auriculo-ventriculaire	En attente du dépôt par le laboratoire d'une demande de modification de l'information (Variation type II).
	Pramipexole / attaques de sommeil	Modification du RCP en urgence + communiqué de l'Agence européenne en août 1999.
09/11/99	**VIAGRA / effets indésirables en France**	Propositions de la Commission Nationale adressées au pays rapporteur (Pays-Bas) lors de l'évaluation du PSUR (02/2000). Une demande de modification de l'information (Variation type II) sera demandée au laboratoire.
	Doxycycline / Atteintes oesophagiennes	Suspension de la forme gélule le 01/02/2000, modification du RCP de la forme comprimé le 04/02/2000 et communiqué de presse le 08/02/2000.
	DISULONE / effets indésirables	Programmé au groupe de travail « dermatologie » du 18/04/2000.
	Méthotrexate / effets indésirables	Groupe de travail des médicaments anticancéreux (GTMAC) de février 2000 dont l'approbation est prévue le 20 mars 2000 (Commission AMM).

C-1

12 Oct 99

Final AR

REVISED ASSESSMENT REPORT

RELEVANCE OF METABOLIC PATHWAYS OF BENFLUOREX TO NORFENFLURAMINE

Medicinal product: Mediaxal®

Manufacturing Authorisation Holder: Laboratoires Servier

Active constituent: benfluorex

Originating Member States: Italy, France

Assessors: Dr. Giuseppe Pimpinella, Dr. Renato Bertini Malgarini

Contact point: Italian Ministry of Health

Pharmacovigilance Unit

TEL: 0039 06 5994 3212

FAX: 0039 06 5994 3554

Confidential

1. BACKGROUND

Following the report of a case of pulmonary hypertension occurred in France, the Colleagues of Agence du Medicament asked the Laboratoires Servier to provide further documentation for safety, efficacy and pharmacokinetic profile of benfluorex compared to those of fenfluramine and dexfenfluramine.

The French experts have also provided to Italian Ministry of Health the Documentation from the Laboratoires Servier and a joint assessment has been carried out.

2. DATA ANALYSIS

Pharmacokinetic parameters after 14 days treatment.

		AUC 24 (ng ml-1 h)	Cmin (24h) (ng ml-1)	Cmax (ng ml-1)
Benfluorex 3x 150 mg	dl -norfenfluramine	1149 ± 286	43 ± 8	59 ± 15
Dexfenfluramine 2x 15 mg	d-fenfluramine	1060 ± 316	34 ± 7	70 ± 15
	d-norfenfluramine	527 ± 281	18 ± 10	26 ± 13
Fenfluramine 60 mg	d-fenfluramine	1014 ± 445	33 ± 12	65 ± 26
	l-fenfluramine	1581 ± 778	54 ± 24	97 ± 47
	d-norfenfluramine	377 ± 136	14 ± 5	21 ± 8
	l-norfenfluramine	586 ± 210	21 ± 9	32 ± 13

From the data in the table, we can derive that an exposition to 450 mg/day of benfluorex (only metabolised to norfenfluramine) leads to a norfenfluramine level that is in the same magnitude order of that observed after a 60 mg/day dose of fenfluramine (the contribution of dl-fenfluramine and dl-norfenfluramine has been taken into account).

2.1 Clinical trials

Only one long term (29 weeks) trial in obese patients with type II diabetes has been carried out. In this study benfluorex was compared to placebo and to metformin. The considered parameters were weight loss and glycosylated haemoglobin.

Weight loss was not significant among the three groups.

Glycosylated haemoglobin showed a significant decrease in benfluorex treated patients with respect to placebo (HbA1c -0,6% and +0,5% respectively).

However, benfluorex was less effective of metformin (-0,6 % and -1% respectively).

It must be pointed out that this study is an unpublished internal report and confidence intervals were not available.

Concerning the indication in hyperlipidaemia, there are no data for therapy duration longer than 1 month and numerous therapeutic alternatives are available.

Furthermore, for these short term studies no quantitative data for serum lipids reduction are provided have been provided by the Company.

3. Pharmacovigilance data.

A part from the case of pulmonary hypertension that is still under evaluation, no new significant data have been submitted.

5. Conclusions

As previously concluded, there are suspicions that patients treated with benfluorex are exposed to a potentially toxic level of norfenfluramine. The drug is less effective than metformin in the management of obese patients with type II diabetes. No data on safety and efficacy of the drug for therapy periods longer than six months have been provided.

Psychiatric reactions (confusion), anaphylactic shock, hepatitis, blood disorders and cardiovascular adverse effects are not listed in the SPC.

The final proposals are the following. They have been decided together with the French Colleagues that will address them to Servier:

- The following questions will be addressed to the Company:
  - What are the values of pharmacokinetic parameters in animals and in humans after long term (more than six months) administration of benfluorex?
  - Have the cardiovascular and neurological effects of benfluorex in animals and in humans been assessed after long-term (more than six months) exposure to benfluorex?
  - Has long term efficacy in lowering serum lipids assessed in controlled studies and compared to currently available therapeutic alternatives (fibrates, statins, etc.)?
  - Has long term efficacy in controlling glycaemic parameters assessed in controlled studies?

- If the above data are not available, the Company should carry out a long term study (more than one year) with periodic echocardiographic, glycaemic, serum lipids level controls and measurement of pharmacokinetic parameters.
- SPC revision as follows:

No data supporting the indication hypetriglyceridaemia were included. This indication as the others are currently under review by National French Authorities. We suggest to wait for the conclusion of such review and to discuss the efficacy and pharmacodynamics issues at national level if deemed necessary.

Section 4.3 Contraindications

...Hypersensitivity to the drug or to any other component of the formulation.

Chronic pancreatitis...

Section 4.4 **Special warnings**

RÉPUBLIQUE FRANÇAISE

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

A-3

Saint-Denis, le 02 FEV. 2000

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 16 Novembre 1999)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. BLAYAC, M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme LAURENT (supppléante de M. COQUEREL), M. ESCHALIER, Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme JOLLIET, Mme DAVID-LAROCHE (suppléante de M. KANTELIP), Mme LE BELLER (représentant le CRPV de Paris-Broussais), Mme GINISTY (représentant le CRPV de Paris-Fernand Widal), Mme LAINE-CESSAC, M. MALLARET, M. MERLE, M. MONTASTRUC, M. OLLAGNIER, Mme CARLHANT-KOWALSKI (représentant le CRPV de Brest), Mme SGRO, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL,M. VIAL.
Mme TUBERT BITTER (représentant Monsieur le Directeur Général de L'INSERM),
Mme CASTOT (représentant Monsieur le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle FRADET
Melle GOEBEL
M. JACQUET
Mme JOLIMOY
Mme JOUSSELIN-PAUTROT
M. LANG
Mme LEREBOURS
M. MASSET
Mme MESSINA-GOURLOT
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Melle ROBINE

Assistaient à la réunion :

DEMEB :
Mme DEGUINES
M. FERNANDEZ
Mme GAUTIER
Mme GREGOIRE
Mme JAGER
Mme OUNNOUGHENE
Mme WECHSLER

CRPV :
Mme ALT
Mme BAGHERI
Mme JASSON

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

Etaient excusés :

M. BEGAUD : Vice-Président
M. NETTER
Madame le Directeur des Hôpitaux
Monsieur le Directeur Général de la Santé

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RÉPUBLIQUE FRANÇAISE

A G E N C E
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE
3295

Direction de l'Evaluation
Des Médicaments et Des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 29 OCT. 1999

Cher(e) Ami(e) et Collègue,

J'ai l'honneur de vous faire connaître que la prochaine réunion du Comité Technique de Pharmacovigilance aura lieu le :

Mardi 16 Novembre 1999 de 9 h 30 à 17 h 30
à l'Agence Française de Sécurité Sanitaire des Produits de Santé
Salle de Réunions n° 1
143 -147 boulevard Anatole France
93200 SAINT-DENIS
(Métro Carrefour Pleyel)

ORDRE DU JOUR

Matin

1°) Adoption du Procès-Verbal de la séance du 12 octobre 1999.

2°) Tour de table des cas marquants et de la littérature.

3°) Elixir Parégorique : syndrome de sevrage chez le nourrisson.
Procédures nationales.
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4°) Colles biologiques (BIOCOL®, TISSUCOL®, BERIPLAST®) : réactions anaphylactiques.
Procédures nationales.
Enquête officielle / CRPV de Paris St-Vincent de Paul.

5°) Héparines de bas poids moléculaire : accidents hémorragiques.
Procédures nationales.
Enquête officielle / CRPV de Toulouse.

.../..

Après-midi

6°) Inhibiteurs de la cathécol-O-méthyltransférase (tolcapone : TASMAR® ; entacapone COMTAN®, COMTESS®) : syndrome sérotoninergique - syndrome malin des neuroleptiques.
Procédures européennes centralisées (IR & FI).
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7°) EFFEXOR® (venlafaxine) : effets indésirables.
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8°) NITOMAN® (tétrabénazine) : morts subites.
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9°) VIAGRA® (sildénafil) : effets indésirables survenus en France.
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11°) Questions diverses.

Le Chef d'Unité de Pharmacovigilance

Carmen KREFT-JAIS

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AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE
Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

RÉPUBLIQUE FRANÇAISE

REÇU LE
02. MAR. 2000
125

Saint-Denis, le 22 FEV. 2000

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 07 Décembre 1999)

Etaient présents :

M. RICHE : Président
M. KLOVZ (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme BAVOUX, M. BIOUR, M. BLAYAC, M. CARON, Mme CHICHMANIAN, M. COQUEREL, Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme JOLLIET, Mme DAVID-LAROCHE (suppléante de M. KANTELIP), Mme LILLO LE LOUET (représentant le CRPV de Paris-Broussais), Mme THOMAS (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, M. MERLE, Mme BAGHERI (suppléante de M. MONTASTRUC), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant de CRPV de Brest), Mme SGRO, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL, M. VIAL
Mme CHOMA (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

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Mme KREFT-JAIS
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Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Melle FRADET
Melle GOEBEL
M. JACQUET
Mme JOLIMOY
Mme JOUSSELIN-PAUTROT
M. LANG
Mme LEREBOURS
M. MASSET
Mme MESSINA-GOURLOT
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Melle ROBINE
M.ROPERS
Mme SCHLOSSER

Assistaient à la réunion :

DEMEB :

Mme ALLUE
M. BURY
Mme CHAUVENET
Mme GUENANECHE
Mme JAGER
M. MEYER
Mme MIGNON
Mme PELLANNE
Mme PHAM-BA
Mme REIDIBOYM
Mme WECHSLER

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

CRPV :

Mme BADET
Mme GERMAIN
Mme MOACHON
Mme MOSQUET
Melle OLIVIER
Mme PERRAULT

Experts :

M. DERAY
M. BAUWENS

Etaient excusés :

Mme AUTRET-LECA
M. MALLARET
Monsieur le Directeur Général de l'INSERM
Monsieur le Directeur des Hôpitaux

XI -POINT SUR LA PHARMACOVIGILANGE EUROPENNE (GROUPE DE TRAVAIL DES 23 ET 24 NOVEMBRE 1999).

- Antiprotéases / rhabdomyolyse :

La possibilité d'une interaction entre les antiprotéases et les inhibiteurs de la HMG-COA réductase avec apparition d'une rhabdomyolyse est toujours en discussion.
En janvier 2000, le groupe de travail européen de pharmacovigilance fera le point pour déterminer si cet effet indésirable est plutôt « un effet de classe » ou bien s'il apparaît uniquement avec certaines statines.

- Halothane / arythmies cardiaques graves et fatales chez des enfants :

Une étude randomisée publiée dans le Lancet a montré que l'incidence de survenue d'arythmie cardiaque est six fois plus élevée avec l'halothane qu'avec le sévofurane chez des enfants ayant subi une anesthésie en chirurgie dentaire.
A la suite de cet article, le Royaume-Uni a décidé de contre-indiquer l'utilisation extra-hospitalière de l'halothane en chirurgie dentaire chez les patients âgés de moins de dix-huit ans.

- Phosphénytoïne (PRODILANTIN®) / effets cardio-vasculaires :

Ce médicament est autorisé selon une procédure de reconnaissance mutuelle et commercialisé en France depuis mai 1995. Le pays rapporteur (le Royaume-Uni) a rapporté 3 décès et 52 effets cardiovasculaires. Devant la gravité de ces cas, le Royaume-Uni a demandé au laboratoire de fournir une revue analytique des effets cardiaques au plan international pour le 23 décembre 1999. Le problème évoqué serait un débit de perfusion trop rapide. L'adaptation posologique s'avère également difficile.
Un essai clinique est en cours en France, incluant en particulier des enfants de moins de cinq ans. Une lettre d'information aux investigateurs a été finalisée au plan national. Ce courrier insiste sur la nécessité d'effectuer un monitoring cardio-respiratoire et sur le respect du débit de perfusion. (cf. annexe 4)

- Ropinirole / accès de sommeil d'apparition soudaine :

Depuis l'envoi d'une lettre d'information aux prescripteurs et aux pharmaciens par la firme entre le 10 et le 15 novembre 1999 relatant la possibilité de survenue d'accès de sommeil d'apparition soudaine sous Requip®, des nouveaux cas ont été notifiés notamment en Allemagne et en France. (11 cas)
Un rectificatif d'AMM a été effectué le 9 novembre 1999 mentionnant les nouvelles mises en garde insistant sur la nécessité de ne pas conduire.
Pour mise en conformité avec l'AMM, de nouvelles notices vont être délivrées aux pharmacies à la mi-décembre 1999. De même, des stickers reproduisant le pictogramme obligatoire (une voiture dans un triangle rouge) devront être apposés sur le conditionnement.

- Benfluorex / hypertension pulmonaire primitive et valvulopathie :

Il a été demandé à la firme de réaliser une synthèse sur les données d'efficacité du médicament et sur la tolérance préclinique et clinique à long-terme et de déposer une demande de modification de l'information dans tous les pays où le produit est autorisé.

- Vigabatrin / restrictions du champ visuel :

Les mesures obligatoires de suivi des patients sous VIGABATRIN® ont été rediscutées (fiches d'observation recueillant les résultats de périmétrie). Les modalités d'application seront définies nationalement du fait d'une trop grande variabilité du nombre de patients traités par cette spécialité en fonction des pays européens (ex : 12 000 en France et 400 en Finlande).

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CENTRE DE PHARMACOVIGILANCE DE MARSEILLE

COMITE TECHNIQUE DU : 7 décembre 1999

N° des cas	Date de survenue	Sexe /Age	Médicaments suspects	Effets observés	Evol.	Imput	G	N	E	Commentaires *Interaction*
Ma99 1079 1181	Oct 99 Nov99	F62 M31	IDARAC	malaise bronchospasm urticaire bronchospas	A A	I2 I2	O N	N N	N N	Qu'en est il au labo? Médecins s'étonnent du maintien du produit
			Préparation amaigrissante à base de: Phenylpropanolamine 60 mg x3fois /j ephedrine 10 mgx3fois/j pendant 3 mois + laxatif ou diurétiques							Question posée par un médecin conseil de la SS sur les risques? Poso et durée non conformes. Pas d'indication dans l'obésité . (plus de 50 ordonn.)
			Norlevo	Pilule demandée dans un but contraceptif avant le rapport à risque . pas de préservatif !						Information sur le bon usage auprès des populations concernées (et les MST ?)
			Mediator	Mesusage : 50% augm des ventes en pharma souvent hors AMM						Chiffres de vente à surveiller.

1061

36

RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

ADOPTE

A-M 1

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance
590.A

Saint-Denis, le 06 MARS 2001

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 19 Décembre 2000)

Etaient présents

M. RICHE : Président
M. CORNIAU (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. BLAYAC, M. CARON, Mme CHICHMANIAN, M. COQUEREL, Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, Mme WELSCH (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme JOLLIET, M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, Mme HENRY(représentant le CRPV de Paris-POMPIDOU), M. MALLARET, M. MERLE, Mme BAGHERI (suppléante de M. MONTASTRUC), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme SGRO, Mme LEBRUN (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL, M. VIAL,
Mme LEGER (représentant Monsieur le Directeur Général de la Santé)
Mme CASTOT (représentant Monsieur le Directeur Général de l'Afssaps).

Conseiller scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme CHOULIKA
Melle DELEAU
M. DHANANI
Mme JOLIMOY
Melle JULLIAN
Mme PARIENTE-KHAYAT
Mme POINSARD
Melle ROBINE
Mme ROCHER

Assistaient à la réunion :

DEMEB:

Mme LORENCE
Mme MORGENSZTJEN

DIE :
Mme SALVETAT

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

CRPV :

Mme ALLAIN – VEYRAC
Mme BURTIN
Melle FRANCES
Mme MOACHON
Mme NGUYEN

Expert :

Mme MILPIED

VIII - PHARMACOVIGILANCE EUROPEENNE (Groupe de Travail européen de pharmacovigilance des 29 et 30 novembre 2000) :

REMICADE® (infliximab) :

REMICADE® est un anti-TNF (facteur nécrosant des tumeurs) utilisé dans le traitement de la maladie de Crohn. Depuis le mois de juin 2000, son indication s'est étendue au traitement de la polyarthrite rhumatoïde résistante aux corticoïdes. Une mesure de restriction urgente a été envoyée le 8 décembre 2000 et concernait les cas de tuberculose sous REMICADE®.
28 cas de tuberculose milliaire et extra-pulmonaire ont été recensés depuis la mise sur le marché de REMICADE® (9 cas aux Etats-Unis et 19 en Europe). La rubrique « Contre-indications » mentionnera donc un message contre-indiquant le produit chez les patients ayant un sepsis ou une tuberculose. Les rubriques « Mises en garde et précautions d'emploi » et « Effets indésirables » seront également modifiées. Un communiqué de presse sera diffusé sur le site de l'EMEA dès le 10 décembre 2000.

ORLAAM® (lévacéthylméthadol) :

ORLAAM® est un produit de substitution utilisé après un échec du traitement par méthadone. Ce produit est commercialisé, par le laboratoire SIPACO, aux Etats-Unis depuis 1994 et en Europe depuis 1999 selon une procédure centralisée dont l'Etat membre de référence est la Belgique. Le laboratoire SIPACO a fait l'objet de 3 inspections afin de vérifier l'évaluation des données en raison du signalement de cas d'arythmies graves au cours des 2ème et 3ème rapports périodiques de pharmacovigilance. Actuellement, on dénombre 10 cas d'arythmies graves (pour environ 100 000 patients exposés) dont 3 cas de torsade de pointe et 2 cas de pose de Pace-Maker. Le laboratoire s'est engagé à ne pas commercialiser le produit dans d'autres pays européens. Une lettre destinées aux prescripteurs sera bientôt rédigée et un communiqué de presse sera diffusé sur le site de l'Agence européenne (EMEA) très prochainement.
M. LAGIER a précisé que lors de l'AMM, il avait été préconisé que les patients soient hospitalisés au moment de l'instauration du traitement afin d'éviter des effets tardifs tels que l'overdose.
Une révision du rapport bénéfice / risque sera réalisée au mois de janvier ou février 2001.

BENEFIX® (nonacog alpha) :

BENEFIX® est un facteur IX recombinant qui a présenté des problèmes d'agglutination lors de son injection. Le laboratoire WYETH-LEDERLE a été inspecté, à cet effet, et doit réaliser des modification de son produit.

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RÉPUBLIQUE FRANÇAISE

A - 12

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance
584A

Saint-Denis, le 06 MARS 2001

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 9 Janvier 2001)

Etaient présents

M. RICHE : Président
M. CORNIOU (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme AUTRET-LECA, Mme BAVOUX, M. BIOUR, M. BLAYAC, Mme GAUTIER (suppléante de M. CARON), Mme BALDIN (suppléante de Mme CHICHMANIAN), Mme LACOTTE (suppléante de M. COQUEREL), Mme LAMAISON (suppléante de M. ESCHALIER), Mme HARAMBURU, Mme WELSCH (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, Mme LILLO-LELOUET(représentant le CRPV de Paris-POMPIDOU), M. MERLE, Mme LAPEYRE-MESTRE (suppléante de M. MONTASTRUC), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme LOUGUET (suppléante de Mme SGRO), Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), Mme GERMAIN (suppléante de M. TRENQUE), Mme PERAULT (suppléante de M. VANDEL), M. VIAL,
Mme LEGER (représentant Monsieur le Directeur Général de la Santé)
Mme CASTOT (représentant Monsieur le Directeur Général de l'Afssaps)

Conseiller scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme CHOULIKA
Melle DELEAU
Mme FOSSET- MARTINETTI
M. JACQUET
Mme JOLIMOY
Mme JOUSSELLIN- PAUTROT
Melle JULLIAN
Mme LEBBE
Mme MESSAN- MURPHY
Mme PARIENTE-KHAYAT
Mme POINSARD
Melle ROBINE
Mme ROCHER
M. SMADJA
Mme WEBER

Assistaient à la réunion :

CRPV :
Mme BREHON
M. RODOR
Mme BROCH-OLIERIC

DEMEB:

Melle BALZON
Mme GRENET
Mme MATTHIEU-BOUE
Mme MORGENSZTJEN
Mme LABOURET
Mme TCHINOU
Mme WECHSLER

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

I - ADOPTION DU PROCES-VERBAL DE LA SEANCE DU MARDI 19 DECEMBRE 2000.

L'adoption du procès-verbal de la séance du 19 décembre 2000 est reportée lors de la séance du 13 février 2001.

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Carole FOSSET → Catherine RAYQUIN
C-2
PTC-2
J. Rogers

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

Madame le Docteur Anne CASTOT
Agence Française de Sécurité
Sanitaire des Produits de Santé
143-147 Boulevard Anatole France
93200 SAINT DENIS

Neuilly-sur-Seine, le 1er février 2001

Direction de l'Evaluation du Médicament
et des Produits Biologiques
Département des Vigilances

N/Réf. : IT/dst/01.0105
☎ 01 55 72 65 34
Fax 01 55 72 33 02

Objet : **MEDIATOR® 150 mg, comprimé enrobé**
Dossier VNL 10008

Madame,

Comme convenu lors de la réunion de pharmacovigilance à l'EMEA en date du 30 novembre 2000, nous vous adressons, ci-joint, pour notre spécialité **MEDIATOR® 150 mg**, comprimé enrobé, le synopsis du protocole d'étude intitulé :

« A one-year, multicentre, international, randomised, double-blind comparison of Benfluorex (150mg to 450mg daily) and Acarbose (150mg to 300mg daily) administered orally for the treatment of type 2 diabetic patients »

Ce synopsis de protocole d'étude d'efficacité de Benfluorex versus Acarbose sur 12 mois inclut également l'étude écho-cardiographique souhaitée.

Nous vous prions de croire, Madame, à l'expression de nos salutations distinguées.

Pierre MONTES
Directeur des Affaires Pharmaceutiques France
Pharmacien Responsable Intérimaire

Mme Carole FOSSET-MARTINETTI
Unité de Pharmacovigilance

SERVIER

S 780
(benfluorex)

STUDY PROTOCOL

Protocol N°:

A ONE-YEAR, MULTICENTRE, *INTERNATIONAL*, RANDOMISED, DOUBLE-BLIND COMPARISON OF BENFLUOREX (150 TO 450 MG DAILY) AND ACARBOSE (150 MG TO 300 MG DAILY) ADMINISTERED ORALLY FOR THE TREATMENT OF TYPE 2 DIABETIC PATIENTS

DRAFT

Coordinator	: *Prof.*
Director of the Therapeutic Research Department	: *Dr L. BESSAC*

CONFIDENTIAL

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE
Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance
895A

1571 ADOPTE

RÉPUBLIQUE FRANÇAISE

A-13

Saint-Denis, le 04 AVR. 2001

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 13 Février 2001)

Etaient présents

M. RICHE : Président
M. CORNIOU (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme JONVILLE BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. CARON, Mme CHICHMANIAN, M. COQUEREL, M. ESCHALIER, Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme JOLLIET, M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, Mme LILLO-LELOUET(représentant le CRPV de Paris-POMPIDOU), M. MERLE, M. MONTASTRUC, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant le CRPV de Brest), Mme SGRO, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL, M. VIAL,
Mme TUBERT-BITTER (représentant Monsieur le Directeur de l'INSERM),
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme LEGER (représentant Monsieur le Directeur Général de la Santé),
M. MEYER (représentant Monsieur le Directeur Général de l'Afssaps).

Conseiller scientifique : M. LAGIER.

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme BIDAULT
Mme CHOULIKA
Melle DELEAU
M. DHANANI
Mme GRENET
Mme GOEBEL
M. JACQUET
Mme LEBBE
Mme MESSAN- MURPHY
Mme PIERRON
Melle ROBINE
Mme ROCHER
Mme WEBER

Assistaient à la réunion :

CRPV :

M. BLANGY
M. EFTEKHARI
Mme LAURENT
Mme WELSCH
Mme ZENUT

DEMEB:

Mme CASTOT
Mme DIALLO
M. LECOMTE
Mme MEUNIER
Mme MORER

143/147, Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01.55.87.30.00

IX - PHARMACOVIGILANCE EUROPEENNE.

Stylos à Insuline et risque de contamination croisée :

Le CRPV de Saint-Etienne avait signalé un problème relatif aux cartouches d'insuline utilisées dans les stylos injecteurs à usage multiple. Ces cartouches sont utilisées dans les services cliniques pour différents patients, en changeant à chaque fois l'aiguille du stylo, mais il n'existe pas de système anti-reflux ce qui pose un problème de remontée de matière biologique avec un risque potentiel de contamination lors de l'échange de celle-ci entre les différents patients. Ce problème a été évoqué au Groupe de travail européen qui a proposé d'inclure dans le RCP des stylos à insuline une information relative au risque de contamination en cas d'utilisation de ces stylos par plusieurs patients différents.

DIPRIVAN® (propofol) et rhabdomyolyse / insuffisance cardiaque :

Un article du Lancet a montré des cas de rhabdomyolyse et d'insuffisance cardiaque, avec possibilité de décès, chez des patients à qui on avait administré du DIPRIVAN® en perfusion avec une posologie supérieure à 4 mg/kg/h pendant 48 heures. Il est rappelé que la posologie du DIPRIVAN® est inférieure à 4 mg/kg/h en France.
Une enquête officielle a été ouverte dont le responsable est le CRPV de Paris Saint-Antoine.

ZIAGEN® (abacavir) et syndrome d'hypersensibilité :

L'abacavir a fait l'objet de 3 mesures de restriction urgente dont la dernière relative au problème de réadministration chez des sujets sensibilisés, remonte au mois d'août 2000. Depuis cette mise en garde, il y a eu un cas grave supplémentaire en France dont l'évolution a été favorable. Ce patient présentait 2 symptômes décrits dans la mise en garde mais son infectiologue lui a dit de reprendre le ZIAGEN®. Le CRPV de Bordeaux a signalé que les infectiologues ne réintroduisaient plus le ZIAGEN® chez les patients ayant déjà fait un syndrome d'hypersensibilité.

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COMITE TECHNIQUE DU : 13 février 2001

CENTRE DE PHARMACOVIGILANCE DE CAEN BASSE-NORMANDIE

La Présidente du Conseil Régional de l'Ordre des Pharmaciens de Basse Normandie a attiré notre attention sur certaines ordonnances probablement à visée amaigrissante, comprenant des préparations à base de:

- Metformine 0,20
- Ovaire 0,10
- Thyroide 0,05

Associé à la prescription de Médiator® (3 cp/jour).

Certains pharmaciens continuent d'honorer ces prescriptions .

La question est: "faut-il accepter de délivrer ce type d'ordonnance?"
"Est t-il souhaitable et possible d'interdire l'exécution de ces préparations ?"

D'après le Code de Santé Publique, il est rappelé (article 5015-60) que le pharmacien peut refuser de dispenser un médicament lorsque l'intérêt de la santé du patient lui paraît l'exiger.

Par ailleurs, le décret n° 82-200 rappelle qu'il est interdit d'incorporer dans une même préparation magistrale du benfluorex (MEDIATOR®) et des hormones thyroïdiennes.

L'association de ces deux produits sur une même ordonnance est-elle considérée comme un contournement du décret ?.

Par ailleurs, la metformine est un anti diabétique oral et les Références Médicales Opposables concernant cette classe thérapeutique précisent qu'"il n'y a pas lieu de commencer un traitement médicamenteux en l'absence de critères de diagnostic suffisants (glycémie)."

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Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 20 Mars 2001)

Etaient présents

M. RICHE : Président
M. CORNIOU (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. BLAYAC, Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme LACOTTE (suppléante de M. COQUEREL), Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, Mme LILLO-LELOUET (représentant le CRPV de Paris-POMPIDOU), M. MERLE, M. MONTASTRUC, M. BLANGY (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant le CRPV de Brest), Mme SGRO, Mme SOUBRIE, Mme BURTIN (suppléante de M. THUILLEZ), M. TRENQUE, Mme PERAULT (suppléante de M. VANDEL), M. BERNARD (suppléant de M. VIAL),
Mme LEGER (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de Agence Française de Sécurité Sanitaire des Produits de Santé).

Conseiller scientifique : M. LAGIER.

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Mme GOEBEL
Mme PARIENTE-KHAYAT
Mme PIERRON
Melle ROBINE
Mme ROCHER
Mme WEBER

Assistaient à la réunion :

DEMEB:

Mme ROUSSELLE
Mme WESCHLER
Mme AURICHE

CRPV :

Mme EFTEKHARI
Mme BREHON

VIII - PHARMACOVIGILANCE EUROPEENNE

Point sur les agonistes dopaminergiques et attaque de sommeil :

Ce dossier a été discuté au Comité des Spécialités Pharmaceutiques (CSP) du 1er mars 2001.

Une attaque de sommeil est un épisode abrupt d'endormissement survenant au cours d'une activité journalière. Cet épisode peut être ou non précédé d'un état de somnolence et peut durer de quelques minutes à quelques heures.
Les molécules concernées sont les suivantes :
bromocriptine, cabergoline, levodopa, pergolide, pramipexole, ropinirole.

Les conclusions du groupe de travail européen de pharmacovigilance, transmises au CSP, ont été les suivantes :

- Les troubles du sommeil peuvent être une composante de la maladie de Parkinson.
- Tous les agonistes dopaminergiques peuvent être associés à une somnolence, l'effet pouvant être accentué en cas d'association médicamenteuse.
- Parmi la notification spontanée, de rares cas d'attaque de sommeil, d'intensité variable, sont rapportés avec l'ensemble des agonistes dopaminergiques. Ces épisodes sont plus fréquemment rapportés avec le ropinirole, le pramipexole et la cabergoline.

Propositions de modification du RCP :

Section 4.4 (mises en garde et précautions d'emploi) **et 4.7** (effets sur l'aptitude à conduire des véhicules et à utiliser des machines) :

Patients being treated with *(TRADENAME)* should be warned that somnolence or sudden sleep onset episodes may occur particularly when therapy is started and during the titration period. Caution therefore should be exercised if patients are to drive or engage in other activities where impaired alertness could put themselves at risk of serious injury or death (e.g. operating machines). Patients being treated with *(TRADENAME)* and already presenting with somnolence or sudden sleep onset episodes must be informed to refrain from driving or engaging in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g . operating machines) until such episodes have resolved. (To be cross referenced to section 4.4 and 4.7)

Section 4.8 (effets indésirables) :

- Based on post-marketing data, extreme somnolence, occasionally when the patient was driving, has been reported rarely with dopamine agonists.
- *Additional wording for bromocriptine and pergolide* :

With () there are isolated reports of sudden onset of sleep.

- *Additional wording for pramipexole, ropinirole and cabergoline* :

With () there are very rare reports of sudden onset of sleep.

- Patients experiencing this phenomenon cannot resist the urge to sleep, and on waking may be unaware of any tiredness prior to the sleep.

Le CSP a souhaité une réflexion au niveau de chaque Etat membre concernant les implications médico-légales de telles mentions. Le dossier sera de nouveau discuté au CSP des 26 - 28 mars 2001.

Etant donné que le lisuride n'est pas inclus dans ces mesures, le CRPV de Toulouse prend en charge l'enquête officielle relative au lisuride et « somnolence excessive ou accès de sommeil soudain ».

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AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

ADOPTE

RÉPUBLIQUE FRANÇAISE

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Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 23 AOUT 2001

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 10 Avril 2001)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), M. CARON, Mme CHICHMANIAN, Mme MOSQUET (suppléante de M. COQUEREL), Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, Mme WELSCH (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme JOLLIET, M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris Fernand WIDAL), Mme LAINE-CESSAC, Mme LE BELLER (représentant le CRPV de Paris-POMPIDOU), M. MALLARET, M. MERLE, M. GILLET (suppléant de M. NETTER), Mme GUY (suppléante de M. OLLAGNIER), Mme CARLHANT (représentant le CRPV de Brest), Mme SGRO, Mme LEBRUN-VIGNES (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL, M. VIAL,
Mme LEGER (représentant Monsieur le Directeur Général de la Santé)
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé).

Conseiller scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Melle DELEAU
M. DHANANI
Mme FOSSET- MARTINETTI
Mme GRENE
Mme JOUSSELIN- PAUTROT
Mme MESSAN- MURPHY
Mme PARIENTE-KHAYAT
Mme PIERRON

Assistaient à la réunion :

DEMEB :
M. CHAPELIN
Mme LEREBOURS
Mme PONS

DEDIM :
Mme MAISONNEUVE

DG Affaires européennes :
Mme DIANI

MILDT :
Mme GUITON

CRPV :
Mme MOACHON
M. QUESTE
Mme ROMIEE
Mme ROUSSILLON
Mme THOMAS
Mme EFTEKHARI

Etaient excusés :
Monsieur le Directeur des Hôpitaux
Monsieur le Directeur Général de l'INSERM

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RÉPUBLIQUE FRANÇAISE

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE
Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 15 Mai 2001)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme JONVILLE BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. COQUEREL, M. ESCHALIER, M. MIREMONT-SALAME (suppléante de Mme HARAMBURU), Mme WELSCH (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), Mme LAROCHE (suppléante de M. KANTELIP), Mme THOMAS (représentant le CRPV de F. Widal), Mme LAINE-CESSAC, Mme LE BELLER (représentant le CRPV de Paris-POMPIDOU), M. MALLARET, M. MERLE, M. BLANGY (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant le CRPV de Brest), Mme SGRO, Mme LEBRUN-VIGNES (suppléante de Mme SOUBRIE), Mme BURTIN (suppléante de M. THUILLEZ), M. TRENQUE, Mme PERAULT (suppléante de M. VANDEL)
Mme LEGER (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé).

Conseiller scientifique : M. LAGIER.

Assistaient à la réunion :

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme CHOULIKA
Melle DELEAU
Mme FOSSET-MARTINETTI
Mme GRENE
M. JACQUET
Mme JOUSSELIN-PAUTROT
Melle JULLIAN
M. LAHAIE
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Mme PIERRON
Melle ROBINE
Mme SCHLOSSER
Mme SOUCHET

CRPV :

Mme CARDONA
Mme MOACHON

143/147 Boulevard Anatole France 93285 Saint-Denis Cedex - Tél. 01 55 87 30 00

III - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Seuls sont signalés les cas d'effets indésirables donnant lieu à des mesures (mise en enquête, notes...) ou faisant l'objet d'une mise au point. La liste complète des cas est jointe en annexe 1.

- **Interaction médicamenteuse NORVIR® (ritonavir) / SINTROM® (acénocoumarol) / CRPV de Paris-Pompidou :**

Survenue d'une interaction médicamenteuse entre NORVIR® et SINTROM® aboutissant à une diminution de l'effet thérapeutique du NORVIR® et une augmentation de l'effet anticoagulant. Deux cas similaires figurent dans la banque nationale de pharmacovigilance et 3 autres cas dans la littérature.
→Une note sera adressée au groupe interaction médicamenteuse.

- **DONORMYL® (sulprostone) / CRPV de Paris-Pompidou :**

Survenue d'une rhabdomyolyse avec malaise et somnolence à la suite d'un surdosage en DONORMYL® chez une jeune fille de 14 ans.
→Un point sera demandé aux CAP (Centres antipoison) et à la DGS (Direction Générale de la Santé).

EXOLYSE® (thé vert) / CRPV de Caen :

Survenue d'une hépatite subfulminante nécessitant une transplantation hépatique chez une femme de 49 ans traitée par EXOLYSE®, SERMION® (nicercoline), TRIVASTAL® (piribédil) et SOLUPRED®. Un produit « pour bronzer » avait également été pris. Un cas similaire figure dans la banque et un cas au niveau du laboratoire.

MEDIATOR® (benfluorex) et mésusage / CRPV de Caen :

La présidente du Conseil de l'Ordre des pharmaciens de Basse Normandie a de nouveau attiré l'attention sur certaines ordonnances à visée amaigrissante associée à la prescription de MEDIATOR®.

NEXEN® (nimésulide) / CRPV de Lyon :

Survenue d'une hépatite fulminante nécessitant une transplantation hépatique en urgence chez un patient de 51 ans traité par NEXEN®. Le patient n'est pas encore rétabli.
→Cet effet figure déjà dans le RCP du NEXEN®.

Immunostimulants / CRPV d'Amiens :

Survenue d'une acrosyndactylie des mains et des pieds chez un nouveau-né à la naissance. Le diagnostic a été posé dès la 22ème semaine d'aménorrhée. Les seuls médicaments pris pendant la grossesse étaient IMOCUR® (fraction d'origine bactérienne), IRS 19® (lysats bactériens en suspension) et AUDISPRAY®.
→Une note sera envoyée à l'évaluateur en charge de cette classe thérapeutique.

LIPIOCIS® (huile d'oeillette)/ LIPIODOL® (huile d'oeillette) / CRPV de Rennes :

Survenue d'une pneumopathie avec détresse respiratoire chez 3 patients traités par LIPIOCIS® et LIPIODOL®. Deux cas ont été fatals, le 3ème patient n'est pas encore rétabli.
La moitié des patients sous par LIPIOCIS® sont traités à Rennes.
→Le CRPV de Rennes est chargé de l'enquête officielle sur les effets indésirables de LIPIOCIS® et LIPIODOL®.

Tisane Ernst RICHTER / CRPV de Paris Saint-Antoine :

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RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 5 Juin 2001)

Etaient présents

M. RICHE : Président
M. CORNIOU (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. BLAYAC, M. CARON, Mme CHICHMANIAN, M. COQUEREL, M. ESCHALIER, Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), M. KANTELIP, Mme GINISTY (représentant le CRPV de F. Widal), Mme LAINE-CESSAC, Mme LILLO-LELOUET (représentant le CRPV de Paris-POMPIDOU), M. NOUAILLE (suppléant de M. MERLE), Mme BAGHERI (suppléante de M. MONTASTRUC), Mme GUY (suppléante de M. OLLAGNIER), Mme BROCH (représentant le CRPV de Brest), Mme SGRO, Mme KHALED (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), Mme ALGERMAIN (suppléante de M. TRENQUE), Mme PERAULT (suppléante de M. VANDEL), M. VIAL
Mme LEGER (représentant Monsieur le Directeur Général de la Santé),
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé).

Conseiller scientifique : M. LAGIER.

Assistaient à la réunion :
Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme CHOULIKA
Melle DELEAU
M. DHANANI
Melle JULLIAN
M. LAHAIE
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Mme PIERRON
Melle SBIHI
Mme SCHLOSSER
Mme WEBER

CRPV :
M. CARLIER
Mme MOACHON

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Lors du Comité Technique de Pharmacovigilance du 7 décembre 2004, plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique ont été rapportées avec MEDIATOR® (benfluorex). Une actualisation des données relatives aux troubles neuro-psychiatriques observés avec cette spécialité pharmaceutique a alors été décidée. Par la suite, du fait d'une notification d'un cas d'hypertension artérielle pulmonaire associée à la prise de MEDIATOR® rapportée lors du Comité Technique du 8 mars 2005, l'enquête menée par le CRPV de BESANCON a été étendue aux hypertensions artérielles pulmonaires.
MEDIATOR® est commercialisé en France depuis 1976 par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés dosés à 150 mg.
Ses indications sont :
- adjuvant du régime adapté dans les hypertriglycéridémies ;
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

HISTORIQUE

Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables de ces produits et étant donné les restrictions de leur délivrance, le Comité Technique de Pharmacovigilance a craint une dérive de l'utilisation du benfluorex comme anorexigène. Ainsi, le benfluorex a été inscrit sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes le 10 mai 1995.

Le dossier relatif aux effets indésirables du benfluorex a été présenté lors de différentes réunions du Comité Technique de Pharmacovigilance en 1998 et au groupe de travail européen de Pharmacovigilance le 30 novembre 2000, entraînant les modifications de la rubrique « effets indésirables » du Résumé des Caractéristiques du Produit (RCP) (ajout des effets indésirables en *italique* ci-dessous) :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, *confusion*, somnolence, état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles ;
- *très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke ;*
- *élévation des enzymes hépatiques, hépatite (très rare).*

RESULTATS DE L'ENQUETE

1.Troubles neuro-psychiatriques

A. Troubles psychiatriques pendant le traitement

Trente cinq cas ont été rapportés dont 10 déclarés depuis l'enquête présentée en juillet 1999. Ils concernent 18 hommes (âge moyen : 58,5 ans) et 17 femmes (âge moyen : 60 ans).

Les troubles psychiatriques sont variés :
- agressivité (4), nervosité (3), irritabilité (1) ;
- cauchemars (2), angoisse (1), stupeur (1), dépression (1) ;
- désorientation (7), confusion (5), aggravation des troubles cognitifs (1) ;
- agitation (3), troubles du comportement (3) ;
- délire (2), bouffées délirantes aiguës (1).

Les cas graves ayant nécessité une hospitalisation sont :
- 4 cas de confusion (dont un provenant de la littérature) chez des patients ayant des traitements associés ;
- 3 cas de désorientation temporo-spatiale ;
- 2 cas de bouffées délirantes aiguës, avec d'autres troubles associés, d'évolution rapidement favorable après traitement symptomatique par neuroleptiques.

B. Troubles psychiatriques au sevrage

Dix notifications de troubles psychiatriques apparaissant lors du sevrage ont été rapportés. Ils concernent 2 hommes de 27 et 34 ans et 8 femmes de 30 à 65 ans (âge moyen : 45,25 ans).

Le délai d'apparition des troubles après l'arrêt du MEDIATOR® est très variable : de 1 jour (après un traitement de 8 ans) à 3 semaines (après un traitement de 4 mois, 6 mois ou 15 mois).
La durée de traitement par MEDIATOR® est très variable : de 1 mois à 8 ans.

Trois cas ont nécessité une hospitalisation chez des femmes ayant par ailleurs des antécédents de troubles psychiatriques. Une évolution favorable a été constatée dans un des cas après traitement symptomatique par neuroleptiques, les deux autres cas sont d'évolution inconnue.

C. Autres troubles neurologiques

Douze notifications ont été rapportées. Elles concernent 8 hommes et 4 femmes :
- 2 cas de convulsions d'évolution favorable ;
- 2 cas de neuropathie, chez deux patients diabétiques présentant de multiples autres étiologies possibles ;
- 7 cas de paresthésies, d'apparition rapide et d'évolution favorable en quelques heures, dont deux mésusages ;
- 1 cas de tremblement des mains.

D. Abus

Deux cas d'abus ont été rapportés :
- chez un homme augmentant les doses de MEDIATOR® à 10 comprimés par jour pendant 11 mois, sans effet indésirable associé ;
- chez un sportif, consommant (sur prescription médicale) des doses croissantes (1comprimé/semaine au début et jusqu'à 9 comprimés/jour) de MEDIATOR® comme « dopant » et présentant une excitation lors du sevrage.

2. Hypertension artérielle pulmonaire (HTAP) :

Dix-sept notifications dont 2 doublons ont été rapportées.

A. Notifications où MEDIATOR® est associé à un anorexigène :

Lors de la présentation du rapport MEDIATOR® en décembre 1998, 11 notifications d'«hypertension artérielle pulmonaire » avaient été rapportées (9 d'entre elles avaient été présentées lors de l'enquête « Anorexigènes et hypertensions artérielles pulmonaires » au Comité Technique du 28 avril 1995) :
- 7 ont été classées en HTAP idiopathique
- 3 en HTAP post-capillaire
- 1 en HTAP post-embolique

Le MEDIATOR® n'était jamais prescrit seul : il était associé à un ou plusieurs anorexigènes :
- ISOMERIDE® : 7 fois ;
- ISOMERIDE® + PONDERAL® : 2 fois ;
- ISOMERIDE ®+ FENPROPOREX® : 1 fois ;
- DININTEL® + TENUATE DOSPAN® + FRINGANOR® : 1 fois ;

La durée de traitement par MEDIATOR® était précisée dans 7 cas sur 11 et allait de plusieurs mois à 5 ans.

Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® était :
- concomitante dans 5 cas ;
- antérieure dans 2 cas ;
- postérieure dans 3 cas ;
- imprécise dans 1 cas.

Sur les 3 cas où la prise de MEDIATOR® était postérieure à la prise d'anorexigènes, 2 cas présentaient une dyspnée avant la prise de MEDIATOR, et un cas une double atteinte valvulaire aortique et mitrale.

B. Notifications où MEDIATOR® n'est pas associé à la prise d'un anorexigène

Six notifications ont été rapportées chez des femmes (dont 2 présentaient une HTAP post capillaire sur valvulopathie et une autre une HTAP sur embolie pulmonaire) n'ayant pas de traitement anorexigène associé. Il est à noter que l'un des cas rapportés est très succinct et ne peut, dans ces conditions, être retenu.

C. Incidence des cas notifiés

Depuis le début de la commercialisation de MEDIATOR®, le nombre de boites de 30 comprimés vendues est de : 110 693 331, correspondant à 45 515 349 mois de traitement (estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés).

Après élimination des HTAP post-emboliques (2) et post-capillaires (5), il reste 10 cas d'HTAP idiopathique soit :
- 1 cas notifié pour 11 069 333 boîtes vendues ;
- ou 1 cas notifié pour 4 551 534 mois de traitement.

Si on considère uniquement les diagnostics d'hypertension artérielle pulmonaire idiopathique en excluant les cas associés aux anorexigènes et les antécédents d'embolie pulmonaire et de valvulopathie, il reste 2 cas soit une incidence très faible de :
- 1 cas notifié pour 55 346 666 boîtes vendues ;
- 1 cas notifié pour 22 757 675 mois de traitement.

Conclusion du rapporteur :

Troubles neuro-psychiatriques : cette enquête confirme la réalité du risque de survenue de « confusions » en présence de Médiator®. Il est proposé que cet effet, déjà mentionné dans le RCP soit détaillé comme suit :
« troubles des fonctions cognitives : désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception : hallucinations. »

Hypertensions artérielles pulmonaires : compte-tenu de l'incidence des HTAP idiopathiques (1 à 2 de cas par million et par an), le nombre de cas d'HTAP idiopathique rapportés dans l'enquête ne constitue pas un signal significatif de toxicité du MEDIATOR® dans la classe organe cardio-vasculaire.

DISCUSSION

Les ventes de MEDIATOR® en Europe sont réalisées en quasi totalité en France. Les données DOREMA d'avril 2005 montrent une utilisation dans 46,3% dans les dyslipidémies, dans 33,5% dans le diabète, dans 9,6% dans l'obésité, dans 2,3% dans la régulation métabolique et dans 8,3% dans d'autres indications. L'effet anorexigène du benfluorex n'a pas été démontré. Toutefois, les membres de la Commission nationale craignent un mésusage, en particulier dans l'obésité. Dans ce contexte, une étude d'utilisation/ de prescription serait utile.
Il est à noter que le renouvellement quinquennal du produit intervient dans 2 ans et que des données d'efficacité dans le diabète de type 2 existent mais restent limitées et mériteraient d'être réévaluées.

Le bilan de pharmacovigilance confirme les données de sécurité d'emploi du MEDIATOR® déjà connues. Les effets neuro-psychiatriques décrits actuellement dans le RCP sous le terme « confusion » doivent être détaillés. Il n'y a pas actuellement assez de données pour affirmer l'existence de syndrome de sevrage. Le faible nombre de cas décrits d'HTAP idiopathique associées au MEDIATOR® doit être interprété par rapport à la sous-notification habituelle en pharmacovigilance.

Afin d'évaluer au mieux les risques potentiels de l'utilisation de MEDIATOR®, la Commission nationale de pharmacovigilance a demandé la réalisation de :
- une étude d'utilisation / prescription de MEDIATOR® ;
- une étude expérimentale sur un modèle animal permettant d'évaluer le potentiel de MEDIATOR® à engendrer des HTAP ;

- une étude au niveau des Centres d'évaluation et d'information sur la pharmacodépendance (CEIP) afin d'évaluer un éventuel problème de pharmacodépendance. A ce titre, une saisine de la Commission nationale des stupéfiants et psychotropes sera effectuée.

Enfin, il a été proposé d'étudier la possibilité d'interroger les registres d'HTAP existant dans 17 centres, afin de rechercher, dans une étude rétrospective cas-témoins, le rôle éventuel du benfluorex.

CONCLUSION

Devant les différentes questions posées par l'enquête de pharmacovigilance, plusieurs membres de la commission ont souhaité un réévaluation du rapport bénéfice/risque du produit. La Commission s'est prononcée en faveur de cette réévaluation par 13 voix pour, 10 voix contre et 5 abstentions.

B-4

II –MEDIATOR® (CHLORHYDRATE DE BENFLUOREX) : MISE A JOUR DES DONNEES DE PHARMACOVIGILANCE, RESULTATS DE LA REEVALUATION DU BENEFICE/RISQUE ET RESULTATS DE L'ETUDE D'UTILISATION

1 – Introduction

Nom commercial	MEDIATOR®
DCI	Chlorhydrate de benfluorex
Formes pharmaceutiques	Comprimé pelliculé à 150 mg
Classe pharmacologique	Hypolipidémiant
Procédure d'enregistrement	Procédure nationale
Titulaire de l'AMM	Laboratoires Servier

Date de passage en Comité technique de pharmacovigilance : 13 mars 2007
Passage en Commission nationale de pharmacovigilance à la demande du Comité technique de pharmacovigilance
Nom du rapporteur : Centre Régional de pharmacovigilance (CRPV) de Besançon

MEDIATOR® (chlorhydrate de benfluorex) a obtenu une AMM lors d'une procédure nationale d'enregistrement en 1974, modifiée en 1987 et 1990. Les indications actuelles sont :
- adjuvant du régime adapté dans les hypertriglycéridémies ;
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Ce médicament est commercialisé en France depuis 1976.

2 – Contexte

En décembre 2004, la notification de plusieurs cas d'effets indésirables, pouvant évoquer un effet de type amphétaminique avec MEDIATOR®, a conduit à une actualisation des données relatives aux effets indésirables neuro-psychiatriques observés avec cette spécialité. Par ailleurs, la notification d'un cas d'hypertension artérielle pulmonaire, rapportée lors du Comité Technique du 8 mars 2005, a justifié une extension de l'enquête aux hypertensions artérielles pulmonaires (HTAP).

Les résultats de cette enquête officielle ont été présentés par le CRPV de Besançon au Comité Technique de Pharmacovigilance le 07 juin 2005 et à la Commission Nationale de Pharmacovigilance le 29 novembre 2005. La Commission avait demandé la réévaluation de la balance bénéfice/risque de Médiator®, une étude d'utilisation/prescription, une étude expérimentale sur un modèle animal permettant d'étudier le potentiel du benfluorex à engendrer des HTAP et une étude au niveau des Centres d'Evaluation et d'Information sur la Pharmacodépendance (CEIP) afin d'identifier un éventuel problème de pharmacodépendance. La réalisation de cette dernière étude n'a pas été jugée immédiatement nécessaire à cette étape de l'évaluation du dossier en raison du fondement théorique de cette demande (substance de type amphétaminique) et de l'absence d'un signal clairement identifié dans les données notifiées.
Les données disponibles ont été présentées au Comité technique de pharmacovigilance du 13 mars 2007 puis à la Commission nationale de pharmacovigilance du 27 mars 2007.

3 - Actualisation de l'enquête de pharmacovigilance sur les HTAP et les troubles neuropsychiatriques

Le CRPV de Besançon a actualisé les données de pharmacovigilance du benfluorex concernant les HTAP et les effets indésirables neuropsychiatriques. Concernant les effets neuro-psychiatriques, 39 cas avaient été notifiés jusqu'à novembre 2005 auxquels s'ajoutent 4 nouveaux cas : 1 cas de dépression, 1 cas d'agitation et 2 cas de délire. Concernant les cas de délire, le premier concerne une femme de 33 ans sans antécédent psychiatrique, traitée par MEDIATOR® 3 comprimés par jour puis 2 comprimés par jour pendant 5 mois, qui a présenté sous traitement un délire de persécution avec confusion, traité par ZYPREXA®, TERCIAN® et XANAX®, d'imputabilité douteuse. Le deuxième cas de délire concerne un homme de 31 ans, avec psychose chronique, traité par MEDIATOR® 2 comprimés par jour pendant 3 ans, qui a présenté un délire avec agressivité, régressif à l'arrêt du traitement, d'imputabilité douteuse.

Concernant les HTAP, 3 nouveaux cas potentiels ont été notifiés et ont fait l'objet d'une expertise :

- Le premier cas concerne une femme de 50 ans avec un indice de masse corporelle (IMC) à 38kg/m2, un diabète de type 2, une hypothyroïdie et une HTA, traitée par MEDIATOR® 3 comprimés par jour de 2000 à 2003. En 2003, apparaît une dyspnée d'aggravation progressive. En octobre 2005, une HTAP pré-capillaire est mise en évidence et est jugée moyennement sévère avec une pression artérielle pulmonaire systolique (PAPs) à 79 mmHg. Une origine multifactorielle est évoquée car, à la prise de benfluorex, s'ajoutent une obésité et un déficit ventilatoire restrictif sur paralysie de la coupole diaphragmatique droite. L'expertise conclut à une HTAP idiopathique ;
- Le deuxième cas concerne une femme de 51 ans avec un IMC de 41 kg/m2, avec un syndrome d'apnée du sommeil, une BPCO post-tabagique, un diabète de type 2 et des antécédents de phlébite. Cette patiente, traitée par MEDIATOR® durant 3 mois 10 ans auparavant, présente en décembre 2006 une pression artérielle pulmonaire moyenne (PAPm) à 60 mmHg avec à la scintigraphie pulmonaire des séquelles minimes post-emboliques. L'expertise conclut à une possible HTAP idiopathique, mais, en l'état et compte tenu de la chronologie, les pathologies associées et les données sont insuffisantes pour retenir ce dossier.
- Le troisième cas concerne une femme de 58 ans avec un IMC à 49 kg/m2, un diabète de type 2 et une HTA. Cette patiente, traitée par MEDIATOR® pendant 10 ans, présente en décembre 2006 une PAPm à 46 mmHg. L'expertise considère que l'HTAP idiopathique est possible mais que le dossier est beaucoup trop succinct pour permettre de statuer.

Par ailleurs, un cas de valvulopathie a été notifié au CRPV de Toulouse.

Les conclusions de l'enquête concernant les troubles neuro-psychiatriques ne sont pas modifiées par les données additionnelles. Elles confirment la réalité de la survenue de confusions sous MEDIATOR® et la nécessité de détailler dans la rubrique « Effets indésirables » du RCP, le terme de confusion, comme cela a été proposé à la Commission nationale du 29 novembre 2005.
Le nombre de cas notifiés d'HTAP idiopathiques, après expertise et prise en compte des nouveaux cas d'HTAP rapportés depuis 2005, est de 3, soit 1 cas pour 41 841 426 boites vendues ou 1 cas pour 17 204 533 mois de traitement. L'incidence naturelle l'HTAP idiopathique est quant à elle de 1 à 2 cas par million et par an. Ainsi, selon l'avis du rapporteur et compte tenu de l'incidence naturelle des HTAP idiopathiques, le nombre de cas d'HTAP d'allure idiopathique retrouvés dans l'enquête ne constitue pas un signal significatif de toxicité du MEDIATOR® dans la classe organe cardiovasculaire.

4 - Etude expérimentale sur un modèle animal permettant d'étudier le potentiel du benfluorex à engendrer des HTAP

Concernant le projet de modèle expérimental chez l'animal, le laboratoire a déposé un projet d'étude chez le rat Fawn-hooded, modèle génétique susceptible de développer spontanément une HTAP (accélérée par l'hypoxie). Après analyse de ce projet d'étude, les conclusions rendues par le groupe de travail préclinique de la Commission d'AMM ont été qu'il n'existe pas de modèle expérimental animal adapté à la question posée.

5 - Revue des données d'efficacité. Conclusion du groupe DEUG

Le Département de l'évaluation thérapeutique des demandes d'AMM de l'Afssaps a présenté aux membres de la Commission nationale de pharmacovigilance une revue des données d'efficacité de MEDIATOR®, reflet des conclusions du Groupe de Travail Diabétologie/ Endocrinologie/ Urologie/ Gynécologie (GT DEUG) de la Commission d'AMM.

L'AMM de MEDIATOR® a été octroyée en plusieurs étapes, en 1987 pour les hypertriglycéridémies et en 1990 pour le diabète.

Action hypolipémiante
Le mécanisme d'action sur les lipides est difficile à préciser malgré les données soumises. *In vitro*, le benfluorex inhiberait la synthèse des acides gras entraînant une baisse des triglycérides (TG). *In vivo* chez l'animal, le benfluorex inhiberait l'acyl-coenzyme A cholestérol : acyltranférase (ACAT), mais le retentissement clinique n'est pas démontré (pas de baisse du LDL-cholestérol) de même que l'effet indépendant de la prise alimentaire.
Dix études cliniques ont été soumises :

- six études versus placebo réalisées entre 1978 et 2006 (au total 394 patients), anciennes à l'exception de l'étude Moulin. Méthodologiquement, il y a un faible nombre de patients, une grande variabilité de la dyslipidémie selon les études et le LDL-cholestérol n'est pas toujours disponible. Dans l'étude Moulin, la plus récente, on observe une diminution de 7% des TG et de 6% du LDL-cholestérol ;

- quatre études versus produits de référence, les fibrates, comprenant au total 163 patients avec une dyslipidémie (IIa, IIb et IV).

Une méta-analyse de l'efficacité de MEDIATOR® sur les TG a été réalisée ; elle comporte 6 études (Louvet, Tomassi, Moulin, Velusi, Del Prato et Biancchi), d'effectif varié de 10 à 242 patients, contre placebo avec tirage au sort. L'efficacité du benfluorex est très modeste sur les TG et non démontrée sur les autres paramètres lipidiques.

Action hypoglycémiante

Plusieurs mécanismes d'action sont évoqués : effet insulino-sensibilisateur chez l'Homme avec effet sur les transporteurs de glucose, effet direct sur le foie et réduction du contenu musculaire en TG.

Les études analysées en 1990, lors de la validation de l'indication dans le diabète sont anciennes: 3 études *versus* placebo où l'on observe une diminution de l'HbA1c de 0,8% (Tomassi) sous régime seul, de 0,9% sous régime seul et sulfamide (Velussi) et de 1,7% (Louvet) sous MEDIATOR® et sulfamide versus placebo et sulfamide. Une étude plus récente (1998), l'étude de Del Prato *versus* placebo et *versus* metformine montre une baisse de 0,86% entre le groupe placebo et le groupe benfluorex mais la qualité de tous ces essais est médiocre.

Finalement, l'étude Moulin est la plus récente. Il s'agit d'une étude multicentrique, randomisée en double aveugle de 18 semaines qui étudie l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex *versus* placebo chez 325 patients diabétiques de type 2 en surpoids (IMC entre 25 et 40 kg/~~m2~~m^2) mal équilibrés (HbA1c entre 7 et 10%) par un sulfamide à dose maximale tolérée depuis au moins 2 mois et intolérants ou ayant une contre-indication à la metformine. Trois sous-groupes ont été définis : HbA1c>8%, âge >65 ans et clairance de la créatinine < 80 ml/min. Cette étude comporte 2 phases : une période en double aveugle de 18 semaines pour démontrer la supériorité du benfluorex *versus* placebo sur l'HbA1c et une période en ouvert de 16 semaines centrée sur le profil de sécurité à long terme en association à un sulfamide ou à l'acarbose.

Les résultats ont montré une diminution de l'HbA1c de 0,82% dans le groupe benfluorex par rapport à la valeur de base et de 1% par rapport au placebo ($p< 0,001$). Cette baisse est significative dès la quatrième semaine et est maintenue jusqu'à 6 mois. On observe également une diminution significative de la glycémie à jeun dès la quatrième semaine sous benfluorex par rapport au placebo. Il existe une perte de poids respectivement de 1,3 kg et de 0,7 kg sous benfluorex et placebo avec une efficacité sur l'HbA1c indépendante de l'évolution pondérale. La baisse de l'HbA1c sous benfluorex par rapport à la valeur de base est plus importante pour les patients dont l'HbA1c de base est > 8% par rapport aux patients dont l'HbA1c ≤ 8%. Lors de la phase en ouvert, l'effet est reproductible dans le groupe initialement traité par placebo.

Au total, l'étude est conforme aux recommandations pour le développement des antidiabétiques oraux (EMEA 2002), et l'effet hypoglycémiant est notable avec une diminution de l'HbA1c de 1% *versus* placebo. Ces résultats sont par ailleurs cohérents avec les études antérieures. L'efficacité en seconde intention en association à un sulfamide semble donc démontrée et ceci indépendamment de la perte de poids, mais les experts ont soulevé des réserves méthodologiques. Par ailleurs, l'efficacité en prévention primaire et secondaire des complications de l'athérosclérose n'est pas démontrée.

En conclusion, le GT DEUG de la Commission d'AMM propose le retrait de l'indication de MEDIATOR® dans les dyslipidémies par insuffisance d'efficacité avec maintien de l'indication « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » dans l'attente de la soumission de résultats complémentaires d'études en cours devant permettre de positionner plus précisément ce produit dans l'arsenal thérapeutique du diabète de type 2.

6 – Résultats de l'étude de prescription/utilisation

Les laboratoires Servier ont présenté aux membres de la Commission les résultats de l'étude de prescription basée sur l'exploitation de l'observatoire Thalès. Deux périodes de 1 an ont été analysées : mai 2004 à mai 2005 et mai 2005 à mai 2006. Il apparaît que 80,3% des prescriptions de MEDIATOR® en 2004-2005 et 80,5% en 2005-2006 sont réalisées dans le cadre de l'AMM chez des patients dyslipidémiques et/ou diabétiques et qu'environ 11% des prescriptions concernent des patients obèses, hors du cadre de l'AMM (11,5% en 2004-2005 et 10,7% en 2005-2006). Ces taux restent donc stables au cours du temps. Par ailleurs, il n'y a pas de saisonnalité des prescriptions, qu'elles soient destinées aux obèses seulement ou à l'ensemble des patients. Enfin, sur les deux périodes, le profil des patients concernés reste stable (âge, sexe, IMC).

7 - Discussions de la Commission nationale de pharmacovigilance

Les membres de la Commission considèrent que le libellé de l'indication retenue par le GT DEUG dans le diabète n'est ni clair, ni conforme aux données des études cliniques. Ils ont d'autre part tenu à souligner que les laboratoires SERVIER n'ont pas déposé de demande de renouvellement de l'AMM de benfluorex en Espagne et en Italie. Ils estiment par ailleurs nécessaire, par rapport à une efficacité du produit jugée modeste

par certains membres de la commission nationale, et établie sur un critère principal (baisse de l'HdA1c) dans la seule étude méthodologiquement acceptable (étude Moulin), de tenir compte dans la réévaluation du rapport bénéficie risque du MEDIATOR® : i) du métabolisme du benfluorex, conduisant à la formation d'un dérivé fenfluraminique, ii) de ses effets indésirables neuropsychiatriques, iii) des rares cas d'HTAP et de valvulopathies notifiés ou décrits pouvant faire évoquer un problème qualitatif similaire à celui ayant amené au retrait du marché des anorexigènes fenfluraminiques sérotoninergiques, iv) d'une utilisation du produit essentiellement en France (88% des ventes). Certains membres de la Commission nationale ont par ailleurs tenu à faire connaître leur opinion en se prononçant pour un rapport bénéfice/risque défavorable du MEDIATOR®. Ce dossier sera présenté en Commission d'AMM le 5 avril 2007.

Mise à disposition par l'Afssaps d'information complémentaire, disponible au moment de la publication de ce compte rendu :

La Commission d'autorisation de mise sur le marché réunie le 5 avril 2007 a émis les propositions suivantes :

1. Avis favorable à la mention des effets indésirables neuropsychiatriques tels que proposés par la Commission nationale de pharmacovigilance au niveau de la rubrique 4.8. "Effets indésirables" du RCP et de la notice : « troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) ».

2. Avis DEFAVORABLE au maintien de l'indication : « Adjuvant au régime adapté dans les hypertriglycéridémies ». L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée, les données soumises ne montrant en effet qu'une efficacité très modeste et inconstante sur les triglycérides et une absence d'efficacité sur les autres paramètres lipidiques tels que le LDL-cholestérol.
Le maintien de cette indication pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et en particulier les triglycérides, ces hypolipémiants ayant démontré par ailleurs une efficacité en termes de prévention cardiovasculaire.

3. Avis FAVORABLE au maintien de l'indication : « Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » dans son libellé actuel.
Néanmoins, aucune conclusion définitive ne peut être portée sur cette efficacité compte tenu de certaines réserves émises sur la méthodologie de l'étude MOULIN, étude pivot dans cette indication. De plus, dans l'attente des résultats d'une autre étude en cours sur les paramètres glucidiques (en association avec d'autres antidiabétiques oraux), aucun motif de protection de la santé publique ne s'oppose à ce que l'indication telle que libellée soit maintenue.

4. Compte tenu des éléments versés dans le dossier de réévaluation, proposition d' inspection de l'essai clinique MOULIN.

5. Les membres de la commission d'AMM souhaitent qu'une communication soit faite sur l'usage hors AMM de ce médicament.

En conséquence, dans la cadre de la procédure contradictoire, un projet de modification de l'AMM du médicament MEDIATOR® a été adressé aux laboratoires SERVIER.

Div-1

CRPV BREST

De: Carmen KREFT-JAIS [Carmen.KREFT-JAIS@afssaps.sante.fr]
Envoyé: jeudi 19 mars 2009 18:33
À: CRPVB
Cc: beatrice.borokhov@afssaps.sante.fr; Scheherazade OUARET; CRPV BESANCON; irene.frachon@chu-brest.fr
Objet: Rép. :

Bonsoir Dominique,

Merci pour cette information qui confirme notre préoccupation sur le produit. En effet nous avons prévu la semaine dernière avec Besançon, de faire le point sur le sujet pour passage en CT au mois de mai. Nous avons aussi été contacté par le CRPV de Grenoble qui aurait 2 cas.

Bonne soirée,

Carmen

Dr Carmen KREFT-JAIS
Chef du Département de Pharmacovigilance
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>>> "CRPVB" <crpv.brest@chu-brest.fr> 19/03/09 16:49 >>>

Bonjour,

Cet après-midi, j'avais rendez-vous avec Irène Frachon, pneumologue au CHU, référente sur l'Ouest pour l'hypertension artérielle pulmonaire. Nous sommes régulièrement en contact, notamment pour des points bibliographiques sur le benfluorex.

A Brest, les pneumologues et cardiologues sont sensibilisés aux effets indésirables du benfluorex et ont d'ailleurs été récemment auteurs de publications sur le sujet (Eur. Respir. J. mars 2009).

C'est à la suite du premier cas de valvulopathie après prise de benfluorex sur Brest en 2008 et qui apparaît dans la publication Eur.Respir.J mars 2009, que des cardiologues brestois ont contacté Irène Frachon au sujet de dossiers d'insuffisances valvulaires sur lesquels ils lui demandaient un avis.

Suite à ces nouveaux cas, Irène a interrogé le département d'information médicale du CHU de Brest :

- Par le biais des codages des maladies (diabète et valvulopathies), il a été possible de recenser 3 nouveaux cas de valvulopathies après prise de benfluorex à déclarer à la pharmacovigilance : en effet il s'agit d'une insuffisance mitrale non expliquée par le contexte clinique avec prise de benfluorex antérieure au diagnostic de valvulopathie.

- Une autre interrogation du département d'information médicale par mots-clés « médiator ou benfluorex » et codage « valvulopathies » a permis de trouver 10 cas d'insuffisances mitrales fuyantes compatibles avec une prise de benfluorex.

- Actuellement, Irène Frachon a entrepris une enquête de plus grande envergure au niveau du département d'information médicale en « screenant » les patients hospitalisés en cardiologie et chirurgie cardiovasculaire entre 2003 et 2009 à Brest, porteurs d'un diagnostic de valvulopathie « insuffisance mitrale de nature inexpliquée » pour lesquels, elle souhaiterait vérifier une éventuelle exposition au benfluorex. Cette dernière enquête est encore à un stade précoce.

Ce jour, nous avons pris contact avec le CRPV de Besançon pour les informer des cas à venir dans la Banque de PV.

Nous sommes à votre disposition pour tout autre renseignement. Irène Frachon serait d'accord pour participer à toute discussion sur ce sujet.

Cordialement

Dominique Carlhant-Kowalski CRPV de Brest

Pour tout contact :

Dominique Carlhant-Kowalski : dominique.kowalski@chu-brest.fr

Irène Frachon : irene.frachon@chu-brest.fr

Christian Riché : christian.riche@chu-brest.fr

Dcu- 1

CRPV BREST

De: Carmen KREFT-JAIS [Carmen.KREFT-JAIS@afssaps.sante.fr]
Envoyé: jeudi 19 mars 2009 18:33
À: CRPVB
Cc: beatrice.borokhov@afssaps.sante.fr; Scheherazade OUARET; CRPV BESANCON; irene.frachon@chu-brest.fr
Objet: Rép. :

Bonsoir Dominique,

Merci pour cette information qui confirme notre préoccupation sur le produit. En effet nous avons prévu la semaine dernière avec Besançon, de faire le point sur le sujet pour passage en CT au mois de mai. Nous avons aussi été contacté par le CRPV de Grenoble qui aurait 2 cas.

Bonne soirée,

Carmen

Dr Carmen KREFT-JAIS
Chef du Département de Pharmacovigilance
AFSSAPS

Tél : 33155873533
Fax : 33155873532
e-mail : carmen.kreft-jais@afssaps.sante.fr

>>> "CRPVB" <crpv.brest@chu-brest.fr> 19/03/09 16:49 >>>

Bonjour,

Cet après-midi, j'avais rendez-vous avec Irène Frachon, pneumologue au CHU, référente sur l'Ouest pour l'hypertension artérielle pulmonaire. Nous sommes régulièrement en contact, notamment pour des points bibliographiques sur le benfluorex.

A Brest, les pneumologues et cardiologues sont sensibilisés aux effets indésirables du benfluorex et ont d'ailleurs été récemment auteurs de publications sur le sujet (Eur. Respir. J. mars 2009).

C'est à la suite du premier cas de valvulopathie après prise de benfluorex sur Brest en 2008 et qui apparaît dans la publication Eur.Respir.J mars 2009, que des cardiologues brestois ont contacté Irène Frachon au sujet de dossiers d'insuffisances valvulaires sur lesquels ils lui demandaient un avis.

Suite à ces nouveaux cas, Irène a interrogé le département d'information médicale du CHU de Brest :

- Par le biais des codages des maladies (diabète et valvulopathies), il a été possible de recenser 3 nouveaux cas de valvulopathies après prise de benfluorex à déclarer à la pharmacovigilance : en effet il s'agit d'une insuffisance mitrale non expliquée par le contexte clinique avec prise de benfluorex antérieure au diagnostic de valvulopathie.

- Une autre interrogation du département d'information médicale par mots-clés « médiator ou benfluorex » et codage « valvulopathies » a permis de trouver 10 cas d'insuffisances mitrales fuyantes compatibles avec une prise de benfluorex.

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Doc - 1

CRPV BREST

De: Irene FRACHON [irene.frachon@chu-brest.fr]
Envoyé: lundi 23 mars 2009 10:40
À: 'Carmen KREFT-JAIS'; 'CRPVB'
Cc: beatrice.borokhov@afssaps.sante.fr; 'Scheherazade OUARET'; 'CRPV BESANCON'
Objet: RE : Rép. :

Bonjour Madame,

Merci pour votre réponse rapide.
Je suis (ainsi que mes collègues cardiologues Yves Etienne et Yannick Jobic) à votre disposition, notamment pour participer, si vous le souhaitez, à une réunion concernant ce médicament.
Très cordialement

Irène Frachon
Praticien Hospitalier
Département de Médecine Interne et Pneumologie
Hôpital de la Cavale Blanche
29609 Brest Cédex
02 98 34 78 26
portable : 06 81 07 53 75

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De : Carmen KREFT-JAIS [mailto:Carmen.KREFT-JAIS@afssaps.sante.fr]
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À : CRPVB
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Nous sommes à votre disposition pour tout autre renseignement. Irène Frachon serait d'accord pour participer à toute discussion sur ce sujet.

Cordialement
Dominique Carlhant-Kowalski CRPV de Brest

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Christian Riché : christian.riche@chu-brest.fr

Doc 1

CRPV BREST

De: Aurore TRICOTEL [Aurore.TRICOTEL@afssaps.sante.fr]
Envoyé: lundi 25 mai 2009 17:44
À: CRPVB
Objet: Rép. : benfluorex

Bien reçu. Je vous remercie beaucoup pour cette recherche.
Bien cordialement,
Aurore Tricotel

>>> "CRPVB" <crpv.brest@chu-brest.fr> 25/05/2009 17:36 >>>

Bonjour,

En 2008, une publication a été faite par plusieurs équipes de pneumologues dont Brest sur les atteintes cardiaques avec le benfluorex.

Depuis, Irène Frachon, pneumologue référent de l'hypertension artérielle pulmonaire sur Brest, a été interrogée plusieurs fois par des cardiologues sur des valvulopathies chez des sujets exposés au benfluorex.

Irène Frachon a décidé de demander au PMSI de lui faire des requêtes (2000-2008) sur les services de cardiologie et de chirurgie cardiaque du CHU de Brest.

1. atteintes valvulaires et diabète comme diagnostic principal ou diagnostic associé significatif (soif ATCD actif ou problème en cours d'hospitalisation)

2. atteintes valvulaires comme diagnostic et benfluorex et mediator comme mots inscrits dans le résumé de sortie

Les codes des atteintes valvulaires correspondent aux codes : I. 05 ; I. 06 ; I 07 ; I. 08 ; I.09 ; I.09 ; I.34 ; I35 ; I.36 ; I.37 ; I38 ; I.39.

La requête la plus intéressante a été la numéro 2 pour laquelle le croisement a ramené 21 patients dont 10 cas qui ont fait l'objet d'une notification de pharmacovigilance comme cas graves.

Il y avait 2 autres cas (un dans la publication antérieure et un autre qu'un cardiologue lui avait mentionné).

Nous avons donc saisis en 2008-2009, à Brest, 12 cas d'atteintes valvulaires sous Médiator.

Actuellement Irène Frachon analyse une autre requête PMSI : sur la même période et dans les mêmes services « cardiologie et chirurgie cardiaque ».

Elle recherche dans les dossiers patients, voire après appel du médecin traitant, l'exposition au benfluorex, Médiator dans 2 populations :

1. les rétrécissements aortiques calcifiés

2. les valvulopathies autres mitrales et aortiques pour lesquelles il n'existe pas d'étiologie franche.

Dans le cadre de cette nouvelle étude nous avons saisi un nouveau cas dans la ANPV accompagné d'un autre cas qu'un confrère brestois lui a signalé.

Donc depuis le dernier comité technique nous avons saisi 2 autres cas d'atteintes valvulaires BR 20090142 et BR 20090143.

Nous avons également saisi 2 cas d'hypertension artérielle pulmonaire sous médiator.

Je sais qu'Irène fait une enquête auprès du réseau des pneumologues HTAP afin de recueillir d'autres cas. Je ne sais pas si elle a des réponses.

Je joins en annexe un article sur les valvulopathies médicamenteuses, une photo d'une des patientes de la série brestoises prise en mars 2009, la publication de l'année dernière des pneumologues, le dossier de Besançon présenté au CT du 5 mai 2009 qui incluent 12 des 14 cas brestois.

Les coordonnées d'Irène Frachon sont : irene.frachon@chu-brest.fr

En espérant vous avoir donné satisfaction

Cordialement

Dominique Carlhant-Kowalski

Doc 1

CRPV BREST

De: Aurore TRICOTEL [Aurore.TRICOTEL@afssaps.sante.fr]
Envoyé: lundi 25 mai 2009 17:44
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Bien cordialement,
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1. atteintes valvulaires et diabète comme diagnostic principal ou diagnostic associé significatif (soif ATCD actif ou problème en cours d'hospitalisation)

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Actuellement Irène Frachon analyse une autre requête PMSI : sur la même période et dans les mêmes services « cardiologie et chirurgie cardiaque ».

Elle recherche dans les dossiers patients, voire après appel du médecin traitant, l'exposition au benfluorex, Médiator dans 2 populations :

1. les rétrécissements aortiques calcifiés

2. les valvulopathies autres mitrales et aortiques pour lesquelles il n'existe pas d'étiologie franche.

Dans le cadre de cette nouvelle étude nous avons saisi un nouveau cas dans la ANPV accompagné d'un autre cas qu'un confrère brestois lui a signalé.

Donc depuis le dernier comité technique nous avons saisi 2 autres cas d'atteintes valvulaires BR 20090142 et BR 20090143.

Nous avons également saisi 2 cas d'hypertension artérielle pulmonaire sous médiator.

Je sais qu'Irène fait une enquête auprès du réseau des pneumologues HTAP afin de recueillir d'autres cas. Je ne sais pas si elle a des réponses.

Je joins en annexe un article sur les valvulopathies médicamenteuses, une photo d'une des patientes de la série brestoises prise en mars 2009, la publication de l'année dernière des pneumologues, le dossier de Besançon présenté au CT du 5 mai 2009 qui incluent 12 des 14 cas brestois.

Les coordonnées d'Irène Frachon sont : irene.frachon@chu-brest.fr

En espérant vous avoir donné satisfaction

Cordialement

Dominique Carlhant-Kowalski

Doc 1

Bonjour Carmen,
Suite à ton appel, je te fais un récapitulatif du dossier brestois « Médiator ».

En 2008, une publication a été faite par plusieurs équipes de pneumologues dont Brest sur les atteintes cardiaques avec le benfluorex.
Depuis, Irène Frachon, pneumologue référent de l'hypertension artérielle pulmonaire sur Brest, a été interrogée plusieurs fois par des cardiologues sur des valvulopathies chez des sujets exposés au benfluorex.
Irène Frachon a décidé de demander au PMSI de lui faire des requêtes (2000-2008) sur les services de cardiologie et de chirurgie cardiaque du CHU de Brest.

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Nous avons donc saisis en 2008-2009, à Brest, 12 cas d'atteintes valvulaires sous Médiator. Je joins un tableau récapitulatif que j'avais fait au CRPV de Besançon en charge de l'enquête nationale de pharmacovigilance sur HTAP et Médiator.

Actuellement Irène analyse une autre requête PMSI : sur la même période et dans les mêmes services « cardiologie et chirurgie cardiaque ».
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Je sais qu'Irène fait une enquête auprès du réseau des pneumologues HTAP afin de recueillir d'autres cas. Je n'ai plus le questionnaire, Christian Riché te l'a remis au dernier comité technique. Je ne sais pas si elle a des réponses.

Je joins en annexe un article sur les valvulopathies médicamenteuses, une photo d'une des patientes de la série brestoises prise en mars 2009, la publication de l'année dernière des pneumologues, le tableau des cas brestois auquel il faut ajouter les derniers cas post comité technique.

Voici notre dossier sur le sujet.
~~En espérant avoir été assez claire~~.
Cordialement
Dominique

Irène souhaiterait avoir le rapport de Besançon pour en lui transmettre ses souhaits

- coordonnées Irène Frachon
- 02 98 14 50 19.
  06 81 07 53 75.

le correspondant échocardiographe d'Irène Frachon et le docteur Yannick Jobic qui a pris contact avec le professeur Christophe Tribouilloy président du groupe d'échocardiographie à la fédération française de cardio.

de Amiens.

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Les coordonnées d'Irène Frachon sont : irene.frachon@chu-brest.fr

En espérant vous avoir donné satisfaction
Cordialement
Dominique Carlhant-Kowalski

qui incluent 12 des 14 cas brestois —

Bonjour Carmen,
Suite à ton appel, je te fais un récapitulatif du dossier brestois « Médiator ».

En 2008, une publication a été faite par plusieurs équipes de pneumologues dont Brest sur les atteintes cardiaques avec le benfluorex.
Depuis, Irène Frachon, pneumologue référent de l'hypertension artérielle pulmonaire sur Brest, a été interrogée plusieurs fois par des cardiologues sur des valvulopathies chez des sujets exposés au benfluorex.
Irène Frachon a décidé de demander au PMSI de lui faire des requêtes (2000-2008) sur les services de cardiologie et de chirurgie cardiaque du CHU de Brest.

1. atteintes valvulaires et diabète comme diagnostic principal ou diagnostic associé significatif (soif ATCD actif ou problème en cours d'hospitalisation)
2. atteintes valvulaires comme diagnostic et benfluorex et mediator comme mots inscrits dans le résumé de sortie

Les codes des atteintes valvulaires correspondent aux codes : I. 05 ; I. 06 ; I 07 ; I. 08 ; I.09 ; I.09 ; I.34 ; I35 ; I.36 ; I.37 ; I38 ; I.39.
La requête la plus intéressante a été la numéro 2 pour laquelle le croisement a ramené 21 patients dont 10 cas qui ont fait l'objet d'une notification de pharmacovigilance comme cas graves.
Il y avait 2 autres cas (un dans la publication antérieure et un autre qu'un cardiologue lui avait mentionné).

Nous avons donc saisis en 2008-2009, à Brest, 12 cas d'atteintes valvulaires sous Médiator. Je joins un tableau récapitulatif que j'avais fait au CRPV de Besançon en charge de l'enquête nationale de pharmacovigilance sur HTAP et Médiator.

Actuellement Irène analyse une autre requête PMSI : sur la même période et dans les mêmes services « cardiologie et chirurgie cardiaque ».
Elle recherche dans les dossiers patients, voire après appel du médecin traitant, l'exposition au benfluorex, mediator dans 2 populations :

1. les rétrécissements aortiques calcifiés
2. les valvulopathies autres mitrales et aortiques pour lesquelles il n'existe pas d'étiologie franche.

Dans le cadre de cette nouvelle étude nous avons saisi un nouveau cas dans la ANPV accompagné d'un autre cas qu'un confrère brestois lui a signalé.
Donc depuis le dernier comité technique nous avons saisi 2 autres cas d'atteintes valvulaires BR 20090142 et BR 20090143.
Nous avons également saisi 2 cas d'hypertension artérielle pulmonaire sous médiator.

Je sais qu'Irène fait une enquête auprès du réseau des pneumologues HTAP afin de recueillir d'autres cas. Je n'ai plus le questionnaire, Christian Riché te l'a remis au dernier comité technique. Je ne sais pas si elle a des réponses.

Je joins en annexe un article sur les valvulopathies médicamenteuses, une photo d'une des patientes de la série brestoises prise en mars 2009, la publication de l'année dernière des pneumologues, le tableau des cas brestois auquel il faut ajouter les derniers cas post comité technique.

Voici notre dossier sur le sujet.
~~En espérant avoir été assez claire~~.
Cordialement
Dominique

Deux

Irène voudrait savoir si on l'a mis au courant de Besançon ?
Pour ~~le~~ les cas qui lui manquent ?
Souhaite

- coordonnées Irène Frachon
- 02 98 14 50 19.
  06 81 07 53 75.

le correspondant échocardiographe d'Irène Frachon et le docteur Jannick Jobic qui a pris contact avec le professeur Christophe Tribouilloy président du groupe d'échocardiographie à la fédération Française de cardio.

Ici à Amiens.

DCU-1

Bonjour,

En 2008, une publication a été faite par plusieurs équipes de pneumologues dont Brest sur les atteintes cardiaques avec le benfluorex.
Depuis, Irène Frachon, pneumologue référent de l'hypertension artérielle pulmonaire sur Brest, a été interrogée plusieurs fois par des cardiologues sur des valvulopathies chez des sujets exposés au benfluorex.
Irène Frachon a décidé de demander au PMSI de lui faire des requêtes (2000-2008) sur les services de cardiologie et de chirurgie cardiaque du CHU de Brest.

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En espérant vous avoir donné satisfaction
Cordialement
Dominique Carlhant-Kowalski

qui incluent 12 des 14 cas brestois —

Dominique Kowalski

Div 2

De: pierre.schiavi@fr.netgrs.com
Envoyé: lundi 7 avril 2008 11:54
À: dominique.kowalski@chu-brest.fr
Cc: patricia.lefeuvre@fr.netgrs.com
Objet: Demande d'informations médicaments Servier

Chère Madame,

Suite à notre visite à Brest avec ma collègue P Lefeuvre, et pour répondre à votre question, je vous prie de trouver ci joint un document décrivant les relations chimiques entre 2 de nos spécialités.

J'espère que ces informations correspondent bien à votre demande.
Peut-être allez-vous à Clermont Ferrand cette semaine au congrès de pharmacologie et de pharmacovigilance? Si oui, je serais ravi de vous y rencontrer.

Bien cordialement

****
Pierre SCHIAVI, *Directeur de Division Scientifique Pharmacologie*, Trésorier de la SFPT
Information Servier, 27 rue du Pont
92578 Neuilly sur Seine Cedex, France
Tel: + 33 (0)1 55 72 70 43 Fax: + 33 (0)1 55 72 74 74
e-mail: pierre.schiavi@fr.netgrs.com
http://www.servier.com http://www.pharmacol-fr.org
****

<<MEDIATOR 150 mg.doc>>

Dominique Kowalski

Div 2

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****

<<MEDIATOR 150 mg.doc>>

Div 2

DONNEES PHARMACOCINETIQUES ET METABOLIQUES CHLORHYDRATE DE BENFLUOREX

I- Pharmacocinétique.

L'absorption gastro-intestinale du chlorhydrate de benfluforex est complète et rapide, le Tmax est compris entre 1h et 2h.
Le volume de distribution est de 0.37+/- 0.03l/kg chez l'homme.
Chez le rat il est de 1.4l/kg.
Chez le chien de 1.6l/kg.
Chez le singe de 0.36l/kg.
Chez le babouin de 0.31l/kg

On notera que le volume de distribution est identique chez les primates et chez l'homme.

II. Métabolisme.

Le benfluorex est rapidement métabolisé au niveau du foie. Il produit au moins 9 métabolites. (Fig 1). Des données récentes utilisant notamment des méthodes de détection spécifiques et sensibles ont permis de montrer qu'il existait deux métabolites principaux (fig 2) :

- le 1-(3 trifluorométhylphényl)-2N-2-(carboxymethyl)amino propane (S1475)
- la norfenfluramine (S 585)

Une étude réalisée chez 6 volontaires sains qui ont reçu pendant 14 jours une dose quotidienne de 3fois 150mg de benfluorex, a montré que :

- l'état stationnaire était atteint en 4 à 5 jours
- au bout des 14 jours la concentration plasmatique de benfluorex était très faible, autour de 10ng/ml, la concentration plasmatique du métabolite S1475 était très importante, aux alentours de 200ng/ml, la concentration plasmatique du norfenfluramine ne dépassait pas 30ng/ml (fig 3).

Il est très intéressant de comparer les métabolites produits par la biotransformation de benfluorex à ceux produits par la biotransformation de la fenfluramine (fig 4). La norfenfluramine représente la voie principale du métabolisme de la fenfluramine avec des concentrations urinaires de 7,4% de la dose pour la forme libre et de 50,7% pour la forme conjuguée à l'acide glucuronique.

Sans qu'il y ait d'explications à partir de la fenfluramine il semble que la norfenfluramine produite ne subit aucune biotransformation supplémentaire, alors que la norfenfluramine produite à partir de benfluorex est transformée en 3-trifluorométhylphényl-1-hydroxypropanone-2. Ce qui explique qu'on ne trouve pas plus de 2% de norfenfluramine dans l'urine.

Dans une étude où pendant 15 jours un groupe de 8 volontaires a reçu une dose journalière de trois fois 20mg de fenfluramine, la concentration sanguine de fenfluramine au bout de cette période était d'environ 120 ng/ml et celle de norfenfluramine d'environ 50ng/ml (fig 5).

En comparant les deux études :

- après fenfluramine le taux circulant de norfenfluramine représente 30% du taux circulant de fenfluramine

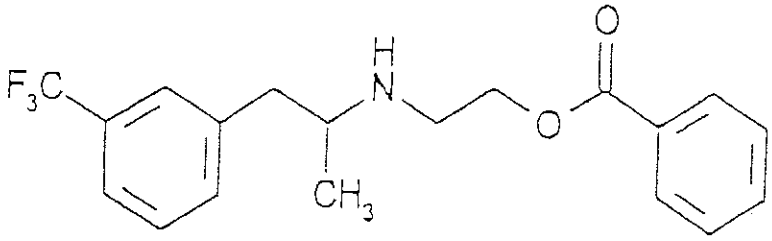
- après benfluorex la norfenfluramine représente 5% du taux circulant du métabolite principal S1475.

Il est impossible d'exclure la possibilité de passage de la barrière hémato-cérébrale de la norfenfluramine produite par le métabolisme de benfluorex.
Il faut toutefois noter qu'après administration de fenfluramine la quantité circulante de norfenfluramine vient s'additionner à celle de la fenfluramine et donc renforcer son action centrale anorexigène.

Nous rappelerons que malgré la production de norfenfluramine, la propriété pharmacodynamique d'anorexigène n'a jamais été attribuée à benfluorex.

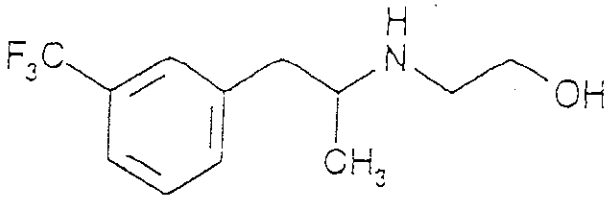
BENFLUOREX

% EXCRETION URINAIRE



chlorhydrate de benfluorex

ND

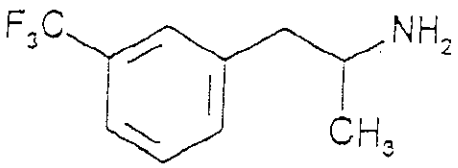


+ Acide benzoique

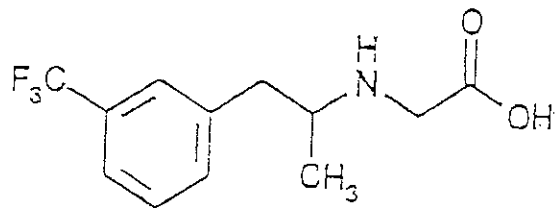
conj. gluc. (14)

1-(3-trifluorométhylphényl)-2N-(2-hydroxyéthyl)amino propane (12)

S 422



(2)



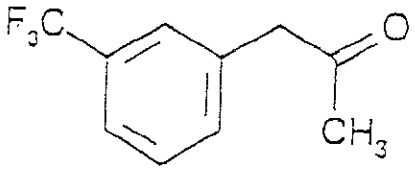
(63)

norfenfluramine

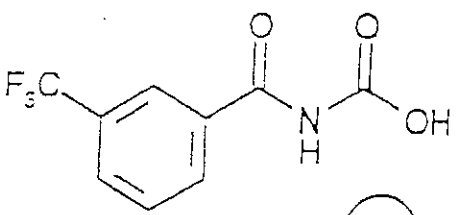
S 595

1-(3-trifluorométhylphényl)-2N–2-(carboxyméthyl)amino propane

S 1425



(3)



(2)

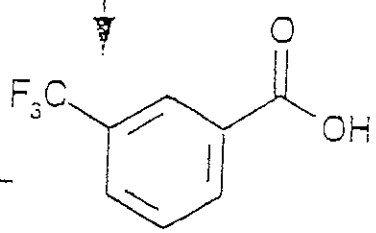


FIG 2

Benfluorex

SCHEMA DU METABOLISME

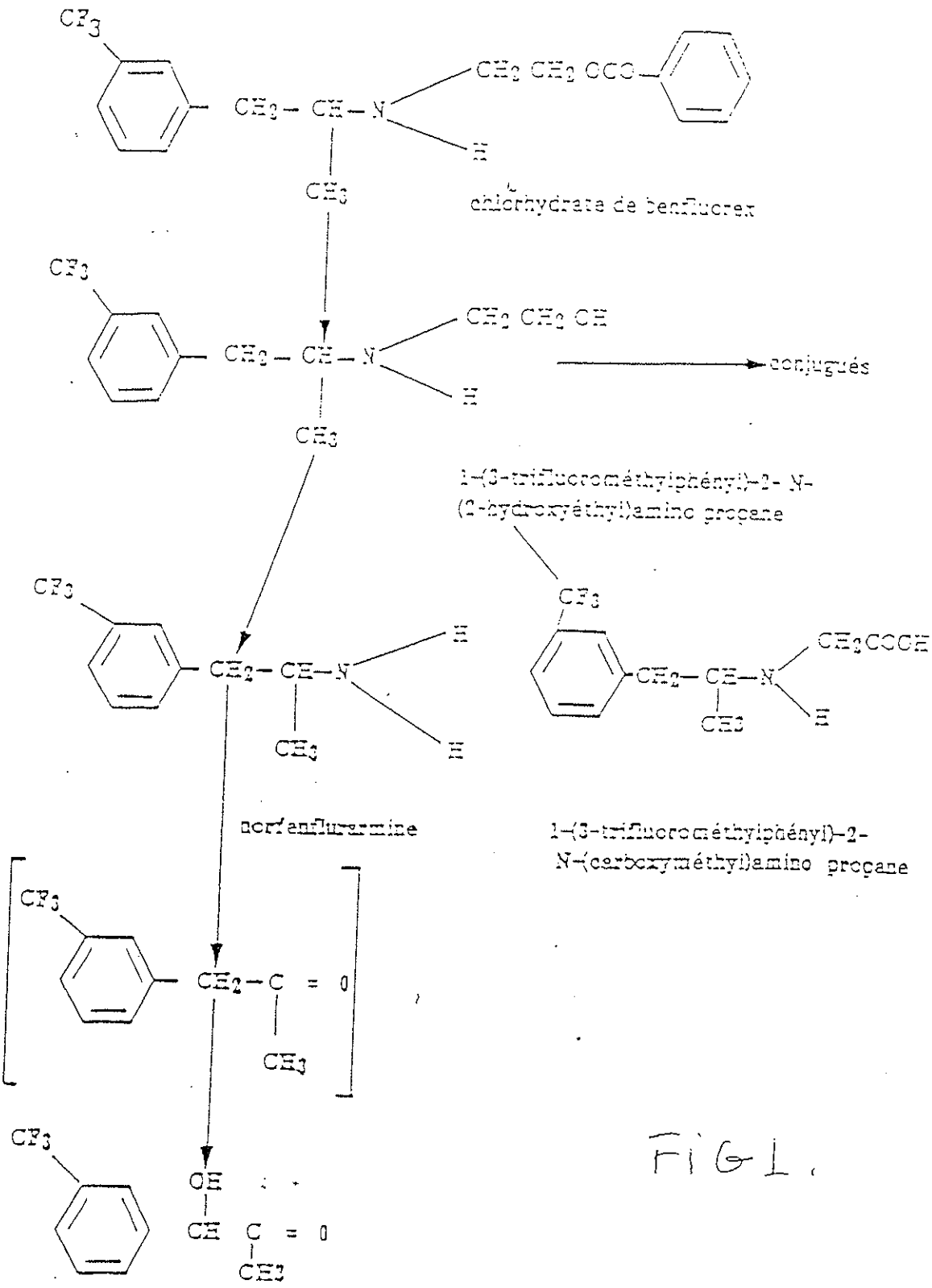
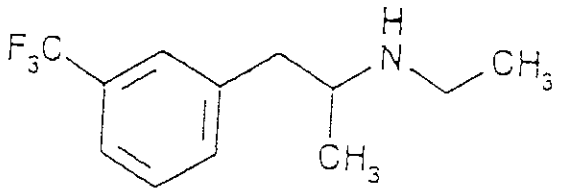


FIG 1.

FENFLURAMINE

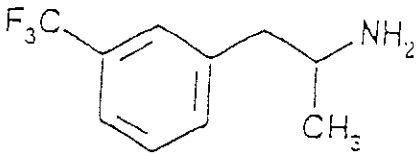
% EXCRETION URINAIRE



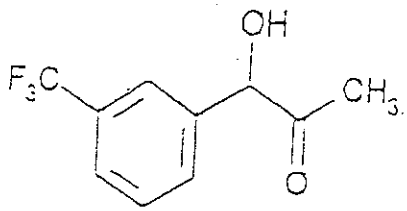
chlorhydrate de fenfluramine

11

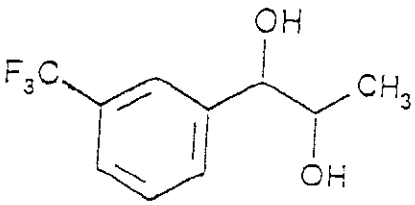
norfenfluramine



pas de biotransformation 7.4



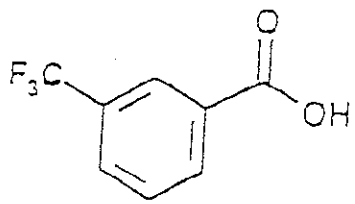
ND



ND

gluc. conj.

50.7



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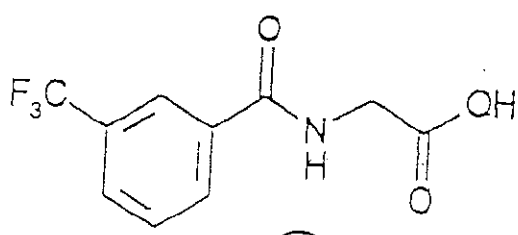


8.4

Fig 4

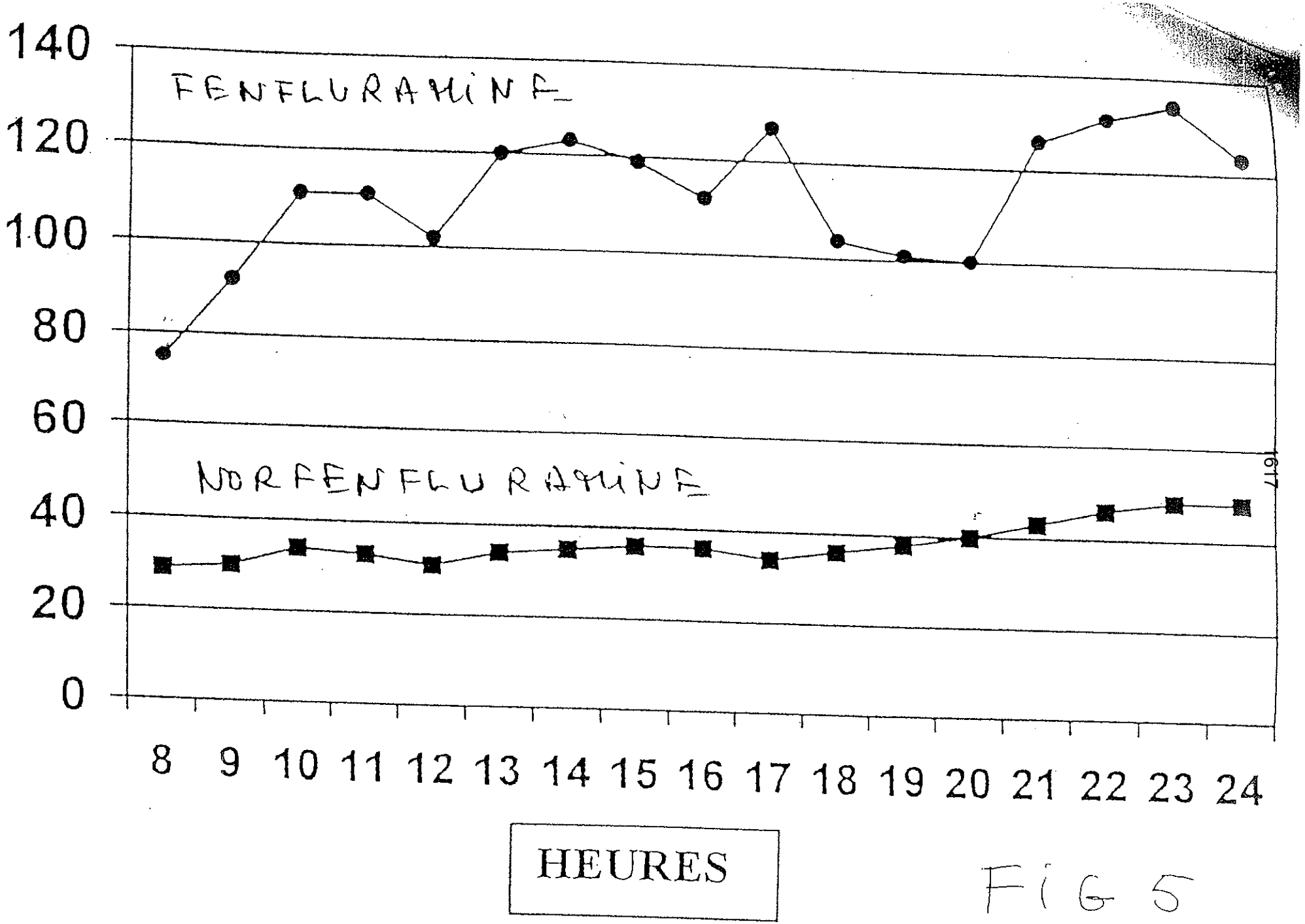
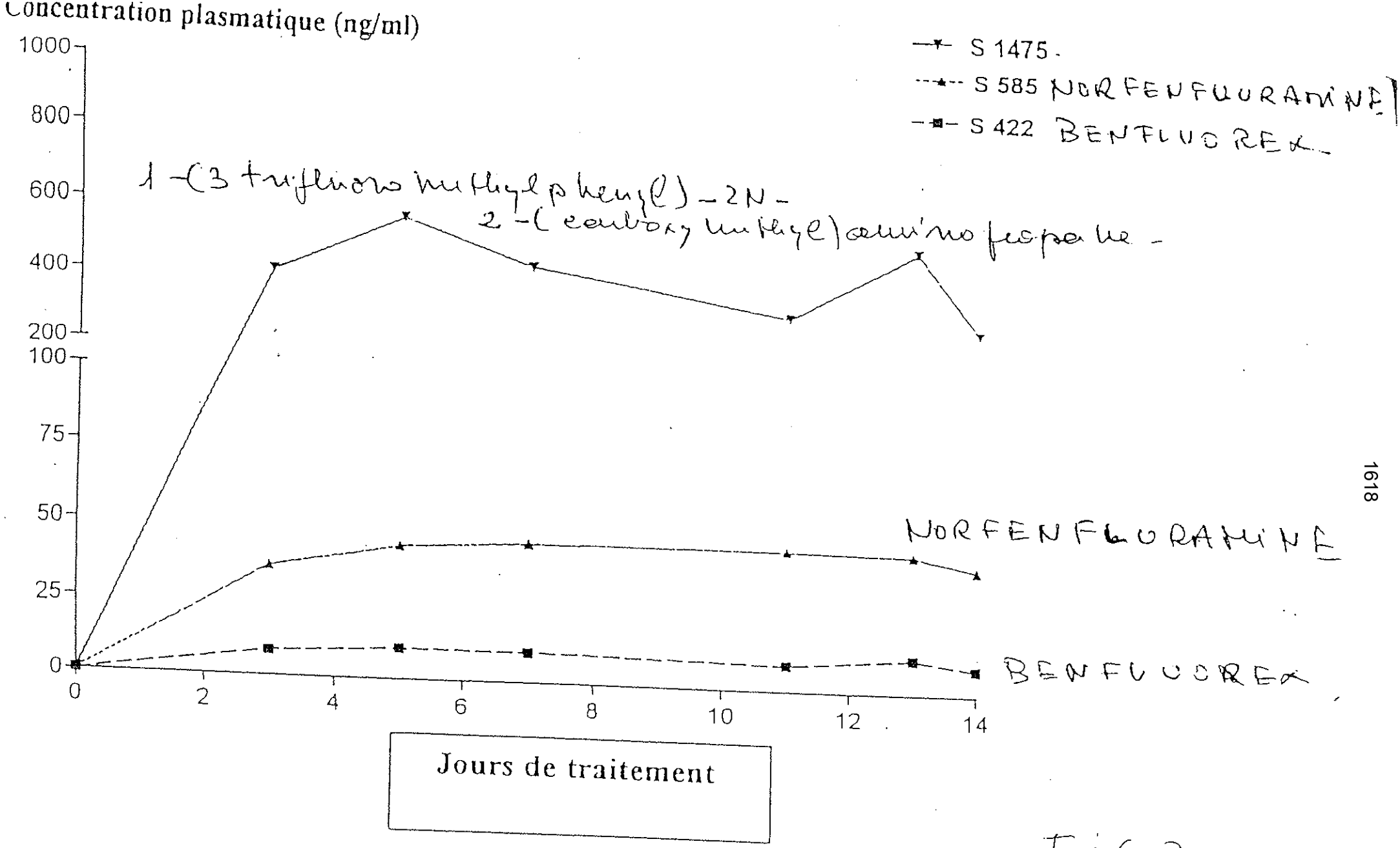

140
120
100
80
60
40
20
0
FENFLURAMINE
NORFENFLURAMINE
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
HEURES

FIG 5


Concentration plasmatique (ng/ml)
1000
800
600
400
200
100
75
50
25
0
0
2
4
6
8
10
12
14
S 1475
S 585 NORFENFLURAMINE
S 422 BENFLUOREX
1-(3 trifluoromethylphenyl)-2N-
2-(carboxymethyl)aminopropane
NORFENFLURAMINE
BENFLUOREX
Jours de traitement

1618

FIG 3.

MEDIATOR 150 mg et les fenfluramines empruntent des voies métaboliques bien distinctes qui expliquent des activités pharmacologiques radicalement différentes.

MEDIATOR 150 mg est rapidement métabolisé pour donner de nombreux métabolites. Les propriétés antidiabétiques de MEDIATOR 150 mg sont liées à deux métabolites actifs (S 1475 et S 422) qui représentent plus de 93 % de la totalité des composés circulants chez l'homme. Un troisième métabolite, dérivé fenfluraminique, ne représente que 2 % de la dose administrée.

A l'inverse, c'est essentiellement le produit parent la fenfluramine qui est retrouvé dans la circulation. Son métabolite principal, la norfenfluramine, représente 40 % du produit parent. L'activité anti-obésité des fenfluramines résulte essentiellement du profil pharmacologique du produit parent.

Enfin il faut souligner que le benfluorex et ses métabolites ne peuvent pas être biologiquement transformés en fenfluramine ou dexfenfluramine.

Ces différences de métabolisme s'expliquent par une structure chimique fondamentalement différente de MEDIATOR 150 mg et des fenfluramines. MEDIATOR 150 mg est un ester benzoïque d'un dérivé alcool alors que les fenfluramines appartiennent à la famille des alkylamines.

Ces particularités chimiques et métaboliques conduisent :

- à des effets cliniques différents : MEDIATOR 150 mg n' a pas d'effet sur la prise alimentaire ; la perte de poids observée chez des patients diabétiques obèses reste très modérée (de l'ordre de 2 kg pour la totalité du traitement) peut-être liée à l'amélioration de l'insulinosensibilité puisque l'activité antidiabétique est observée dès les premières semaines de traitement en l'absence de diminution pondérale ;

- à une tolérance différente : les effets indésirables les plus souvent rapportés avec MEDIATOR 150 mg sont des vertiges, des nausées et des troubles digestifs, une somnolence, ainsi que des réactions de nature allergique cutanée (rash, urticaire, prurit) ; ces événements sont peu ou pas rapportés avec les fenfluramines.

En conclusion, MEDIATOR 150 mg se distingue radicalement des fenfluramines tant en termes de structure chimique et de voies métaboliques que de profil d'efficacité et de tolérance.

Div 2

DONNEES PHARMACOCINETIQUES ET METABOLIQUES CHLORHYDRATE DE BENFLUOREX

I- Pharmacocinétique.

L'absorption gastro-intestinale du chlorhydrate de benfluforex est complète et rapide, le Tmax est compris entre 1h et 2h.
Le volume de distribution est de 0.37+/- 0.03l/kg chez l'homme.
Chez le rat il est de 1.4l/kg.
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On notera que le volume de distribution est identique chez les primates et chez l'homme.

II. Métabolisme.

Le benfluorex est rapidement métabolisé au niveau du foie. Il produit au moins 9 métabolites. (Fig 1). Des données récentes utilisant notamment des méthodes de détection spécifiques et sensibles ont permis de montrer qu'il existait deux métabolites principaux (fig 2) :

- le 1-(3 trifluorométhylphényl)-2N-2-(carboxymethyl)amino propane (S1475)
- la norfenfluramine (S 585)

Une étude réalisée chez 6 volontaires sains qui ont reçu pendant 14 jours une dose quotidienne de 3fois 150mg de benfluorex, a montré que :

- l'état stationnaire était atteint en 4 à 5 jours
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Sans qu'il y ait d'explications à partir de la fenfluramine il semble que la norfenfluramine produite ne subit aucune biotransformation supplémentaire, alors que la norfenfluramine produite à partir de benfluorex est transformée en 3-trifluorométhylphényl-1-hydroxypropanone-2. Ce qui explique qu'on ne trouve pas plus de 2% de norfenfluramine dans l'urine.

2'

Dans une étude où pendant 15 jours un groupe de 8 volontaires a reçu une dose journalière de trois fois 20mg de fenfluramine, la concentration sanguine de fenfluramine au bout de cette période était d'environ 120 ng/ml et celle de norfenfluramine d'environ 50ng/ml (fig 5).

En comparant les deux études :

- après fenfluramine le taux circulant de norfenfluramine représente 30% du taux circulant de fenfluramine

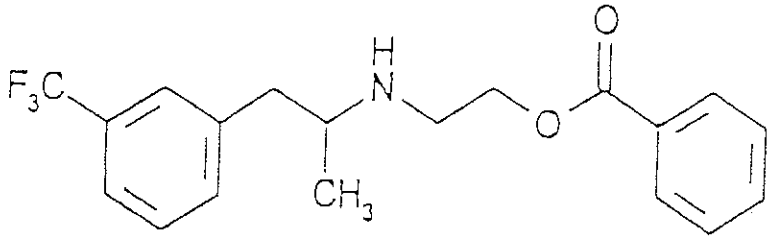
- après benfluorex la norfenfluramine représente 5% du taux circulant du métabolite principal S1475.

Il est impossible d'exclure la possibilité de passage de la barrière hémato-cérébrale de la norfenfluramine produite par le métabolisme de benfluorex.
Il faut toutefois noter qu'après administration de fenfluramine la quantité circulante de norfenfluramine vient s'additionner à celle de la fenfluramine et donc renforcer son action centrale anorexigène.

Nous rappelerons que malgré la production de norfenfluramine, la propriété pharmacodynamique d'anorexigène n'a jamais été attribuée à benfluorex.

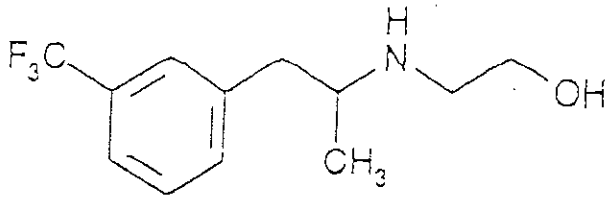
BENFLUOREX

% EXCRETION URINAIRE



chlorhydrate de benfluorex

ND

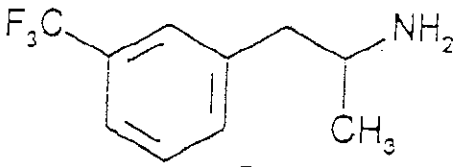


+ Acide benzoique

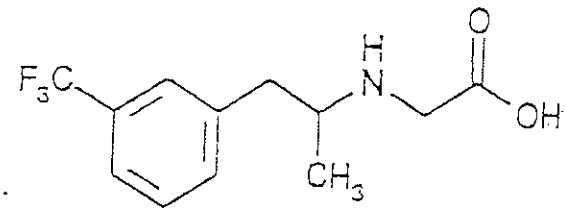
conj. gluc. (14)

1-(3-trifluorométhylphényl)-2N-(2-hydroxyéthyl)amino propane (12)

S 422



(2)



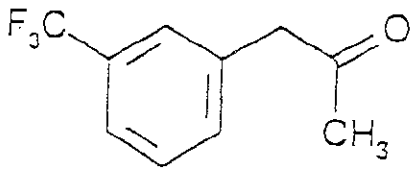
(63)

norfenfluramine

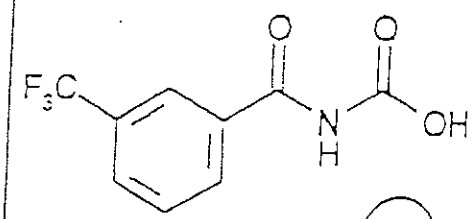
S 585

1-(3-trifluorométhylphényl)-2N–2-(carboxyméthyl)amino propane

S 1425



(3)



(2)

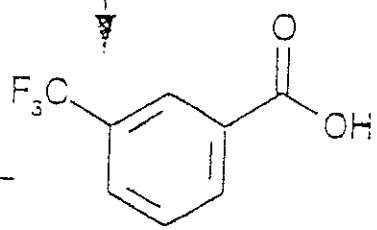


FIG 2

Benfluorex

SCHEMA DU METABOLISME

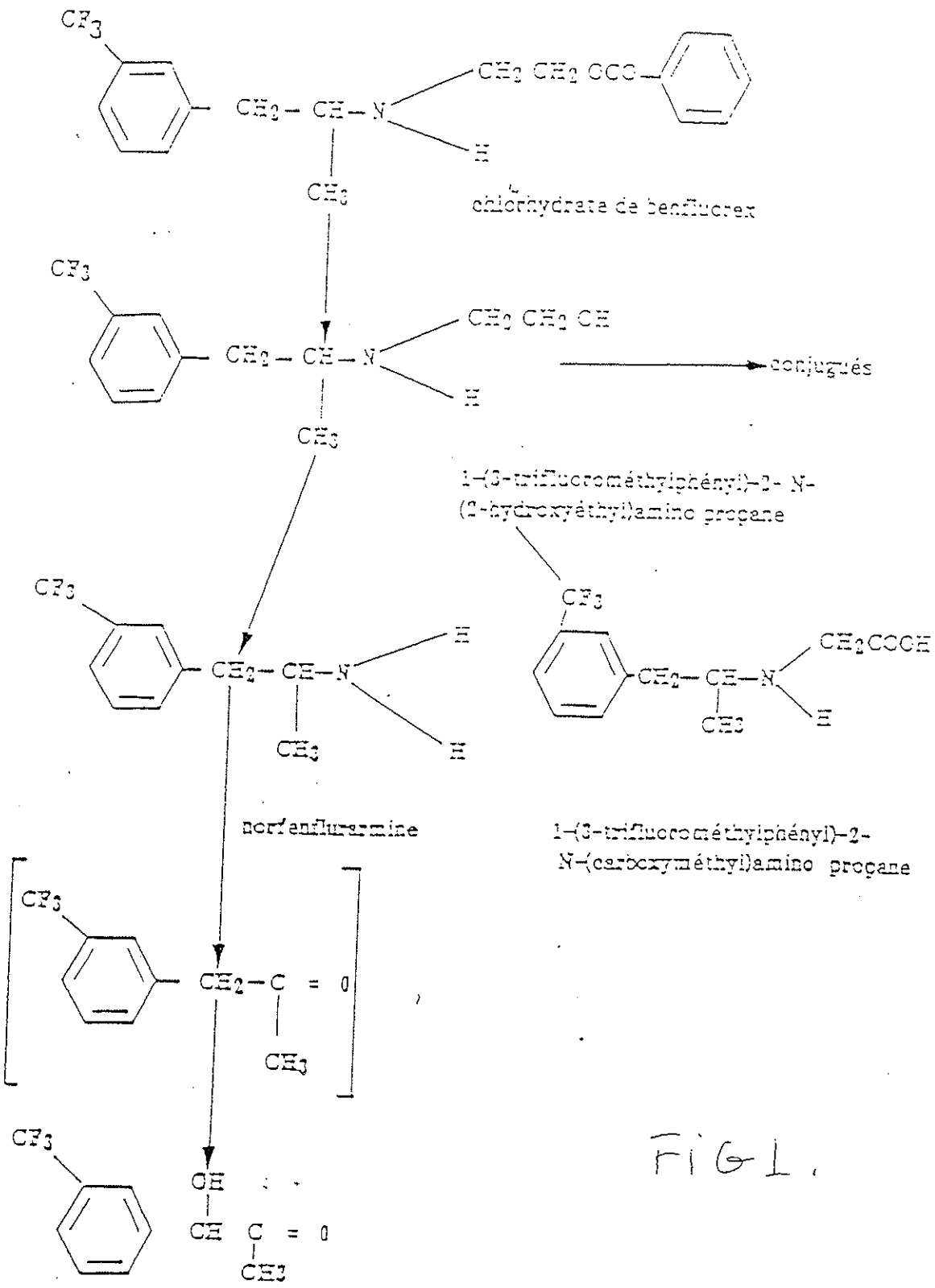
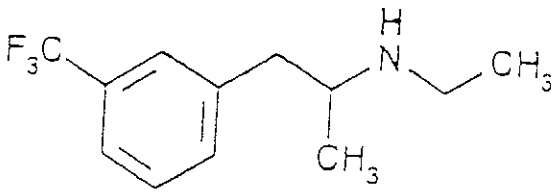


FIG 1.

FENFLURAMINE

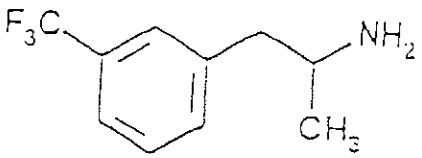
% EXCRETION URINAIRE



chlorhydrate de fenfluramine

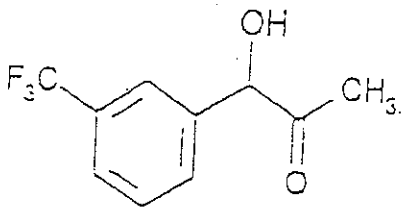
11

norfenfluramine

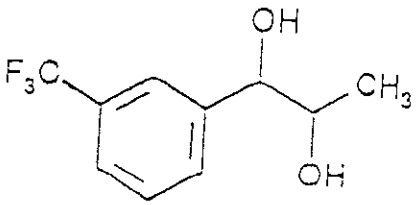


pas de biotransformation

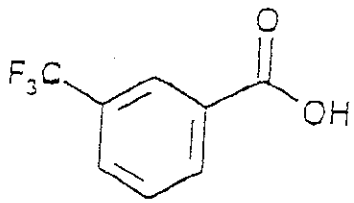
7.4



ND



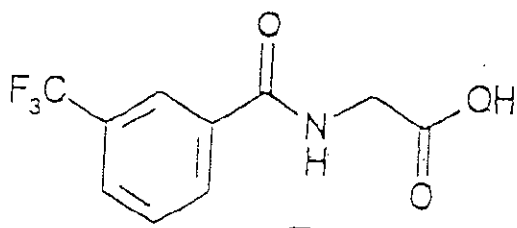
ND



ND

gluc. conj.

50.7



8.4

FIG 4

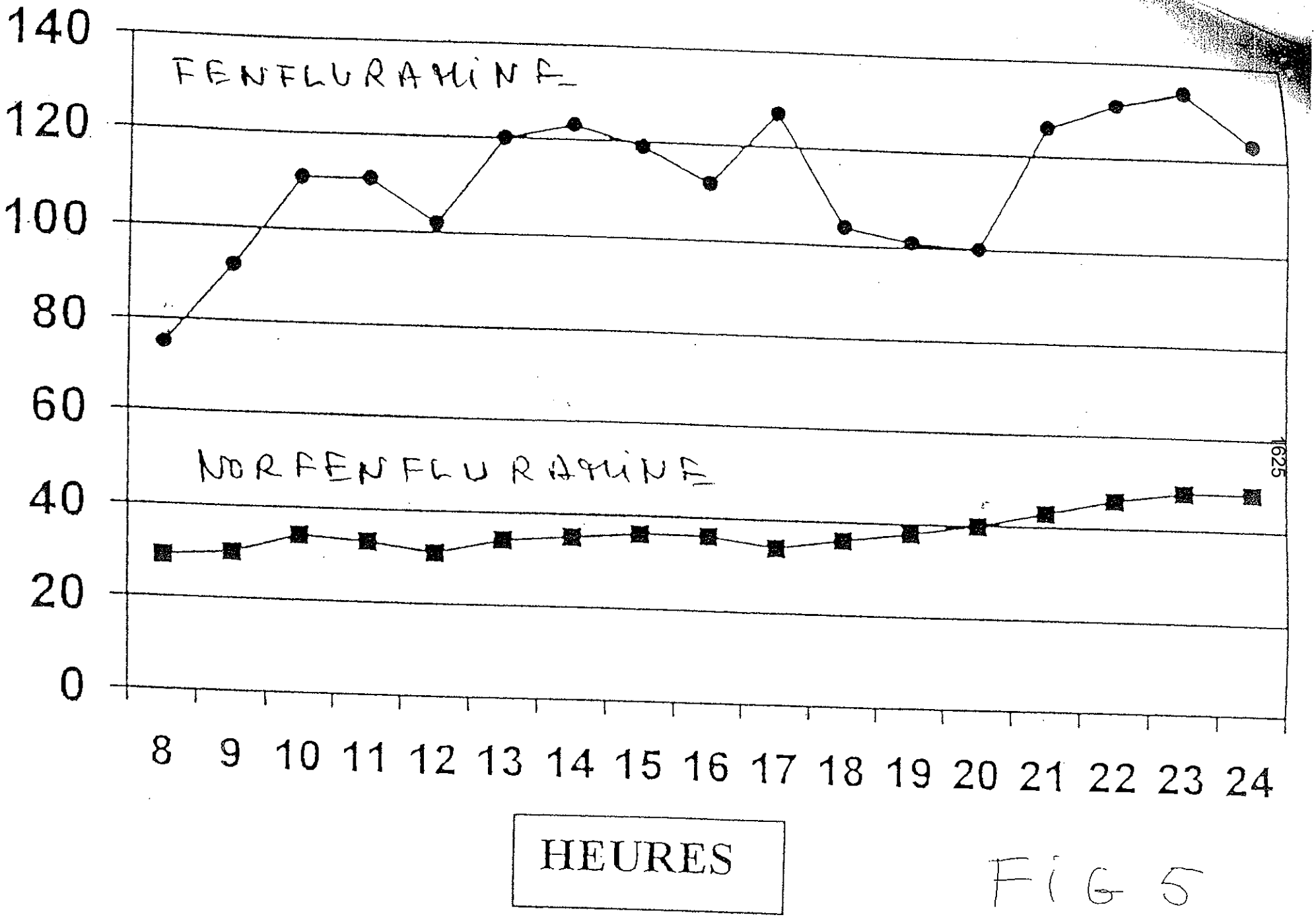
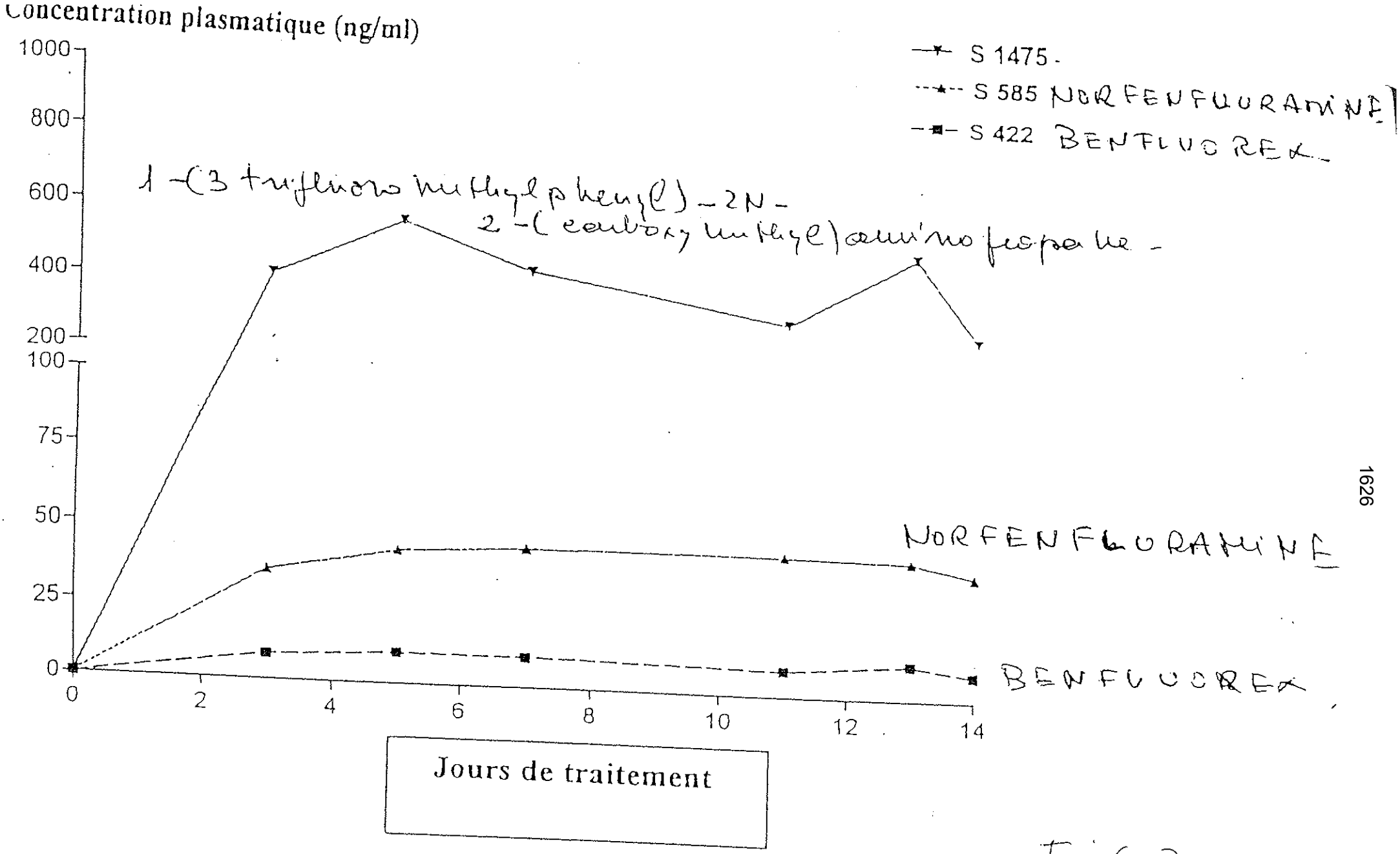

140
120
100
80
60
40
20
0
FENFLURAMINE
NORFENFLURAMINE
1625
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
HEURES

FIG 5


Concentration plasmatique (ng/ml)
1000
800
600
400
200
100
75
50
25
0
0
2
4
6
8
10
12
14
S 1475.
S 585 NORFENFLURAMINE
S 422 BENFLUOREX
1-(3 trifluoromethylphenyl)-2N-
2-(carboxymethyl)aminopropane
NORFENFLURAMINE
BENFLUOREX
Jours de traitement

1626

FIG 3.

MEDIATOR 150 mg et les fenfluramines empruntent des voies métaboliques bien distinctes qui expliquent des activités pharmacologiques radicalement différentes.

MEDIATOR 150 mg est rapidement métabolisé pour donner de nombreux métabolites. Les propriétés antidiabétiques de MEDIATOR 150 mg sont liées à deux métabolites actifs (S 1475 et S 422) qui représentent plus de 93 % de la totalité des composés circulants chez l'homme. Un troisième métabolite, dérivé fenfluraminique, ne représente que 2 % de la dose administrée.

A l'inverse, c'est essentiellement le produit parent la fenfluramine qui est retrouvé dans la circulation. Son métabolite principal, la norfenfluramine, représente 40 % du produit parent. L'activité anti-obésité des fenfluramines résulte essentiellement du profil pharmacologique du produit parent.

Enfin il faut souligner que le benfluorex et ses métabolites ne peuvent pas être biologiquement transformés en fenfluramine ou dexfenfluramine.

Ces différences de métabolisme s'expliquent par une structure chimique fondamentalement différente de MEDIATOR 150 mg et des fenfluramines. MEDIATOR 150 mg est un ester benzoïque d'un dérivé alcool alors que les fenfluramines appartiennent à la famille des alkylamines.

Ces particularités chimiques et métaboliques conduisent :

- à des effets cliniques différents : MEDIATOR 150 mg n' a pas d'effet sur la prise alimentaire ; la perte de poids observée chez des patients diabétiques obèses reste très modérée (de l'ordre de 2 kg pour la totalité du traitement) peut-être liée à l'amélioration de l'insulinosensibilité puisque l'activité antidiabétique est observée dès les premières semaines de traitement en l'absence de diminution pondérale ;

- à une tolérance différente : les effets indésirables les plus souvent rapportés avec MEDIATOR 150 mg sont des vertiges, des nausées et des troubles digestifs, une somnolence, ainsi que des réactions de nature allergique cutanée (rash, urticaire, prurit) ; ces événements sont peu ou pas rapportés avec les fenfluramines.

En conclusion, MEDIATOR 150 mg se distingue radicalement des fenfluramines tant en termes de structure chimique et de voies métaboliques que de profil d'efficacité et de tolérance.

Dominique Kowalski

De: francis.wagniart@fr.netgrs.com
Envoyé: jeudi 5 mars 2009 17:34
À: dominique.kowalski@chu-brest.fr
Objet: RE: Benfluorex (MEDIATOR)

Bonjour,

Je viens de lire la publication parue dans **l'European Respiratory Journal** du mois de Mars 2009 et nous avons pu identifier sans ambiguité les 6 observations:

La 1 (PAH) correspond à notre référence 126V79 (origine CRPV Paris Saint Antoine, Ref PS9900385);

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La 5 (PAH) correspond à notre référence S08005656 (origine CRPV Brest, Ref BR20080383);

La 6 (VHD) correspond à notre référence S08002916 (origine CRPV Brest, Ref BR20080051).

Au total seul le cas n° 2 n'a pas de n° de CRPV et nous ne l'avons pas reçu de l'Afssaps.

Bien cordialement.

Francis Wagniart

De : WAGNIART Francis IRIS
Envoyé : 16 December 2008 17:03
À : 'dominique.kowalski@chu-brest.fr'
Objet : RE: Benfluorex (MEDIATOR)

Bonjour,

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D'autre part, la présence des Prs Simonneau et Humbert parmi les auteurs laisse supposer que tous les cas ne viennent pas de Brest.

Bien cordialement.
Francis Wagniart

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/oyé : 23 October 2008 15:57
. : 'dominique.kowalski@chu-brest.fr'
Objet : Benfluorex (MEDIATOR)

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Merci d'avance. Bien cordialement.

Francis Wagniart

Directeur de la Pharmacovigilance

Institut de Recherches Internationales Servier (I.R.I.S.)

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Fax 01 55 72 65 88

mail francis.wagniart@fr.netgrs.com

Dcv 2

Dominique Kowalski

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1632

Dom-K

Dominique Kowalski

De: francis.wagniart@fr.netgrs.com
Envoyé: jeudi 23 octobre 2008 15:57
À: dominique.kowalski@chu-brest.fr
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Institut de Recherches Internationales Servier (I.R.I.S.)

Tel 01 55 72 70 70
Fax 01 55 72 65 88

email francis.wagniart@fr.netgrs.com

Dominique Kowalski

De: francis.wagniart@fr.netgrs.com
Envoyé: mardi 16 décembre 2008 17:03
À: dominique.kowalski@chu-brest.fr
Objet: RE: Benfluorex (MEDIATOR)

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De : WAGNIART Francis IRIS
Envoyé : 23 October 2008 15:57
À : 'dominique.kowalski@chu-brest.fr'
Objet : Benfluorex (MEDIATOR)

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1634

Dom-E

Dominique Kowalski

De: francis.wagniart@fr.netgrs.com
Envoyé: jeudi 23 octobre 2008 15:57
À: dominique.kowalski@chu-brest.fr
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Petit rappel de notre conversation téléphonique de l'autre jour: le 26 novembre nous recevons le cas BR20080383 communiqué, me dites-vous, par Mme Frachon comme étant l'une des observations de la série.

Il nous restait à identifier seulement 2 cas de PAH: les numéros 2 et 3 de la série (cf précédent mail).

Or on ne peut pas dire que les informations du nouveau cas (BR20080383) coincident vaiment avec ces deux cas manquants de PAH:
- dans l'abstract, seuls les cas 5 (PAH) et 6 (VHD) ont une prise de fenfluramine,
- les ages ne vont pas,
- tous les cas de l'abstract ont un niveau de gravité NYHA III, à mettre en rapport avec une PAP moyenne à 28, relativement modérée (et sous réserve qu'on ne dispose que d'une seule mesure).

D'autre part, la présence des Prs Simonneau et Humbert parmi les auteurs laisse supposer que tous les cas ne viennent pas de Brest.

Bien cordialement.
Francis Wagniart

De : WAGNIART Francis IRIS
Envoyé : 23 October 2008 15:57
À : 'dominique.kowalski@chu-brest.fr'
Objet : Benfluorex (MEDIATOR)

Vous trouverez ci-joint l'abstract de la communication à l'ERS (Berlin, 6 Octobre 2008).

A priori il y a 3 observations identifiables avec une quasi certitude:

La 1 (PAH) correspond à notre référence 126V79 (origine CRPV Paris Saint Antoine, Ref PS9900385);

La 4 (PAH) correspond à notre référence S07001089 (origine CRPV Brest, Ref BR0700050);

La 5 (PAH) correspond à notre référence S07001172 (origine CRPV Brest, Ref BR0700051).

La valvulopathie de Brest BR20080051 pourrait correspondre avec un peu d'imagination mais il y a une différence d'age (date de naissance le 14 Septembre 1956 qui ne va pas avec un age de 62 ans au moment du diagnostic 2007); il y a bien eu de l'Isoméride 20 ans auparavant et 6 ans de Médiator au lieu de 5 dans la publication.

Bien entendu nous sommes intéressés par une confirmation de la correspondance des cas de la publication et les détails des cas que nous n'avons pas.

Merci d'avance. Bien cordialement.

Francis Wagniart

Directeur de la Pharmacovigilance

Institut de Recherches Internationales Servier (I.R.I.S.)

Tel 01 55 72 70 70
Fax 01 55 72 65 88

Doc 2

CRPV BREST

De: francis.wagniart@fr.netgrs.com
Envoyé: jeudi 2 juillet 2009 09:18
À: crpv.brest@chu-brest.fr
Objet: RE: Valvulopathie / exposition benfluorex

Bonjour et merci beaucoup.
Par ailleurs l'Afssaps nous a transmis dans l'après midi les 4 cas suivants de Brest: BR20080051 (que nous avions déjà), BR20090188, BR20090189 et BR20090190.
Nous avons donc nos 18 observations annoncées à la réunion de concertation si nous incluons les 2 hypertensions pulmonaires BR20090140 et BR20090141.

Bien cordialement.

Francis Wagniart

De : CRPVB [mailto:crpv.brest@chu-brest.fr]
Envoyé : 01 July 2009 16:13
À : WAGNIART Francis IRIS
Objet : Valvulopathie / exposition benfluorex

Bonjour,
Voici la méthodologie qui a permis de recenser les cas brestois de « valvulopathie » après exposition au benfluorex :
En 2008, une publication a été faite par plusieurs équipes de pneumologues dont Brest sur les atteintes cardiaques avec le benfluorex.

Depuis, Irène Frachon, pneumologue référent de l'hypertension artérielle pulmonaire sur Brest, a été interrogée plusieurs fois par des cardiologues sur des valvulopathies chez des sujets exposés au benfluorex.

Irène Frachon a décidé de demander au PMSI de lui faire des requêtes (2000-2008) sur les services de cardiologie et de chirurgie cardiaque du CHU de Brest.

1. atteintes valvulaires et diabète comme diagnostic principal ou diagnostic associé significatif (soif ATCD actif ou problème en cours d'hospitalisation)
2. atteintes valvulaires comme diagnostic et benfluorex et mediator comme mots inscrits dans le résumé de sortie

Les codes des atteintes valvulaires correspondent aux codes : I. 05 ; I. 06 ; I 07 ; I. 08 ; I.09 ; I.09 ; I.34 ; I35 ; I.36 ; I.37 ; I38 ; I.39.
La requête la plus intéressante a été la numéro 2 pour laquelle le croisement a ramené 21 patients dont 10 cas qui ont fait l'objet d'une notification de pharmacovigilance comme cas graves.

Actuellement Irène Frachon analyse une autre requête PMSI : sur la même période et dans les mêmes services « cardiologie et chirurgie cardiaque ».
Elle recherche dans les dossiers patients, voire après appel du médecin traitant, l'exposition au benfluorex, Médiator dans 2 populations :

1. les rétrécissements aortiques calcifiés
2. les valvulopathies autres mitrales et aortiques pour lesquelles il n'existe pas d'étiologie franche.

Cordialement
Dominique Carlhant-Kowalski
CRPV de Brest

Doc 2

CRPV BREST

De: francis.wagniart@fr.netgrs.com
Envoyé: jeudi 2 juillet 2009 09:18
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Objet: RE: Valvulopathie / exposition benfluorex

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Nous avons donc nos 18 observations annoncées à la réunion de concertation si nous incluons les 2 hypertensions pulmonaires BR20090140 et BR20090141.

Bien cordialement.

Francis Wagniart

De : CRPVB [mailto:crpv.brest@chu-brest.fr]
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1. les rétrécissements aortiques calcifiés
2. les valvulopathies autres mitrales et aortiques pour lesquelles il n'existe pas d'étiologie franche.

Cordialement
Dominique Carlhant-Kowalski
CRPV de Brest

Annexe 3-43

ADOPTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 13 Février 2001)

Etaient présents

M. RICHE : Président
M. CORNIOU (suppléant de Mme ALBENGRES), Mme POLARD (suppléante de M. ALLAIN), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme JONVILLE BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. CARON, Mme CHICHMANIAN, M. COQUEREL, M. ESCHALIER, Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme JOLLIET, M. KANTELIP, Mme GINISTY (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, Mme LILLO-LELOUET(représentant le CRPV de Paris-POMPIDOU), M. MERLE, M. MONTASTRUC, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant le CRPV de Brest), Mme SGRO, Mme SOUBRIE, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VANDEL, M. VIAL,
Mme TUBERT-BITTER (représentant Monsieur le Directeur de l'INSERM),
Mme LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Mme LEGER (représentant Monsieur le Directeur Général de la Santé),
M. MEYER (représentant Monsieur le Directeur Général de l'Afssaps).

Conseiller scientifique : M. LAGIER.

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme BIDAULT
Mme CHOULIKA
Melle DELEAU
M. DHANANI
Mme GRENET
Mme GOEBEL
M. JACQUET
Mme LEBBE
Mme MESSAN- MURPHY
Mme PIERRON
Melle ROBINE
Mme ROCHER
Mme WEBER

Assistaient à la réunion :

CRPV :

M. BLANGY
M. EFTEKHARI
Mme LAURENT
Mme WELSCH
Mme ZENUT

DEMEB:

Mme CASTOT
Mme DIALLO
M. LECOMTE
Mme MEUNIER
Mme MORER

I - ADOPTION DU PROCES-VERBAL DES SEANCES DU MARDI 19 DECEMBRE 2000 ET DU MARDI 9 JANVIER 2001.

- ADOPTION DU PROCÈS-VERBAL DE LA SÉANCE DU 19 DECEMBRE 2000.

Le procès-verbal de la séance du 19 décembre 2000 a été adopté avec les corrections suivantes :

Annexe 3-43

Page 6 : **Paragraphe II - Tour de table des cas marquants et de la littérature** :

- Thé amaigrissant chinois KANCURA / CRPV de Besançon :
Remplacer « Ce produit avait été acheté sur un site internet. » par « Ce produit avait été acheté dans une boutique à Besançon mais peut être acheté sur internet. »

Page 8 : **Paragraphe III - Point sur les effets indésirables de Ritaline® (méthylphénidate) :**

- ligne 5 : supprimer « THADA »
- ligne 8 : remplacer « Ce médicament est inscrit sur la liste des stupéfiants et nécessite une prescription sur carnet à souches limitée à 28 jours » par « Ce médicament nécessite une prescription sur ordonnance sécurisée avec limitation à 28 jours. »
- 6ème paragraphe, 5ème ligne : remplacer « 22 cas de dépression » par « 22 cas de dépression ou d'état dépressif . »

Page 9 : ligne 12 : remplacer « diarrhées et douleurs abdominales » par « diarrhées et/ou douleurs abdominales. »

Page 12 : **Paragraphe V - Enquête officielle sur les effets indésirables cutanés et hépatiques du kétoprofène gel :**

- 3ème paragraphe, 5ème ligne: remplacer « 75 % des cas surviennent » par « 75 % de l'ensemble des cas survenant ».

- 3ème paragraphe, 8ème ligne : ajouter « Le rôle aggravant de la prise simultanée d'aspirine, d'autres anti-inflammatoires non stéroïdiens ou de fibrates a également été remarqué. ».

- 4ème paragraphe, 1ère ligne : remplacer « 4 cas de rémanence confirmés » par « 4 cas de photosensibilité recidivantes confirmés ».

- 5ème paragraphe, 3ème ligne : ajouter après prescripteurs «Il a proposé l'ajout dans la rubrique « Contre-indications » des phrases suivantes :

- *antécédents d'allergie au kétoprofène ou aux substances d'activité proche tel que l'acide tiaprofénique,*
- *antécédent de réaction cutanée allergique après utilisation d'un produit solaire ou de réaction allergique aux parfums,*
- *antécédent d'allergie à un médicament de la famille des fibrates (fénofibrate, gemfibrozil, bézafibrate...,*

la modification de l'ordre des précautions d'emploi et les ajouts suivants :

- *protéger les zones traitées par le port d'un vêtement durant toute la durée d'application du traitement et les deux semaines qui suivent l'arrêt du traitement,*
- *la prise simultanée d'un autre anti-inflammatoire non stéroïdien, par voie locale ou générale, est déconseillée,*
- *la prise simultanée d'un médicament de la famille des fibrates (fénofibrate, bezafibrate) est déconseillée.*

Page 16 : Paragraphe VI - Enquête officielle sur les effets indésirables de la NANBACINE® :

Remplacer:

NANBACINE® SUSPENSION BUVABLE	
< AVRIL 1997	> AVRIL 1997

Par :

NANBACINE® SUSPENSION BUVABLE	
< MAI 1997	> MAI 1997

Page 22 : Paragraphe IX – Questions diverses :

Allocation chômage / CRPV de Paris Saint-Vincent de Paul : remplacer « Le CRPV de Paris Saint-Vincent de Paul… ne sera pas suffisante » par « Le CRPV de Paris Saint-Vincent de Paul a signalé qu'au moment de la fusion Cochin/ St-Vincent de Paul, la prise en charge de la subvention du CRPV a été faite par des équipes de Cochin : depuis 1999-2000, à la suite de départ de Chefs de clinique et de médecins vacataires, l'hôpital a dû verser des allocations pertes d'emploi. Il a donc été demandé au CRPV de Paris St-Vincent de Paul de bloquer une somme de la subvention du Centre afin de prévoir la possibilité de régler l'allocation chômage des différentes personnes vacataires du Centre. »

- **ADOPTION DU PROCÈS-VERBAL DE LA SÉANCE DU 9 JANVIER 2001.**

Le procès-verbal de la séance du 9 janvier 2001 a été adopté avec les corrections suivantes :

Page 5 : Paragraphe III – Enquête officielle sur les effets indésirables du GEMZAR® :

Point 3, 1ère ligne : remplacer « Manifestations ischémiques artérielles et veineuses. » par « Manifestations ischémiques artérielles et musculaires. »

Page 6 : 2ème paragraphe, 8ème ligne : remplacer « manifestations ischémiques artérielles et veineuses » par « manifestations ischémiques artérielles et musculaires. »

Page 10 : **Paragraphe VI – Point sur les antirétroviraux et grossesse :**

- 1er paragraphe, 3ème ligne : remplacer « mitochondriales avec la zidovudine et la lamivudine.» par « mitochondriales au sein de l'essai ANRS 075, AZT + 3 TC à partir de 32 SA. »

- 2ème paragraphe, 2ème ligne : remplacer « L'EPF, qui a débuté en 86, inclut » par « L'EPF, qui a débuté en 86 (mère et enfant réunis), inclut ».

- 2ème paragraphe, 3ème ligne : remplacer « une analyse rétrospective des dossiers » par « une analyse rétrospective faite par l'EPF des dossiers ».

- 3ème paragraphe, dernière ligne : ajouter « Il n'existe pas actuellement de consensus international. »

- 4ème paragraphe, 4ème ligne : remplacer « sur une base spécifique grossesse » par « sur une base spécifique antirétroviraux et grossesse ».

- 4ème paragraphe, 9ème ligne : remplacer « 1 cas de mitochondriopathie établie… (inclus dans la cohorte) » par « Parmi ces dossiers, on retrouve 2 cas de mitochondriopathie dans la cohorte : 1 cas de mitochondiopathie établie et 1 cas de forte suspicion. »

- 4ème paragraphe, 11ème ligne : remplacer « 55 effets indésirables… nés en 2000. » par « 55 effets indésirables chez des nouveau-nés séronégatifs ont été analysés parmi les 71 bébés nés en 1999. 17 effets indésirables chez des nouveau-nés séronégatifs ont été analysé parmi les 71 bébés nés en 1999. »

Page 12 : **Paragraphe VII – Point sur les anticancéreux et grossesse :**

- 2ème paragraphe, dernière ligne : ajouter « Rappel sur les risques lors d'une exposition intra-utérine :
  - risque malformatif morphogenèse, exposition au 1er trimestre définition restrictive
  - risque fœtal et néonatal direct et indirect
  - risque retardé

- 3ème paragraphe, dernière ligne : remplacer « le risque fonctionnel » par « le risque fœtal et néonatal ».

- 4ème paragraphe, 4ème ligne : remplacer « des cas rapportés isolés…anthracyclines) . » par « des cas rapportés isolés d'atteintes hématologiques (atteintes isolées ou non des 3 lignées, aplasie), digestives, infectieuses, cardiaques (cardiomyopathies avec les anthracyclines). »

- 4ème paragraphe, 10ème ligne : ajouter « Certaines pathologies n'ont pas été publiés chez le nouveau-né exposé in utero, mais nécessitent la surveillance étant donné les informations des données adultes (ex : Holoxan® et rein, Asparginase et hémostase…) »

- 5ème paragraphe, 4ème ligne : remplacer « Il est donc recommandé de préconiser…progressive de l'alimentation » par « Il est donc recommandé de préconiser dans ces cas :

- une surveillance anténatale intensive avec des échographies fœtales répétées pour surveiller la croissance fœtale,
- des échographies cardiaques fœtales en cas d'exposition aux anthracyclines,
- en cas de menace d'accouchement prématuré, pratiquer une prévention de la maladie des membranes hyalines par l'administration de bétaméthasone,
- prévoir une naissance à distance de la dernière cure (minimum 3 à 4 semaines variable selon l'hématotoxicité des anticancéreux),
- pratiquer une surveillance clinique et biologique adaptée du nouveau-né (NFS, bilan infectieux, échographie cardiaque si exposition à risque) et la mise en route progressive de l'alimentation. »

Page 13 : -2ème paragraphe, 7ème ligne : remplacer « dans des pathologies « bénignes » » par « dans des pathologies non cancéreuses ».

Annexe 3-43

II - VACCINS CONTRE L'HEPATITE B : MISE A JOUR DES DONNEES DE PHARMACOVIGILANCE DEPUIS LA COMMERCIALISATION JUSQU'AU 31 DECEMBRE 2000.

Les centres régionaux de Pharmacovigilance chargés de l'enquête officielle sur les effets indésirables au cours d'une vaccination contre l'hépatite B ont présenté le suivi de l'enquête relative aux :

-Affections démyélinisantes centrales et périphériques pour le CRPV de Strasbourg,
-Maladies auto-immunes pour les CRPV de Strasbourg et Nancy,
-Atteintes hématologiques pour le CRPV de Brest,
-Atteintes auditives pour le CRPV de Paris-Pompidou.

Ce point fait état des observations rapportées depuis la date de commercialisation des vaccins contre l'hépatite B jusqu'au 31 décembre 2000.

1. ATTEINTES DEMYELINISANTES : 862 cas.

1)Atteintes démyélinisantes centrales

➢769 cas ont été retenus par les centres régionaux de pharmacovigilance. Cependant, toutes les observations n'ont pas encore été validées par les experts neurologues. Il s'agit de 560 cas de scléroses en plaque dont "415 SEP première poussée" et de 209 atteintes démyélinisantes du système nerveux central qui se répartissent en :

- ✓41 atteintes médullaires et/ou encéphaliques (dont 28 myélites, 6 encéphalomyélites, 6 encéphalites et 1 méningo-myélo-radiculonévrite),
- ✓ 59 cas d'atteintes ophtalmologiques (dont 47 névrites optiques rétrobulbaires, 10 papillites et 2 diplopies),
- ✓ 109 cas de symptômes divers (paresthésie, hémiparésie, dysesthésie,...).

Ces cas sont survenus chez 558 femmes (72,6 %) et 211 hommes. L'âge des patients varie de 2 à 66 ans. Le délai de survenue est inférieur ou égal à 2 mois dans 45,4 % des cas.

➢ Quarante-cinq (45) observations concernent des enfants de 15 ans ou moins. Il s'agit de 19 cas de sclérose en plaques dont 18 SEP "première poussée" et 26 atteintes démyélinisantes du système nerveux central qui se répartissent en :

- ✓ 9 cas d'atteinte médullaire ou encéphalique (dont 4 myélites, 2 encéphalomyélites et 3 encéphalites),
- ✓ 12 cas d'atteinte ophtalmologique (dont 6 névrites optiques rétrobulbaires, 5 papillites et 1 diplopie),
- ✓ 5 cas de symptômes divers (paresthésie, hémiparésie, dysesthésie,...).

Ces cas sont survenus chez 28 filles et 17 garçons. L'âge des patients varie de 2 à 15 ans. Le délai de survenue est inférieur ou égal à 2 mois dans 44,5 % des cas. Aucun cas n'a été rapporté chez les enfants 2 ans ou moins.

2)Atteintes démyélinisantes périphériques

➢93 cas ont été retenus par les centres régionaux de pharmacovigilance. Cependant, toutes les observations n'ont pas encore été validées par les experts neurologues. Il s'agit de 43 cas de syndrome de Guillain-Barré, 37 cas de syndrome de Parsonage-Turner, 8 cas de polyradiculonévrite chronique et 5 cas de neuropathie. Ces cas sont survenus chez 31

femmes et 62 hommes. L'âge des patients varie de 2 à 68 ans. Le délai de survenue est inférieur ou égal à 2 mois dans 78,5 % des cas. Quinze (15) observations ont été rapportés chez des enfants de 15 ans ou moins.

2. MALADIES AUTO-IMMUNES

L'ANALYSE A PORTE PLUS PARTICULIEREMENT SUR LES PATHOLOGIES SUIVANTES :

- **68 cas de maladie lupique** : Ces cas sont survenus chez 59 femmes et 9 hommes. L'âge moyen est de 28 ans (6 à 56 ans). Des antécédents familiaux de maladie auto-immune sont retrouvés dans 9 cas. Des antécédents personnels de lupus sont retrouvés dans 9 cas. Des antécédents personnels de maladie auto-immune sont retrouvés dans 4 cas. Le délai moyen de survenue est de 165 jours (1 jour à 4 ans). Douze observations ont été non retenues.

- **74 cas de polyarthrite rhumatoïde (PR)** : Ces cas sont survenus chez 50 femmes et 24 hommes dont 3 chez des enfants de 15 ans ou moins (2, 13 et 15 ans). L'âge moyen est de 39 ans (2 à 62 ans). Des antécédents familiaux de PR sont retrouvés dans 6 cas. Des antécédents personnels de PR sont retrouvés dans 5 cas. Des antécédents personnels de maladie auto-immune sont retrouvés dans 5 cas. Le délai moyen de survenue est d'environ 137 jours (1 jour à 5 ans).

- **32 cas de thyroïdites** : Ces cas sont survenus chez 30 femmes et 2 hommes d'âge moyen 36 ans (11 à 59 ans). Des antécédents familiaux de maladie auto-immune sont retrouvés dans 7 cas. Des antécédents personnels de disthyroïdie sont retrouvés dans 2 cas. Le délai moyen de survenue est de 221 jours (1 jour à 4 ans).

- **10 cas de polymyosite (PM) et dermatomyosite (DM)** : Ces cas sont survenus chez 9 femmes d'âge moyen 15 ans (2 à 48 ans). Des antécédents familiaux de maladie auto-immune sont retrouvés dans 1 seul cas. Le délai moyen de survenue est de127 jours (2 jours à 25 mois).

- **48 cas de diabète de type 1** : Pour les 20 cas supplémentaires rapportés en 1999 (11) et 2000 (9), il s'agit de 7 femmes et 13 hommes âgés de 12 à 55 ans. 4 dossiers concernent des enfants âgés de 15 ans ou moins (12, 13 et 14 ans). Des antécédents familiaux de diabète sont retrouvés dans 4 cas.

Plus d'une soixantaine d'observations concernent des enfants de 15 ans ou moins. Un cas d'évolution fatale chez un enfant âgé de 2 ans a été rapporté en 2000. Il s'agit d'une dermatomyosite Il n'y a aucune donnée dans la littérature concernant la survenue de ce type d'effet indésirable après administration d'un vaccin. Certains auteurs ont rapporté des taux de mortalité atteignant 25 % au cours de la dermatomyosite infantile. Le rapport de l'expert clinicien conclut à l'absence de lien entre la vaccination et la survenue de la dermatomyosite.

3. ATTEINTES HEMATOLOGIQUES

L'ANALYSE A PORTE PLUS PARTICULIEREMENT SUR LES PATHOLOGIES SUIVANTES :

- **14 cas d'APLASIE MEDULLAIRE DE TYPE IDIOPATHIQUE.** Sept cas chez l'enfant âgé de moins de 15 ans (3 filles et 4 garçons) et 3 décès chez 3 enfants (2 en post-greffe et 1 sans motif détaillé) ont été signalés. Le délai de survenue varie de 15 jours à 3 mois.

- **74 cas de THROMBOPENIE** dont 9 purpuras thrombopéniques auto-immuns (PTAI), 34 purpuras thrombopéniques idiopathiques (PTI) et 31 "autres thrombocytopénies".

Annexe 3-43

Parmi les PTAI, il a été dénombré 7 observations de thrombopénies sévères (< 30 G/L) avec signes hémorragiques associés présents dans 4 dossiers. 7 cas chez l'enfant de 15 ans ou moins (6 filles et 1 garçon) ont été signalés. Le délai de survenue varie de 27 jours à 1,5 ans. Pour les PTI, 22 cas chez l'enfant de 15 ans ou moins (12 filles et 10 garçons) ont été signalés. Le délai de survenue varie de 2 jours à 11 mois.
Enfin, parmi les "autres thrombocytopénies", 11 cas chez l'enfant de 15 ans ou moins ont été signalés. Le délai de survenue varie de 1 jour à 1,5 ans.

Huit (8) observations de thrombopénie ont été expertisées et retenus chez l'enfant de 2 ans ou moins. Il s'agit de 6 PTI et 2 autres thrombocytopénies.

4. ATTEINTES AUDITIVES

57 observations d'atteintes auditives ont été rapportées. Il s'agit notamment de 16 cas d'acouphène ou bourdonnements d'oreille, 31 cas de surdité, hypoacousie ou aggravation d'une surdité préexistante, 1 cas d'hyperacousie et 9 cas d'atteinte vestibulaire (dont 6 cas de vertiges et 3 cas de syndrome vestibulaire).

10 observations concernent des enfants de 15 ans ou moins. Chez le nourrisson, aucun cas d'atteinte auditive n'a été rapporté à la date d'aujourd'hui.

CONCLUSION

Ce bilan qui a porté, plus particulièrement, sur les atteintes démyélinisantes et les maladies auto-immunes, n'apporte pas de nouvelles données qui permettraient de remettre en cause le dernier bilan présenté à la Commission Nationale de Pharmacovigilance du 22 mars 2000.

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III - POINT SUR LES EFFETS GASTRO-INTESTINAUX DES INHIBITEURS DE LA CYCLO-OXYGENASE DE TYPE 2 : VIOXX® (ROFECOXIB) ET CELEBREX® (CELECOXIB), PROCEDURES DE RECONNAISSANCE MUTUELLE (UK, SE)/ CRPV DE CLERMONT-FERRAND .

Le Centre régional de pharmacovigilance de Clermont-Ferrand a présenté un point sur les effets gastro-intestinaux de VIOXX® (rofécoxib) commercialisé en France depuis avril 2000 par les laboratoires MSD et de CELEBREX® (célécoxib) commercialisé en France depuis novembre 2000 par les laboratoires Searle et Pfizer.
Ce point avait été décidé à la suite du rapport d'observations graves d'effets indésirables gastro-intestinaux par plusieurs centres régionaux de pharmacovigilance lors de précédents Comités techniques.

VIOXX® et CELEBREX® sont des médicaments anti-inflammatoires non stéroïdiens (AINS), inhibiteurs sélectifs de la cyclo-oxygénase-2 (COX-2). Ils bénéficient d'une autorisation de mise sur le marché européenne et sont enregistrés selon une procédure centralisée, France destinataire.
Ils sont tous les 2 indiqués dans le « soulagement des symptômes dans le traitement de l'arthrose ».
CELEBREX® est également indiqué dans le « soulagement des symptômes dans le traitement de la polyarthrite rhumatoïde ».

• Données internationales

791 cas d'effets indésirables gastro-intestinaux (dont 459 cas d'hémorragie digestive et 20 décès) ont été rapportés chez des patients (âge moyen : 70 ans) traités par VIOXX® pendant la période couverte par les 3 premiers rapports périodiques de pharmacovigilance.
290 cas (dont 274 cas d'hémorragie digestive et 4 décès) ont été rapportés pour CELEBREX® pendant une période équivalente, pour un nombre de patients traités plus important.
Dans la majorité des cas, les patients avaient des facteurs de risque (antécédents d'ulcère, de perforation, de saignement, traitements associés)
Le rapporteur s'est étonné du faible nombre d'observations concernant CELEBREX® (sous-notification ?)

• Données nationales

Aucun cas de décès n'a été rapporté en France à ce jour chez des patients traités par VIOXX® ou CELEBREX®.
Un total de 27 observations (ou 33 effets indésirables), dont 18 graves, ont été colligés avec ces 2 médicaments (18 observations concernent VIOXX® et 9 CELEBREX®). Il s'agit de 12 ulcères gastro-duodénaux, 18 hémorragies digestives et 3 perforations rapportés chez des patients d'âge moyen de 75 ans. Dans 18 cas sur 27, les patients avaient des facteurs de risque et la posologie était respectée dans presque tous les cas (25/27).
Le rapporteur a souligné la faiblesse du nombre d'observations françaises liée à la mise sur le marché récente de ces médicaments.

Au vu des données, le profil de ces effets indésirables de VIOXX® et CELEBREX® est identique à celui des autres AINS. Au vu des données disponibles depuis la commercialisation, ces médicaments semblent présenter un risque légèrement moindre de complications gastro-intestinales par rapport aux autres AINS ; cependant, ce bénéfice apparaît faible et disparaît lorsque ces médicaments sont associés à l'aspirine.
Les facteurs de risque étant les mêmes que ceux observés avec les autres AINS, le rapporteur a proposé que les RCP soient harmonisés.
Le rapporteur a également proposé que soit rajouté dans la rubrique « interactions médicamenteuses » le risque d'associer VIOXX® ou CELEBREX® à un autre AINS et que le risque d'associer VIOXX® à un médicament de la même famille que la warfarine soit mentionné dans cette rubrique, à l'image de ce qui est indiqué pour CELEBREX®.

Le Comité technique suit l'avis du rapporteur. Cependant, il souhaite également que les atteintes hépatiques, les pancréatites, les atteintes cutanés et les accidents thrombo-emboliques fassent l'objet d'un point supplémentaire lors d'un prochain Comité technique.
La rubrique « grossesse et allaitement » devra également être revue à cette occasion étant données les disparités existant entre les RCP de VIOXX® et de CELEBREX® (ce dernier étant contre-indiqué pendant toute la grossesse contrairement au premier).

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IV – ENQUETE OFFICIELLE SUR LES EFFETS INDESIRABLES HEMATOLOGIQUES ET CARDIAQUES DU NORSET® (MIRTAZAPINE). PROCEDURE NATIONALE/ CRPV DE NICE.

Le CRPV de Nice a présenté les résultats de l'enquête officielle de pharmacovigilance portant sur les effets cardiologiques et hématologiques du Norset®.
Norset® (mirtazapine) est un antidépresseur de structure tétracyclique, commercialisé depuis le 1er Septembre 1999 par les laboratoires Riom-Cerm (désormais Azko Nobel), appartenant à la classe des pipérazinozépines. Le principe actif, la mirtazapine, est un dérivé 6-aza de la miansérine.
L'enquête couvre la période du 1/9/99 au 1/12/00.

RISQUE HEMATOLOGIQUE

Essais cliniques internationaux de phases II et III (2796 patients)
2 cas d'agranulocytoses et 1 cas de neutropénie sévère ont été enregistrés, avec un délai de survenue inférieur à 15 jours, tous d'évolution favorable. Le taux d'incidence a été estimé à 1/1000 mais l'échantillon était petit (2796 patients) et l'intervalle de confiance grand (3 cas/1000 à 2,2 cas pour 10000).

Notification spontanée (France)
7 notifications (1 neutropénie sévère, 4 neutropénies, 1 aggravation d'une leucopénie associée à une thrombopénie, 1 leucopénie) ont été rapportées entre le 1/9/99 et le 1/12/00. Le délai de survenue moyen était de 58 jours et l'évolution favorable dans 6 cas.
Pour une durée moyenne de prescription de 30 jours et une posologie quotidienne moyenne de 1,7 comprimé, le nombre de patients traités en médecine de ville, la 1ère année de commercialisation (entre le 1/9/99 et le 1/12/00), est de 155 000 patients dont 77 000 avec une 1ère prescription.

DONNEES INTERNATIONALES (DU 1/9/1997 AU 1/9/2000)

Pays	*Vente de mirtazapine (en 10^3 traitements)*	*Nb d'agranulocytose + Aplasie médullaire*	*Taux de notifications(en 10^6 traitements)*
Finlande	**106,76**	**2**	**18,77**
Allemagne	**660,76**	**2**	**3,03**
GB	**258,61**	**4**	**15,47**
Pays-Bas	**310,48**	**1**	**3,22**
Suède	**162,87**	**1**	**6,14**
USA	**2535,06**	**6**	**2,37**
Total	**5261,24**	**16**	**3,04**

Un traitement est défini comme une prise de 30 mg/jour de mirtazapine pendant 3 mois.
Une discordance a été mise en évidence entre l'incidence de survenue d'agranulocytose et de neutropénie sévère lors des essais cliniques et celle de la notification spontanée.
Il a été estimé que le petit nombre de patients traités en France (155 000) au cours de la 1 ère année de commercialisation ne permettait pas de conclure sur le risque hématologique. Les membres du Comité technique

de Pharmacovigilance ont souhaité que la firme fournisse le pourcentage d'anciens et nouveaux traitements pour les données internationales, en particulier celle de la Finlande et du Royaume-Uni.
L'information actuelle du RCP sur le risque hématologique a été jugé suffisante. L'avis de la prochaine Commission Nationale de Pharmacovigilance sera sollicité.

EFFETS CARDIOLOGIQUES
L'évaluation concerne les troubles du rythme : bradycardie, tachycardie, fibrillation auriculaire, arythmie et anomalies de l'ECG (allongement du QT, bloc de branche et onde Q) ainsi que l'insuffisance cardiaque, l'infarctus du myocarde et l'angor.

Essais cliniques internationaux de phases II et III
L'incidence des anomalies de l'ECG des 1221 patients ayant eu un enregistrement électrocardiographique est similaire dans le groupe traité (3,2%) et le groupe placebo (3,3%) sans autre précision. L'incidence des cas d'angor, infarctus du myocarde et bradycardie varie de 1/100 à 1/1000 patients. 1 cas de décès brutal d'un patient de 76 ans, probablement lié à un infarctus massif ou à des troubles du rythme à J7 d'un traitement par Norset®, a été notifié au cours d'une étude prospective multicentrique.

Notification spontanée (France)
Essais cliniques : un décès brutal chez un patient de 76 ans dans un contexte d'infarctus du myocarde ou de troubles du rythme à J7 d'un traitement par 30 mg de mirtazapine ».
3 cas de bradycardie (délai de survenue connu dans 1 cas (5j), évolution inconnue dans tous les cas) et 2 cas d'arythmies (délai de survenue J3 et J22, évolution favorable dans tous les cas) ont été enregistrés.

Données internationales
Essais cliniques (1600 patients)
1 cas de dyspnée avec bloc de branche, cardiomégalie et augmentation de poids chez un patient de 41 ans a été notifié. L'évolution a été favorable. L'imputabilité est plausible.

Notification spontanée
6 cas de bradycardie, parfois sévères, de délai de survenue inférieur à 2 jours dans 5 cas et d'évolution favorable dans 4 cas ont été enregistrés.
Ont été également notifiés : 9 cas de tachycardie d'évolution favorable dans 6 cas (imputabilité vraisemblable 1 fois avec rechallenge positif), 6 cas d'arythmies dont 2 décès, 4 cas de fibrillation auriculaire (imputabilité plausible 3 fois, évolution favorable dans tous les cas), 4 cas d'allongement de QT (imputabilité douteuse 2 fois et non déterminée 2 fois, évolution favorable 2 fois, inconnue 2 fois), 5 cas d'insuffisance cardiaque dont 2 décès, 7 cas d'infarctus du myocarde dont 6 décès, 3 cas d'angor dont 2 décès, 1 arrêt cardiaque après 8 jours de traitement, d'évolution favorable et d'imputabilité plausible.
Le RCP ne mentionne pas la survenue d'effets indésirables cardiaques. Le rapporteur propose l'ajout de "bradycardie ou tachycardie" à la rubrique "Effets indésirables".
Ce dossier sera présenté à la Commission Nationale du 13 mars 2001.

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V – POINT SUR LE REFERENTIEL.

M. MEYER, adjoint au directeur chargé des Affaires Médicales, a présenté un point sur le référentiel : ce point fait suite à une demande des CRPV relative à la possibilité de mise à disposition des informations sur le médicament (RCP, liste des spécialités…). M. MEYER a présenté Mme DIALLO, pharmacien, qui anime un groupe de 5 pharmaciens travaillant sur le référentiel. Celui-ci regroupera l'ensemble des RCP des différentes spécialités disposant d'une AMM. Les RCP sont rédigés au sein de l'Afssaps puis une édition papier (contenant les annexes I, II, III) est envoyée aux laboratoires pharmaceutiques concernés, à la Direction des Laboratoires et des Contrôles de l'Afssaps ainsi qu'à différentes bases de données dont le Dictionnaire Vidal. Cette copie papier du RCP est archivée à l'Afssaps mais également entrée dans la base de données interne à l'Afssaps, la base CODEX (anciennement base LIBRA) : celle-ci contient les données administratives de chaque spécialité pharmaceutique. Les RCP sont archivés sous forme de fichiers électroniques dans la base MOCATOR pour les RCP récents (depuis octobre 98). Les RCP plus anciens ont été scannés par une société extérieure, JOUVE, qui est interrogeable en interne grâce à une interface. Certains dossiers n'ont pas été scannés et ont été rangés dans un fichier « vrac » (dossiers « oubliés »).

L'interrogation au niveau interne de l'Afssaps se déroule donc comme suit :

- Interrogation de la base CODEX pour avoir le numéro de dossier puis :
  - ✓ Interrogation de la base MOCATOR pour les dossiers les plus récents
  - ✓ Interrogation de la base JOUVE pour les dossiers les plus anciens
  - ✓ Interrogation du fichier « vrac » pour les dossiers « oubliés »

L'idéal serait d'accéder directement à l'information mais tout ceci n'est pas encore réalisable. De plus, pour chaque AMM modifiée, le RCP n'est pas réédité en entier donc l'accès à ces informations par le public n'est pas encore prévu.

Dans le projet de financement de la Sécurité Sociale, il est prévu « d'ici janvier 2003, que l'Afssaps mette à disposition du public une base dont les modalités d'accès seront fixées par décret ».
Il reste encore plusieurs points à régler (un numéro de dossier unique, état de commercialisation, coordination européenne pour un langage informatique compatible…) mais les choses avancent.
Les membres du Comité technique souhaiteraient disposer de l'historique des compositions et de la mention des excipients.
Mme JOLLIET, Présidente de la Commission de Publicité, a rappelé qu'une charte avait été signée entre le Directeur Général de l'Afssaps et le SNIP à propos de l'information disponible sur le site internet des laboratoires pharmaceutiques concernant leurs spécialités : cette information pose de nombreux problèmes car ce n'est pas de la publicité donc elle ne répond pas à la réglementation relative à la publicité des spécialités pharmaceutiques. De plus, cette information provient souvent de la notice mais elle n'est pas complète et il n'existe encore aucune obligation de mise à jour des informations sur internet. Le référentiel permettrait sans doute régler ce problème.

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VI - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Seuls sont signalés les cas d'effets indésirables donnant lieu à des mesures (mise en enquête, notes...) ou faisant l'objet d'une mise au point. La liste complète des cas est jointe en annexe 1.

- **RIFADINE® (rifampicine) / CRPV de Strasbourg :**

Survenue d'un choc anaphylactique avec un oedème de Quincke chez une femme de 75 ans moins de 5 minutes après la perfusion de RIFADINE® pour un problème ostéo-articulaire. La patiente a été intubée pendant 24 heures et l'évolution a été favorable à l'arrêt du traitement. La rubrique « Effets indésirables » du RCP mentionne « des réactions cutanées modérées et peu étendues pouvant apparaître et ne semblant pas être des réactions d'hypersensibilité [...]. Des réactions d'hypersensibilité cutanées plus sérieuses peuvent apparaître mais ne sont pas fréquentes ».

⇨Une lettre sera adressée aux laboratoires afin qu'ils déposent une demande de modification de l'information.

- **Interférons alfa / CRPV de Marseille :**

Le CRPV de Marseille a signalé que les effets psychiatriques des interférons alfa étaient mal connus des psychiatres et peu pris en compte par les hépatologues. Le Centre souhaiterait que l'information soit renforcée et diffusée auprès des prescripteurs.

⇨ Le CRPV de Montpellier est chargé de l'enquête officielle sur les effets indésirables psychiatriques des interférons alfa.

- **COZAAR® (losartan) / CRPV de Dijon :**

Le CRPV de Dijon a signalé la survenue d'un malformation pulmonaire suivi d'un décès d'un enfant de 4 jour. La mère avait été traitée par COZAAR® pendant la grossesse. Cette mention ne figure pas dans le RCP.

Un cas similaire est survenu à Reims et un autre a été publié dans la littérature.

⇨ Une Note sera transmise au groupe grossesse afin d'ajouter eet effet indésirable dans le RCP.

- **AINS et grossesse / CRPV de Marseille :**

Le CRPV de Marseille a signalé qu'il y avait beaucoup de questions sur le risque des AINS en fin de grossesse. Il semblerait que le message ne soit toujours pas passé et qu'il faudrait peut être faire une information plus large incluant également le grand public

⇨Une réflexion sera envisagée avec le CRPV de Paris Saint-Vincent de Paul.

- **Préparations magistrales à base de metformine / CRPV de Caen et de Tours :**

La Présidente du Conseil Régional de l'Ordre des Pharmaciens de Basse Normandie a attiré l'attention sur des préparations magistrales à base de metformine, d'hormone thyroïdiennes et de MEDIATOR® (benfluorex).

Le CRPV de Tours a ajouté qu'il y avait beaucoup de préparations magistrales amaigrissantes à base de metformine et que la Pharmacie Centrale des Hôpitaux la délivrait en vrac.

⇨Une note sera adressée aux Affaires Réglementaires afin de leur signalé ce mésusage.

- **PRO-DAFALGAN® (propacétamol) / CRPV de Limoges :**

Survenue d'une hyperthermie une heure après une injection de PRO-DAFALGAN® par voie intra-veineuse rapide chez un homme de 62 ans. Le PRO-DAFALGAN® a été dilué dans 5 ml de sérum physiologique (au lieu de 100 ml). Au niveau de la rubrique « Modalités d'administration » il est mentionné que le produit doit être reconstitué dans une poche de 100 ml de sérum glucosé à 5 % ou de sérum physiologique à 9 ‰ et à administrer en perfusion de 15 minutes. Mais la présentation ne fournie pas cette poche de 100 ml.

⇨Une note sera adressée aux Affaires Réglementaires afin de modifier la présentation du produit.

- **LOVENOX® (énoxaparine) / CRPV de Rennes :**

Survenue de deux cas de thrombocytose chez un homme de 67 ans et un autre de 58 ans après administration de LOVENOX® 40 mg. L'évolution a été favorable dans les deux cas et les myélogrammes étaient normaux.

Cet effet indésirable ne figure pas à la rubrique « Effets indésirables » du RCP.

⇨ Le CRPV de Toulouse était chargé de l'enquête officielle sur les HBPM et parmi les effets indésirables figuraient les hémorragies et les thrombocytoses. Il a été précisé qu'une réflexion, dans le cadre du Comité de la

iatrogénie, avait débuté sur les héparines de bas poids moléculaires (HBPM). Le compte-rendu du Comité de la iatrogénie sera transmis aux CRPV afin de poursuivre la réflexion.

- ZERIT® (stavudine), VIDEX® (didanosine) et acidose lactique / CRPV de Paris Saint-Vincent de Paul :
Survenue d'une acidose lactique à 35 semaines d'aménorrhée chez une femme traitée par Zérit®, Videx® et Sustiva® (éfavirenz).
L'équipe de réanimation chirurgicale n'avait pas reçu la lettre d'information, envoyée aux CISIH et aux CRPV, à propos du risque d'acidose lactique avec l'association ZERIT® / SUSTIVA®.
➪Ce problème est en cours au niveau de l'Europe. Il avait été demandé aux CISIH de diffuser la lettre d'information.

- DHEA (déhydroépiandrostérone) / CRPV de Paris-F. WIDAL :
Le CRPV de Paris-F. WIDAL a signalé qu'il recevait des questions fréquentes à propos de la tolérance de la DHEA.
Ce produit n'a pas d'autorisation de mise sur le marché mais des essais cliniques et une réflexion à propos de ce produit sont en cours.
➪Une information sur le protocole d'essais clinique sera présentée lors d'un prochain Comité technique.

- Usage criminel des benzodiazépines / CRPV de Paris-F. WIDAL :
Le CRPV de F. WIDAL a parlé du dossier relatif à l'usage criminel de benzodiazépines. Cette information est parue dans la presse et une enquête sous la direction du CRPV de F. WIDAL est en cours. Le Centre fera très rapidement un rapport complet sur le sujet . Les observations colligées concernent les 3 réseaux CRPV, Centres antipoison (CAP) et Centres d'évaluation et d'information des pharmacodépendances CEIP). 149 dossiers ont été récupérés dont 146 sont parisiens : le CRPV de F. WIDAL souhaiterait récupérer les cas provenant de la province.

- Modification du tour de table :
Le Président de la Commission nationale de pharmacovigilance souhaite modifier le fonctionnement du tour de table des cas marquants : les cas marquants seront, dorénavant, transmis avant le Comité technique à Virginie BACQUET(unité de pharmacovigilance). Les observations seront ensuite distribuées aux évaluateurs concernés.

- EPITOMAX® (topiramate) / CRPV de Lyon :
Tentatives de suicide et suicide survenus chez un homme de 32 ans, sans antécédents psychiatriques, et traité par EPITOMAX® depuis 3 mois.
➪Cinq cas de suicide figure dans le dernier rapport périodique de pharmacovigilance dont 3 suicides violents survenus chez des patients sans antécédents.
L'unité de pharmacovigilance a demandé au laboratoire de fournir un bilan de tous les cas de suicide déclarés au niveau international.

- ARAVA® (léflunomide) / CRPV de Dijon :
Survenue d'une hypertension maligne chez un homme de 56 ans traité par ARAVA®. Cette hypertension a persisté pendant 3 semaines malgré l'administration de 3 comprimés par jour de LOXEN® (nicardipine).
➪Le CRPV de Dijon est chargé de faire un point sur les effets indésirables d'ARAVA®.
➪Le CRPV de Nice sera chargé de réaliser un point sur les effets indésirables du REMICADE®.

- DI-ANTALVIC® (dextropropoxyphène + paracétamol) / CRPV de Paris Saint-Antoine :
Le CRPV de Paris Saint-Antoine a signalé un cas de périnée en lambeaux chez une patiente traitée par DI-ANTALVIC® en suppositoire. Le Président du groupe hépato-gastrologie demande si la pharmacovigilance pouvait intervenir sur ce sujet.
➪L'unité de pharmacovigilance demandera à l'unité pharmaco-toxico-clinique si le bénéfice de cette forme galénique est toujours supérieur au risque.

- TAVANIC® (lévofloxacine) / CRPV de Saint-Etienne :
Survenue d'une rupture bilatérale du tendon d'Achille et d'une tendinite chez une femme de 67 ans et une autre de 66 ans traitées par TAVANIC®. Cinq autres cas similaires figurent dans la banque nationale de pharmacovigilance et un cas d'allongement de l'espace QT.

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⇨Le CRPV de Saint-Etienne est chargé de l'enquête officielle sur les effets indésirables du TAVANIC®.

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VII - POINT SUR LES EFFETS INDESIRABLES DE LA FLAMMAZINE® (SULFADIAZINE ARGENTIQUE)
PROCEDURE NATIONALE/ CRPV DE NANCY.

Le centre régional de pharmacovigilance de Nancy a présenté un point sur les effets indésirables de la Flammazine®. Ce point fait suite à la présentation par le CRPV de Nancy lors du Comité Technique du 12/09/2000 d'un cas de leuconeutropénie sévères chez un enfant traité par Flammazine® crème pour des brûlures au 2ème et 3ème degré sur 20 % de la surface corporelle.
40 cas d'effets indésirables ont été notifiés dans la base nationale de pharmacovigilance, 5 cas n'ont pas été analysés (imputabilité insuffisante). On dénombre :
- 27 effets cutanés dont 19 eczémas de contact, 2 réactions de photosensibilité, 2 toxidermies, 1 vascularite cutanée, 1 hypertrichose, 2 purpuras
- 3 cas d'argyrie dont 2 avec effets neurologiques (1 encéphalopathie, 1 convulsion)
- 2 effets rénaux : 2 syndromes néphrotiques impurs
- 3 effets hématologiques : 3 leuconeutropénies sévères (une patiente présente simultanément un syndrome néphrotique)
- 1 atteinte hépatique

Il s'agit de 21 femmes, d'âge moyen 46,5 ans et de 14 hommes d'âge moyen 52,5 ans.
L'évolution était favorable sans séquelle dans 24 cas sur 35. Le suivi était incomplet ou inexistant pour 10 patients et un patient est décédé d'une pathologie sans relation avec le traitement.

1. leucopénies :
Parmi les 3 cas, un seul s'est compliqué d'un syndrome infectieux, d'évolution favorable. Dans les 3 cas le myélogramme montre un aspect de blocage de la maturation médullaire. La récupération est spontanée dans 2 cas sur 3 à l'arrêt du traitement.
La revue de la littérature montre que les leucopénies surviennent généralement avant le cinquième jour chez 3 à 68% des patients traités. L'évolution est toujours favorable, avec ou sans interruption du traitement, en 3 à 5 jours, sans complication infectieuse imputable.

2. atteintes rénales :
Le diéthylène glycol présent dans certaines formulations de sulfadiazine argentique a été incriminé dans la survenue de plusieurs cas d'insuffisances rénales aiguës oligoanuriques avec évolution mortelle.

3. atteintes cutanées :
Elles représentent l'effet indésirable le plus souvent rapporté. La plupart des eczémas de contact sont dus au propylèneglycol contenu dans la préparation. Sa responsabilité a été démontrée par des tests cutanés de même que celle d'autres adjuvants : l'alcool cétylique et l'argent.

4. argyrie :
Si l'accumulation d'argent dans les tissus reste le plus souvent asymptomatique, elle peut entraîner des effets neurologiques graves même pour de faibles surfaces traitées. L'existence d'une insuffisance rénale associée majore ce risque.

En conclusion, le RCP devrait faire mention de la survenue de leucopénies en des termes tels que « ont été rapportés » et non « de rares cas » ; leur apparition se produisant dans les 5 premiers jours, il semble nécessaire de surveiller quotidiennement la numération de formule sanguine (NFS) pendant cette période. Enfin, l'accumulation d'argent dans les tissus devrait être signalée plus clairement et recherchée chez tout patient présentant des complications neurologiques ; le RCP doit attirer l'attention sur les risques dus aux doses cumulatives dans les traitements prolongés.
Le Comité Technique a souhaité l'ouverture d'une enquête officielle afin d'obtenir plus d'informations concernant les chiffres de vente, les données internationales et l'utilisation du produit.

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VIII - ENQUETE OFFICIELLE EFFETS INDESIRABLES DE L'ALMITRINE (DUXIL®, VECTARION®). PROCEDURE NATIONALE/ CRPV DE STRASBOURG.

Le centre régional de pharmacovigilance (CRPV) de Strasbourg a présenté les résultats de l'enquête officielle de pharmacovigilance portant sur les cas de neuropathies périphériques et/ou amaigrissement rapportés avec l'almitrine (Vectarion®, Duxil®).
Cette enquête fait suite à un courrier de particulier rapportant une neuropathie lors d'un traitement par Duxil®.

Actuellement, l'almitrine est commercialisée en France sous deux spécialités, chacune sous deux formes (Vectarion® comprimés 50 mg et injectable, Duxil® comprimé 30 mg et solution buvable).
Les indications de ces 2 spécialités sont :

Duxil® comprimé et suspension buvable :

- *traitement à visée symptomatique du déficit pathologique cognitif et neuro-sensoriel chronique du sujet âgé (à l'exclusion de la maladie d'Alzheimer et d'autres démences),*
- *traitement d'appoint des baisses d'acuité et troubles du champ visuel présumés d'origine vasculaire,*
- *traitement d'appoint des baisses d'acuité auditive et de certains syndromes vertigineux et/ou acouphènes présumés d'origine vasculaire.*

Vectarion® injectable :

- *hypoxémie et hypercapnie de l'hypoventilation alvéolaire,*
- *épisodes de décompensation respiratoire aiguë compliquant les bronchopneumopathies obstructives, sevrage de l'assistance respiratoire artificielle,*
- *dépression respiratoire musculaire induite par les analgésiques centraux, les neuroleptiques, le fluothane.*

Vectarion® comprimé :

Insuffisance respiratoire avec hypoxémie en rapport avec une bronchite chronique obstructive.

En 1985, une première présentation des données de l'enquête concernant Duxil® et Vectarion® révélait que 151 observations de neuropathie périphérique et/ou amaigrissement avaient été rapportées avec l'une ou l'autre des spécialités. Ces éléments avaient conduit à des modifications du RCP de Duxil® et Vectarion®.
Une nouvelle présentation fut effectuée en 1990 et révéla que la fréquence des neuropathies et/ou amaigrissements diminuait nettement, apparemment plus que les chiffres de vente, aussi bien pour Duxil® que pour Vectarion®.

La présente enquête couvre la période du 1er janvier 1990 au 31 décembre 1999 et regroupe toutes les observations de neuropathie et/ou amaigrissement notifiées aux CRPV et/ou aux laboratoires concernés.
Pour Duxil® comprimé et suspension buvable, 344 observations ont été colligées : 276 concernent des atteintes neurologiques périphériques dont 89 associées à une perte de poids et 68 concernent une perte de poids isolée.
Pour Vectarion® comprimé et injectable, 140 observations ont été colligées : 125 concernent des atteintes neurologiques périphériques dont 38 associées à une perte de poids et 15 concernent une perte de poids isolée. Parmi ces observations, seul 1 cas implique la voie injectable.
Les caractéristiques des observations sont résumées dans le tableau suivant :

	DUXIL®		VECTARION®	
	Atteintes neurologiques périphériques avec ou sans perte de poids	Perte de poids isolée	Atteintes neurologiques périphériques avec ou sans perte de poids	Perte de poids isolée
Nombre d'observations	276 (98 CRPV, 178 labo.)	68 (16 CRPV, 52 labo.)	125 (60 CRPV, 65 labo.)	15 (7 CRPV, 8 labo.)

EIs rapportés	73 paresthésies 36 anomalies neurologiques 167 neuropathies confirmées	perte de poids	37 paresthésies 19 anomalies neurologiques* 69 neuropathies confirmées	perte de poids
Age moyen (extrêmes)	70 ans (37-93 ans)	73 ans (37-92 ans)	67 ans (42-90 ans)	67 ans (46-91 ans)
Posologie moyenne (extrêmes)	62 mg/jour (30-120 mg/jour)	60 mg/jour (30-120 mg/jour)	94 mg/jour (50-150 mg/jour)	92 mg/jour (50-100 mg/jour)
Durée moyenne du traitement (extrêmes)	1 063 jours (2,9 an) (4-7 305 jours)	702 jours (1,9 an) (20-3 318 jours)	598 jours (1,6 an) (4-5 813 jours)	329 jours (7-911 jours)
Délai moyen de survenue (extrêmes)	860 jours (2,4 an) (4-7 305 jours)	648 jours (1,8 an) (20-3 287 jours)	574 jours (1,6 an) (3-4 579 jours)	282 jours (7-911 jours)
Avec perte de poids	89	-	38	-
Perte de poids moyenne (extrêmes)	7 kg (2-33 kg)	7 kg (2-17 kg)	10 kg (2-40 kg)	10 kg (3-25 kg)
Evolution	46 guérisons sans séquelle 184 non encore rétablis 44 non précisés 2 décès (non reliés)	23 guérisons sans séquelle 29 non encore rétablis 15 non précisés 1 décès (non relié)	14 guérisons sans séquelle 77 non encore rétablis 30 non précisés 4 décès (non reliés)	5 guérisons sans séquelle 8 non encore rétablis 2 non précisés

*définies par des signes objectifs : diminution de la sensibilité superficielle et/ou profonde, diminution ou abolition des réflexes ostéotendineux

En ce qui concerne les atteintes neurologiques, les observations graves sont moins fréquentes sous Vectarion® (18%) que sous Duxil® (23%). Par ailleurs, la posologie quotidienne recommandée est inférieure pour Duxil® par rapport à Vectarion® alors que la durée moyenne de traitement et le délai moyen de survenue sont plus courts pour Vectarion®.
Ces différences confortent la dose-dépendance habituelle des neuropathies médicamenteuses ainsi qu'une durée-dépendance évoquant la possibilité d'un effet cumulatif.
Ces différences pourraient aussi être expliquées par un effet additif du vieillissement ou des pathologies concomitantes telles que polyneuropathies au cours de l'insuffisance respiratoire chronique ou chez les personnes âgées.

CONCLUSION
La neuropathie à l'almitrine est une neuropathie axonale, tout comme la plupart des neuropathies médicamenteuses. Cette neurotoxicité est dose-dépendante ; il n'y a pas d'élément en faveur d'un facteur immuno-allergique. Lorqu'un diagnostic précoce permet l'arrêt du traitement, la neuropathie guérit sans séquelle.

Duxil® : l'efficacité de cette spécialité a été étudiée lors d'essais sur de petits nombres de patients et pendant des durées brèves ne permettant pas de saisir la neurotoxicité. Dans ces conditions, et malgré sa relative rareté, mais compte tenu de la gravité potentielle d'une neuropathie axonale, notamment lorsque le diagnostic n'est pas effectué précocément, une réévaluation du bénéfice du traitement semble devoir être envisagée.

Vectarion® comprimé: l'almitrine est une molécule originale qui ne peut être comparée à aucun médicament existant dans l'insuffisance respiratoire avec hypoxémie en rapport avec une bronchite chronique obstructive. La démonstration de l'efficacité du Vectarion® sur la morbidité chez les patients insuffisants respiratoires est faite.
La neuropathie périphérique est un effet indésirable rare du Vectarion®. Il est proposé qu'une nouvelle sensibilisation des prescripteurs et qu'une reformulation du RCP insistant notamment sur la nécessité impérative

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d'arrêter le traitement devant toute perte de poids inexpliquée (et non seulement lorsqu'elle est supérieure à 5%) et/ou devant l'existence de paresthésies des membres inférieurs soient effectuées.

Les résultats de cette enquête seront examinés par la Commission Nationale de pharmacovigilance du 13 mars 2001.

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IX - PHARMACOVIGILANCE EUROPEENNE.

Stylos à Insuline et risque de contamination croisée :

Le CRPV de Saint-Etienne avait signalé un problème relatif aux cartouches d'insuline utilisées dans les stylos injecteurs à usage multiple. Ces cartouches sont utilisées dans les services cliniques pour différents patients, en changeant à chaque fois l'aiguille du stylo, mais il n'existe pas de système anti-reflux ce qui pose un problème de remontée de matière biologique avec un risque potentiel de contamination lors de l'échange de celle-ci entre les différents patients. Ce problème a été évoqué au Groupe de travail européen qui a proposé d'inclure dans le RCP des stylos à insuline une information relative au risque de contamination en cas d'utilisation de ces stylos par plusieurs patients différents.

DIPRIVAN® (propofol) et rhabdomyolyse / insuffisance cardiaque :

Un article du Lancet a montré des cas de rhabdomyolyse et d'insuffisance cardiaque, avec possibilité de décès, chez des patients à qui on avait administré du DIPRIVAN® en perfusion avec une posologie supérieure à 4 mg/kg/h pendant 48 heures. Il est rappelé que la posologie du DIPRIVAN® est inférieure à 4 mg/kg/h en France. Une enquête officielle a été ouverte dont le responsable est le CRPV de Paris Saint-Antoine.

ZIAGEN® (abacavir) et syndrome d'hypersensibilité :

L'abacavir a fait l'objet de 3 mesures de restriction urgente dont la dernière relative au problème de réadministration chez des sujets sensibilisés, remonte au mois d'août 2000. Depuis cette mise en garde, il y a eu un cas grave supplémentaire en France dont l'évolution a été favorable. Ce patient présentait 2 symptômes décrits dans la mise en garde mais son infectiologue lui a dit de reprendre le ZIAGEN®. Le CRPV de Bordeaux a signalé que les infectiologues ne réintroduisaient plus le ZIAGEN® chez les patients ayant déjà fait un syndrome d'hypersensibilité.

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X - QUESTION DIVERSES.

1) Questions administratives

- **PRODILANTIN® (fosphénytoïne)** : Une mesure de restriction urgente avait été instaurée en mars 2000 pour modifier l'information sur le conditionnement afin d'éviter les surdosages. Cette mesure avait été accompagnée d'un rappel de lot (en mai 2000 et en septembre 2000). Un cas de surdosage avec une ancienne forme de PRODILANTIN® est survenu chez un enfant de 4 ans. Les parents ont porté plainte contre l'hôpital en raison de la gravité de l'effet et des séquelles neurologiques. Le Département Accident a diligenté une enquête auprès de la DRASS.

-ATRIUM® (fébarbamate, difébarbamate et phénobarbital) : la Commission d'AMM a réévalué le rapport bénéfice / risque de l'ATRIUM® en raison de la survenue d'atteintes hépatiques et cutanées parfois graves. Celui-ci s'est avéré être défavorable. Deux fax ont été envoyés à l'ensemble des CRPV pour leur notifier la suspension d'AMM de l'ATRIUM® à partir du 14 mars 2001.

- **DROLEPTAN® (dropéridol) :** en raison de troubles cardiaques graves, le rapport bénéfice / risque de la spécialité DROLEPTAN® a été réévalué et s'est avéré être négatif. Les laboratoires JANSSEN-CILAG ont décidé d'arrêter la commercialisation de leur produit à partir du 1er avril 2001. Cet arrêt de commercialisation s'accompagnera d'un retrait de lot de toutes les formes de DROLEPTAN® disponibles.

- **Phénobarbital :** en raison d'effets cutanés graves (syndromes de Lyell et de Stevens-Johnson) le bénéfice / risque des spécialités contenant du phénobarbital (hors indication anti-épileptique) a été réévalué par la Commission d'AMM et s'est avéré négatif. Une Commission mixte (AMM et pharmacovigilance) s'est réunie le 8 février 2001 et a décidé une inscription sur liste I de ces spécialités contenant du phénobarbital ainsi que la suspension de leur AMM à partir du 9 avril avec retrait des lots restant sur le marché. Un communiqué de presse sera très prochainement disponible sur le site de l'Afssaps (http://afssaps.sante.fr).

- **Ateliers de pharmacovigilance de la Baule :**
Plusieurs CRPV ont signalé que la prise en charge de l'hôtel lors de la prochaine réunion des ateliers de la Baule ne sera pas possible. Cette question sera soulevée lors de la prochaine réunion de l'association des Centres le 6 mars 2001.

2) Nouvelles enquêtes officieuses et officielles de pharmacovigilance :

- Enquête officielle sur les interférons alfa et effets indésirables psychiatriques / CRPV de Montpellier
- Enquête officielle sur le TAVANIC® et effets indésirables / CRPV de Saint-Etienne
- Point sur les effets indésirables rapportés avec ARAVA® (léflunomide) / CRPV de Dijon
- Point sur les effets indésirables rapportés avec REMICADE® (infliximab) / CRPV de Nice.

3) Documents distribués :

- Tableau de conclusion du WPPh des 31 et 1er février 2001
- RCP de VISYDINE® (vertéporfine)
- Tableau des DMI en cours
- Tableau VIH–PHARMACOVIGILANCE
- RCP de KALETRA® (lopinavir + ritonavir)
- Notes au Directeur Général de l'Afssaps sur le PRODILANTIN® (fosphénytoïne)

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RÉPUBLIQUE FRANÇAISE

1

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE
Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 15 Mai 2001)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), Mme GRAS-CHAMPEL (suppléante de M. ANDREJAK), Mme JONVILLE BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), M. COQUEREL, M. ESCHALIER, M. MIREMONT-SALAME (suppléante de Mme HARAMBURU), Mme WELSCH (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), Mme LAROCHE (suppléante de M. KANTELIP), Mme THOMAS (représentant le CRPV de F. Widal), Mme LAINE-CESSAC, Mme LE BELLER (représentant le CRPV de Paris-POMPIDOU), M. MALLARET, M. MERLE, M. BLANGY (suppléant de M. NETTER), M. OLLAGNIER, Mme BROCH (représentant le CRPV de Brest), Mme SGRO, Mme LEBRUN-VIGNES (suppléante de Mme SOUBRIE), Mme BURTIN (suppléante de M. THUILLEZ), M. TRENQUE, Mme PERAULT (suppléante de M. VANDEL)
Mme LEGER (représentant Monsieur le Directeur Général de la Santé), excusé
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé).

Conseiller scientifique : M. LAGIER.

Assistaient à la réunion :

Unité de pharmacovigilance :

Mme KREFT-JAIS
Melle BACQUET
Mme CHOULIKA
Melle DELEAU
Mme FOSSET-MARTINETTI
Mme GRENE
M. JACQUET
Mme JOUSSELIN-PAUTROT
Melle JULLIAN
M. LAHAIE
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Mme PIERRON
Melle ROBINE
Mme SCHLOSSER
Mme SOUCHET

CRPV :

Mme CARDONA
Mme MOACHON

III - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Seuls sont signalés les cas d'effets indésirables donnant lieu à des mesures (mise en enquête, notes...) ou faisant l'objet d'une mise au point. La liste complète des cas est jointe en annexe 1.

- **Interaction médicamenteuse NORVIR® (ritonavir) / SINTROM® (acénocoumarol) / CRPV de Paris-Pompidou :**

Survenue d'une interaction médicamenteuse entre NORVIR® et SINTROM® aboutissant à une diminution de l'effet thérapeutique ~~du NORVIR® et une augmentation de l'effet~~ anticoagulant. Deux cas similaires figurent dans la banque nationale de pharmacovigilance et 3 autres cas dans la littérature.
→Une note sera adressée au groupe interaction médicamenteuse.

- **DONORMYL® (sulprostone) / CRPV de Paris-Pompidou :**

Survenue d'une rhabdomyolyse avec malaise et somnolence à la suite d'un surdosage en DONORMYL® chez une jeune fille de 14 ans.
→Un point sera demandé aux CAP (Centres antipoison) et à la DGS (Direction Générale de la Santé).

EXOLYSE® (thé vert) / CRPV de Caen :

Survenue d'une hépatite subfulminante nécessitant une transplantation hépatique chez une femme de 49 ans traitée par EXOLYSE®, SERMION® (nicergoline), TRIVASTAL® (piribédil) et SOLUPRED®. Un produit « pour bronzer » avait également été pris. Un cas similaire figure dans la banque et un cas au niveau du laboratoire.

MEDIATOR® (benfluorex) et mésusage / CRPV de Caen :

La présidente du Conseil de l'Ordre des pharmaciens de Basse Normandie a de nouveau attiré l'attention sur certaines ordonnances à visée amaigrissante associée à la prescription de MEDIATOR®.

NEXEN® (nimésulide) / CRPV de Lyon :

Survenue d'une hépatite fulminante nécessitant une transplantation hépatique en urgence chez un patient de 51 ans traité par NEXEN®. Le patient n'est pas encore rétabli.
→Cet effet figure déjà dans le RCP du NEXEN®.

Immunostimulants / CRPV d'Amiens :

Survenue d'une acrosyndactylie des mains et des pieds chez un nouveau-né à la naissance. Le diagnostic a été posé dès la 22ème semaine d'aménorrhée. Les seuls médicaments pris pendant la grossesse étaient IMOCUR® (fraction d'origine bactérienne), IRS 19® (lysats bactériens en suspension) et AUDISPRAY®.
→Une note sera envoyée à l'évaluateur en charge de cette classe thérapeutique.

LIPIOCIS® (huile d'oeillette)/ LIPIODOL® (huile d'oeillette) / CRPV de Rennes :

Survenue d'une pneumopathie avec détresse respiratoire chez 3 patients traités par LIPIOCIS® et LIPIODOL®. Deux cas ont été fatals, le 3ème patient n'est pas encore rétabli.
La moitié des patients sous par LIPIOCIS® sont traités à Rennes.
→Le CRPV de Rennes est chargé de l'enquête officielle sur les effets indésirables de LIPIOCIS® et LIPIODOL®.

Tisane Ernst RICHTER / CRPV de Paris Saint-Antoine :

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ADOPTE

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Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du mardi 7 Décembre 2004)

Etaient présents :
M. CARON : président
M. ANDREJAK : vice-président
Mme POLARD (suppléante de M. ALLAIN), Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), Mme CHICHMANIAN, Mme DE LA GASTINE (suppléante de M. COQUEREL), Mme ZENUT (suppléante de M. ESCHALIER), M. GILLET, Mme HARAMBURU, Mme JEAN-PASTOR, Mme VEYRAC (suppléante de Mme JOLLIET), Mme LAROCHE-DAVID (suppléante de M. KANTELIP), Mme EFTEKHARI (suppléante de M. CALVO), Mme LAINE-CESSAC, Mme LEBRUN-VIGNES, M. LE LOUET, Mme LE BELLER (suppléant de Mme LILLO-LE LOUET), M. MALLARET, M. MERLE, M. MONTASTRUC, M. OLLAGNIER, Mme PERAULT, Mme CARLHANT-KOWALSKI (suppléante de M. RICHE), Mme SGRO, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VIAL.
Mme DAHAN (représentant Monsieur le Directeur Général de la Santé)

Unité de Pharmacovigilance :
Mme KREFT-JAIS
Mme BIDAULT
Mlle BOUTRON
Mme CARDONA-GIORDANO
Mme CHOULIKA
Mlle DELEAU
M. DHANANI
Mlle FERARD
Mme GOEBEL
Mme GRENE
Mlle HENRY
M. JACQUET

Mme LAHMAR
Mme OUARET
Mlle PAGE
Mme POINSARD.
Mme POROKHOV
Mlle ROBINE
Mme SCHLOSSER
M. VESQUE

Internes :
Melle ANDRIANTAFIKA
Melle FAYE

Stagiaire :
Melle DAUDET

DEMEB :
M. FERNANDEZ
Mme LABOURET
Mme COURNE
Mme DIARTE

CRPV :
Melle SOUYRI

DEMEIS :
Mme DIARTE

Etaient excusés :
Mme WELSCH
M. le Directeur Général de l'INSERM
M. le Directeur de l'Hospitalisation et de l'Organisation des Soins
M. le Président de la Commission Nationale de Pharmacovigilance vétérinaire

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I - ADOPTION DU PROCES-VERBAL DU 12/10/2004

Le procès-verbal de la séance du 12 octobre 2004 a été adopté avec les corrections suivantes :

Page 4 : II – Tour de table des cas marquants et de la littérature

- Ajouter après « 450 mg deux fois par jour de NEORAL » soit « 4 à 9 fois la dose usuelle ».

Page 7 : III – Bilan des données de pharmacovigilance des vaccins contre l'hépatite B au 31/12/2003

- Ligne 29 : supprimer « Enfin, le CRPV de Strasbourg suggère que l'incidence nationale des formes graves d'hépatopathies virales aiguës ou chroniques liées au virus de l'hépatite B fasse l'objet d'un suivi rigoureux durant les 10 années à venir. »

Page 9 : IV – Effets neuro-excitateurs de la morphine par voie générale

- Ligne 60 : remplacer « 3 par voie sous-cutanée, dont 2 représentaient une IR sévère» par « 3 par voie sous-cutanée (dans deux cas avec une dose de 10 mg/jour, dans un autre cas avec une dose non calculable) ».

Page 10 : IV – Effets neuro-excitateurs de la morphine par voie générale

- Ligne 1 : remplacer « 3 par voie intra-veineuse » par « 3 par voie intra-veineuse (dans un cas avec une dose de 500 mg/ jour, dans un cas avec une dose de 16 mg en 30 heures, et dans un dernier cas avec une dose inconnue mais probablement élevée chez un toxicomane) ».
- Ligne 6 : remplacer « Le remplacement, ou la diminution de la posologie de la morphine doivent être envisagés » par « La diminution de la posologie de la morphine ou sa substitution par un autre opiacé doivent être envisagés ».

Page 14 : V –Point sur les hyperkaliémies induites par l'association inhibiteurs de l'enzyme de conversion et spironolactone

- Ligne 13 : ajouter après « les notifications ne sont pas toutes spontanées » la phrase « comme en témoigne la répartition des observations en fonction du CRPV. En effet deux CRPV, Amiens et Angers, totalisent 46% des observations de la période post-RALES. Début 2003, le CRPV d'Angers a recueilli dans le cadre d'une enquête prospective une quarantaine de cas d'hyperkaliémie médicamenteuse. »
- Ligne 23 : remplacer « le taux de prescription de la SPIRO est passée de 34/1000 patients à 149/1000 » par « le taux de prescription de la SPIRO chez des patients hospitalisés sous IEC pour insuffisance cardiaque est passé de 34/1000 patients à 149/1000 ».
- Ligne 24 : remplacer « le taux d'hospitalisation pour hyperkaliémie est passé de 2,4/1000 patients à 11/1000 patients » par « le taux d'hospitalisation pour hyperkaliémie est passé de 2,4/1000 à 11/1000 chez ces mêmes patients ».

Page 15 : V –Point sur les hyperkaliémies induites par l'association inhibiteurs de l'enzyme de conversion et spironolactone

- Ligne 4 : rajouter « et la dose de spironolactone » aprés « essai ».

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Page 21 : VII – Questions diverses

- Ligne 19 : supprimer « significative ».

Page 22 : VII – Questions diverses

- Ligne 18 : remplacer « aucune valvulopathie chez les témoins » par « l'absence de signe de valvulopathie chez les témoins ».

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II - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Sont signalés les cas d'effets indésirables, de mésusages, d'erreurs et de manque de cohérence de l'information ainsi que les risques potentiels d'effets indésirables, pouvant donner lieu à des mesures (mises en enquête, notes...) ou pouvant faire l'objet d'une mise au point, dans le cadre de la prévention du risque médicamenteux.
La liste complète des cas est jointe en annexe 1.

Effets indésirables avérés :

Agénésie de la coupole diaphragmatique et hypoplasie pulmonaire bilatérale chez un nouveau-né de mère traitée par KEPPRA (lévétiracétam) pendant la grossesse/ CRPV de Clermont-Ferrand

Le CRPV de Clermont-Ferrand a signalé un cas d'hypoplasie pulmonaire bilatérale fatale chez un nourrisson né à 35 semaines d'aménorrhée d'une mère traitée par KEPPRA (lévétiracétam) et EPITOMAX (topiramate) pendant la grossesse.
→ Une note sera transmise à la cellule grossesse afin de signaler ce nouveau cas.

Oedèmes des membres inférieurs bilatéraux en présence de différents vaccins / CRPV de Clermont-Ferrand

Le CRPV de Clermont-Ferrand a signalé, à la suite de l'administration de différents vaccins, plusieurs observations d'oedèmes des membres inférieurs bilatéraux, nécessitant pour deux d'entre elles une hospitalisation (9 cas sous PENTACOQ®, 2 cas sous PENTAVAC®, 2 cas sous PREVENAR® associé à PENTAVAC® ou HBVaxPRO®). Le CRPV de Paris-HEGP a également signalé 4 cas sous PENTAVAC®.
→ Une enquête prospective des cas d'oedèmes survenant en présence de vaccins sera effectuée par les CRPV de Clermont-Ferrand, Dijon, Tours avec la collaboration des Centres de Protection Maternelle et Infantile.

TROXERUTINE MAZAL et choc anaphylactique / CRPV de Dijon

Le CRPV de Dijon a signalé un cas de choc anaphylactique sous TROXERUTINE MAZAL® sachet, qui est un générique de VEINAMITOL®.
→ Une note sera transmise au département pharmaceutique afin de connaître les excipients contenus dans la spécialité TROXERUTINE MAZAL® susceptibles d'être à l'origine d'un choc anaphylactique.

DEROXAT (paroxétine) et colite lymphocytaire / CRPV de Lyon

Le CRPV de Lyon a signalé un 10ème cas de colite lymphocytaire sous inhibiteurs sélectifs de la recapture de la sérotonine (DEROXAT®) avec normalisation aprés arrêt du traitement. Des cas de colites lymphocytaire sous paroxétine ont été rapportés dans une étude clinique rétrospective de 199 patients atteints de colites lymphocytaires publiés récemment dans Gut 2004 ; 53:536-541.
→ Une revue des données sur les colites lymphocytaires et les diarrhées chroniques sera demandée aux firmes commercialisant les inhibiteurs sélectifs de la recapture de la sérotonine (citalopram, escitalopram, fluoxétine, fluvoxamine, paroxétine, sertraline).

MIRENA (lévonorgestrel) et alopécie / CRPV Marseille

Le CRPV de Marseille a signalé un cas d'alopécie majeure 5 semaines après la pose de MIRENA (lévonorgestrel) chez une femme de 35 ans. 6 cas de chutes de cheveux ou d' alopécie sont signalés dans la base nationale de pharmacovigilance. Cet effet n'est pas mentionné dans le RCP de ce médicament. Dans la littérature, ce médicament semble entraîner plus d'alopécie que d'autres produits contraceptifs.
→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification d'information pour cette spécialité afin d'ajouter cet effet indésirable.

Intoxication au méthotrexate / CRPV de Marseille

Le CRPV de Marseille a signalé un cas d'intoxication au méthotrexate (20 fois le taux attendu) avec insuffisance rénale aiguë d'apparition retardée à la suite de l'administration de doses recommandées de DANTRIUM (dantrolène) et de méthotrexate à forte posologie. Le CRPV de Montpellier a fait état des nombreux surdosages en méthotrexate associé au développement d'une insuffisance rénale. Le seul antidote efficace est le carboxypeptidase G2, a priori seulement disponible en Allemagne

→ Un point sera effectué par le CRPV de Montpellier sur le sujet et en particulier les modalités du suivi thérapeutique des traitements par méthotrexate.

CHLORAMINOPHENE (chlorambucil) et neuropathie périphérique / CRPV de Marseille

Le CRPV de Marseille a signalé un cas de neuropathie sensitivo-motrice sous CHLORAMINOPHENE (chlorambucil) chez un homme de 48 ans. Cinq autres cas sont signalés dans la base nationale de pharmacovigilance et cet effet n'est pas mentionné dans le RCP de cette spécialité.

→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification d'information pour cette spécialité afin d'ajouter ce type d'effet indésirable.

BRONCHODERMINE et troubles du comportement / CRPV de Marseille

Le CRPV de Marseille a signalé le cas d'un enfant de 20 mois traité par ADVIL, OCTOFENE, BRONCHODERMINE suppositoires, BRONCHOKOD, CELESTENE, hospitalisé pour troubles du comportement pendant 12 heures avec somnolence, aréactivité et regard fixe. La spécialité BRONCHODERMINE (cinéole ou eucalyptol, gaïacol, huile essentielle de pin) contient un dérivé terpénique pouvant être à l'origine de ces effets indésirables. La forme suppositoire n'est pas contre-indiquée chez l'enfant de moins de 30 mois. Seules les formes en application cutanée ou nasale sont contre-indiquées chez l'enfant de moins de 30 mois suite à une décision de la Commission d'AMM en 1996. Le 3 décembre 2004, le baume Vicks BABYBALM, contenant deux dérivés terpéniques avait été retiré du marché et il était envisagé une révision des spécialités contenant des dérivés terpéniques.

→ Ce cas sera signalé au groupe de travail concerné pour suite à donner.

UVESTEROL vitaminé A, D, E, C (vitamines A, D2, E, C) et volume de délivrance inadapté aux nouveaux-nés / CRPV de Montpellier

Le CRPV de Montpellier a signalé trois cas de cyanose dont un avec hospitalisation, chez des nouveaux-nés à la suite de fausses routes lors de la prise d'UVESTEROL (vitamines A, D2, E, C). L'injection trop rapide du volume nécessaire de la pipette (1 ml) aurait entraîné ces fausses routes.

→ Un point sur l'utilisation de l'UVESTEROL vitaminé A, D, E, C (vitamines A, D2, E, C) chez les nouveaux-nés sera effectué par les CRPV de Nantes et de Paris – Saint-Vincent de Paul.

FUZEON (enfuvirtide) et pneumopathies bactériennes / CRPV de Paris – Henri-Mondor

Le CRPV de Paris – Henri-Mondor a signalé deux cas de pneumopathies bactériennes survenues deux à quatre semaines après le début d'un traitement par FUZEON (enfuvirtide) chez une femme de 38 ans et un homme de 41 ans, sans qu'il y ait de mise en garde dans le RCP sur ce risque.

→ L'unité pharmacovigilance vérifiera les données d'essais cliniques sur le risque de survenue d'infections bactériennes précoces.

Mode d'administration des collyres et information dans les notices / CRPV de Paris – Saint-Vincent de Paul

Le CRPV de Paris – Saint-Vincent de Paul a fait état d'un cas étranger de surdosage massif lié à l'utilisation du collyre SKIAKOL (cyclopentolate), avec état de mal et décès survenu chez un enfant de 4 ans. Les notices des collyres précisent mal leurs modalités pratiques d'administration de ces produits.

→ Un point sur l'informativité des notices quant aux modes d'administration des collyres sera réalisée par le CRPV de Paris - Saint-Vincent de Paul.

MEDIATOR (benfluorex) et bouffées délirantes / CRPV Toulouse
Le CRPV de Toulouse a signalé un cas de vision floue et malaise et un cas de bouffée délirante sous MEDIATOR (benfluorex), produit amphétaminique. Cette spécialité fait l'objet d'un large mésusage comme anorexigène.
→ Une mise à jour de l'enquête MEDIATOR sera effectuée par le CRPV de Besançon. Une relance sera effectué auprès de l'Italie sur ce sujet.

Effets indésirables potentiels

PROTOPIC (tacrolimus) et intolérance à l'alcool / CRPV Tours
Le CRPV de Tours a signalé deux cas d'érythèmes de la face sous PROTOPIC (tacrolimus) pommade, après la prise d'une boisson alcoolisée. Cet effet est mentionné en rubriques 4.4 et 4.8 du RCP de PROTOPIC pommade, alors qu'il n'est pas mentionné dans le RCP de PROGRAF gélule (tacrolimus).
→ L'unité de pharmacovigilance demandera l'avis du groupe de travail concerné.

Association MEXITIL® et CORDARONE® / CRPV Tours
A la suite d'une question posée au CRPV de Tours sur le RCP de MEXITIL (méxilétine), il a été observé une anomalie dans la rubrique « interaction médicamenteuse » puisque l'association avec l'amiodarone (CORDARONE®) est citée à deux niveaux : « contre-indiquée » et « nécessitant des précautions d'emploi » ce qui peut induire un risque de confusion.
→ Une note sera adressée à l'unitè interaction médicamenteuse afin de signaler ce risque de confusion.

ZOMETA (acide zolédronique) et ostéonécrose de la mâchoire / CRPV Lille
Le CRPV de Lille a signalé un cas d'osctéonécrose de la mâchoire chez un patient atteint de myélome et traité par ZOMETA. Ce problème, soulevé au niveau européen, a conduit à la modification de la rubrique « effets indésirables » du RCP de ZOMETA et à l'ajout de cet effet indésirable. Par ailleurs, une DMI d'AREDIA (acide pamidronique) devant intégrer cet effet indésirable est en cours de finalisation par le CRPV de Reims.
→ Une information relative aux ostéonécroses des mâchoires pouvant survenir lors de traitement par acide zolédronique ou acide pamidronique sera effectuée auprès des prescripteurs.

Trimétazidine et syndrome extrapyramidal / CRPV Toulouse
Le CRPV de Toulouse a évoqué la publication de 8 cas de syndromes parkinsoniens observés avec la trimétazidine. Une vingtaine d'observations de ce type sont par ailleurs retrouvées dans la base nationale de pharmacovigilance.
→ Un point sur les syndromes parkinsoniens observés sous trimétazidine sera effectué par la CRPV de Toulouse.

MICROPAKINE (acide valproïque) et hyponatrémie / CRPV Reims
Le CRPV de Reims a signalé un cas d'hyponatrémie ayant entraîné une hospitalisation chez une patiente de 77 ans traitée avec MICROPAKINE. Plusieurs observations de ce type avec ce médicament sont retrouvées dans la base nationale de pharmacovigilance et dans la littérature.
→ Une analyse de l'ensemble des cas d'hyponatrémie rapportés avec l'acide valproïque sera demandée à la firme par l'unité de pharmacovigilance.

Documents distribués :

- Lettres aux pharmaciens hospitaliers et neurologues relatives au rappel des conditions de prescriptions d'ELSEP® et de suivi des patients atteints de sclérose en plaque selon l'autorisation de mise sur le marché.

Nouvelles enquêtes officieuses et officielles de pharmacovigilance :
- Une enquête prospective des cas d'oedèmes survenant en présence de vaccins sera effectuée par les CRPV de Clermont-Ferrand, Dijon, Tours avec la collaboration des Centres de Protection Maternelle et Infantile.

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- Un point sera effectué par le CRPV de Montpellier sur le sujet et en particulier les modalités du suivi thérapeutique des traitements par méthotrexate.
- Un point sur l'utilisation de l'UVESTEROL vitaminé A, D, E, C (vitamines A, D2, E, C) chez les nouveaux-nés sera effectué par les CRPV de Rennes et de Paris – Saint-Vincent de Paul.
- Une mise à jour de l'enquête MEDIATOR sera effectuée par le CRPV de Besançon.
- Un point sur l'informativité des notices quant aux modes d'administration des collyres sera réalisée par le CRPV de Paris - Saint-Vincent de Paul.

III - ENQUETE OFFICIELLE RELATIVE AUX EFFETS INDESIRABLES GRAVES OBSERVES AVEC LA DESMOPRESSINE

Le Centre Régional de Pharmacovigilance (CRPV) de Caen a présenté l'enquête officielle relative aux effets indésirables graves observés avec la desmopressine.

Introduction

La desmopressine est un principe actif analogue de la vasopressine naturelle, aussi appelée hormone anti-diurétique (ADH). Cette dernière posséde deux actions principales : une action anti-diurétique et un effet vasopresseur puissant. La structure chimique de la desmopressine différe de celle de l'ADH, ce qui lui confère une demi-vie beaucoup plus longue et une forte diminution de l'effet vasopresseur au profit de l'effet anti-diurétique.

Statut

La desmopressine a obtenu une autorisation de mise sur le marché (AMM) en France le 22 janvier 1980. La spécialité Minirin®, commercialisée depuis 1982, existe sous 3 formes : Minirin® solution injectable 4µg/ml Intraveineuse (IV), Intramusculaire (IM) ou sous-cutanée (SC), Minirin® comprimé 0,1mg et 0,2mg (la forme sublinguale n'est pas encore disponible), Minirin® intranasal soit sous forme de Minirin® 0,1 mg/ml avec tube gradué (Rhinyle®) pour les posologies inférieures à 10 µg, soit Minirin® spray 10 µg/dose pour les posologies supérieures à 10 µg/dose.
Trois voies d'administration sont donc possibles, avec des indications distinctes :
Voie INTRA-NASALE :

- diabète insipide central pitresso-sensible ;
- traitement symptomatique de courte durée (3 mois) de l'énurésie nocturne de l'enfant de plus de 5 ans après élimination d'une pathologie organique sous-jacente ;
- étude du pouvoir de concentration du rein.

Voie ORALE :

- diabète insipide central pitresso-sensible ;
- traitement symptomatique de l'énurésie nocturne de l'enfant de plus de 6 ans après élimination d'une pathologie organique sous-jacente, la durée d'utilisation étant limitée à 6 mois ;
- depuis août 2003, extension des indications au traitement symptomatique de la nycturie chez l'adulte âgé de moins de 65 ans, lorsqu'elle est associée à une polyurie nocturne.

Voie INJECTABLE :

- traitement correcteur et préventif des accidents hémorragiques observés dans l'hémophilie A modérée et atténuée, maladie de Willebrand en dehors des formes sévères ou de type IIB, allongement inexpliqué du temps de saignement en particulier au cours de l'insuffisance rénale chronique ;
- traitement du diabète insipide central pitresso-sensible en particulier quand l'administration intra-nasale est malaisée ou impossible ;
- étude de pouvoir de concentration du rein.

Il existe une autre spécialité Octim® commercialisée en France depuis 1998, présente sous une seule forme à 150 µg/dose pour une administration intra-nasale, indiquée pour la prévention et la correction des accidents hémorragiques (tels que déjà définis ci-dessus).

Objectifs de l'enquête

- caractériser les effets indésirables (EI) les plus fréquents de la desmopressine et déterminer l'imputabilité du médicament ;
- comparer l'incidence des EI graves avec l'indication, l'âge des patients et la posologie ;
- évaluer les mesures préventives susceptibles de minimiser le risque.

Données de vente, données d'exposition

Le laboratoire Ferring titulaire de l'AMM de Minirin® et d'Octim® a transmis les données de vente pour la France et au niveau mondial.
Entre 1995 et 2003, **11,6 millions de patients** ont été traités par desmopressine dans le monde (11 millions par Minirin® et 600 000 par Octim®), ce qui représente 1,29 millions de patients traités par an.

En France, la voie intra-nasale est toujours la plus utilisée, même s'il apparaît que la voie orale prenne de plus en plus d'importance. Ainsi, en 1997, 10,4 fois plus de patients étaient traités par voie nasale que par voie orale, alors qu'en 2002 ce rapport n'est plus que de 1,9.
Au niveau mondial, depuis 2001 (et contrairement aux années 1996-2000), la desmopressine est plus souvent utilisée par voie orale que par voie intra-nasale, avec un rapport de 2,25 pour l'année 2003.

Analyse des cas notifiés en France
Les cas rapportés sont issus de la base nationale de pharmacovigilance et des cas enregistrés par le laboratoire Ferring.

La base nationale de pharmacovigilance contient 118 fiches d'effets indésirables (87 graves) en rapport avec la desmopressine dont 61 en relation avec une intoxication par l'eau. Il existe par ailleurs 29 autres observations en rapport avec une intoxication par l'eau dans la base du laboratoire. Au total 90 observations d'intoxication par l'eau ont été notifiées en France depuis la commercialisation.

- *Observations non liées à une intoxication par l'eau.*

Sur les 118 observations d'effets indésirables, 57 n'avaient pas de rapport avec une intoxication par l'eau. Sur les 57 observations, 29 concernent des effets indésirables graves. Dans 7 cas, l'imputabilité est vraisemblable. Il faut souligner la notification d'un décés par hépatite fulminante sur cirrhose (la desmopressine a une imputabilité douteuse).

- *Observations en rapport avec une intoxication par l'eau.*

Sur les 118 observations, 61 (dont 59 concernent des effets indésirables graves) concernent une intoxication par l'eau. Ces observations sont marquées par la survenue d'une hyponatrémie aiguë, associée ou non, en fonction de la gravité, aux signes cliniques suivants : asthénie, céphalées, nausées, vomissements, rétention hydrique, hypertension artérielle, œdème cérébral, troubles de l'humeur, confusion, coma, convulsions, détresse respiratoire.
L'imputabilité est vraisemblable dans 83,6% des cas.

Par ailleurs, le laboratoire Ferring a enregistré 29 observations françaises d'effets indésirables graves en rapport avec une intoxication par l'eau avec une imputabilité vraisemblable de la desmopressine.

La voie d'administration (connue dans 86/90 cas) se répartit en: **intra-nasale dans 77,9% (**67 cas), intra-veineuse dans 15,1% (13 cas) et orale dans 7% des cas (6 cas).
Les indications se répartissent en : **énurésie 53,3% (48 cas),** diabète insipide 13 cas, anomalies de la coagulation 12 cas, troubles mictionnels 11 cas, hypotension orthostatique 3 cas, test au Minirin® 1 cas, indication inconnue 1 cas.
L'âge des patients se répartit en : 58 cas concernent des enfants entre **0 et 15 ans, soit 64,4%.** Une majorité d'enfants est concernée par la voie d'administration intra-nasale qui représente les trois quarts des notifications, avec 86% de prescriptions dans l'indication énurésie. Pour la voie orale, la majorité des cas d'intoxication par l'eau concerne des adultes de plus de 65 ans (dans 2/3 des cas). En ce qui concerne la voie intra-veineuse, dans 12 cas sur 13, l'indication est en rapport avec un trouble hémorragique et les patients concernés sont des adultes de moins de 65 ans dans 62% des cas et des enfants de 0 à 16 ans dans 38% des cas.
La posologie par kilogramme de poids et par jour a été estimée dans 63 cas. Par voie intra-nasale la posologie moyenne est de **1,33 µg/kg/jour**, par voie intra-veineuse de **0,63 µg/kg/jour** et par voie orale, de **5,33 µg/kg/jour**. Une très grande disparité entre les valeurs extrêmes des posologies pour les formes intra-nasale et intra-veineuse, avec un rapport de 1 à 40 est mise en évidence. Pour la forme orale, il existe un rapport de 7,7 seulement entre les posologies les plus extrêmes.

Analyse des cas cliniques internationaux
Le laboratoire Ferring a reçu 1830 observations d'effets indésirables survenus sous desmopressine, dont 36,8% sont des cas graves (674). Sur ces 674 cas graves, 632 sont associés au Minirin® (dont 371 par voie intra-nasale) et 42 à Octim/Octostim®. Parmi les 1156 effets non graves, 1106 sont associés au Minirin® dont 766 lors d'une administration intra-nasale.

L'analyse des cas a porté sur les observations d'effets indésirables graves en rapport avec une intoxication par l'eau, ce qui représente **315 observations** issues de 25 pays. On observe que :

- dans plus de 2/3 des cas, il s'agit de formes intra-nasales (67,9%) ;
- l'indication la plus souvent retrouvée est l'énurésie (43,2%) ;
- l'âge est inférieur ou égal à 16 ans dans 52,7% des cas (dont 1 sur 3 inférieur à 5 ans), entre 17 et 64 ans dans 23,5%, supérieur à 65 ans dans 15,6%.

Indications	Voies d'administration				
	Intranasale	Intraveineuse	Orale	Inconnue	TOTAL
Enurésie	**127**	0	10	1	**138**
Diabète insipide	49	6	9	2	66
Troubles mictionnels	8	0	20	1	29
Troubles de la coagulation	13	38	0	2	53
Test au Minirin®	11	5	0	1	17
Inconnue	6	0	3	3	12
TOTAL	**214**	41	42	10	**315**

Répartition des observations internationales d'effets indésirables graves relatives à une intoxication par l'eau sous desmopressine, en fonction de l'indication et de la voie d'administration.

Indications	Age					
	< 5 ans	5 – 16 ans	17 – 64 ans	> 65 ans	Inconnu	TOTAL
Enurésie	6	**103**	17	4	8	**138**
Diabète insipide	18	6	25	5	12	66
Troubles mictionnels	0	0	2	27	0	29
Troubles de la coagulation	16	2	21	9	5	53
Test au Minirin®	13	0	3	1	0	17
Inconnue						12
TOTAL	53	**111**	68	46	25	**315**

Répartition des observations internationales d'effets indésirables graves relatives à une intoxication par l'eau sous desmopressine, en fonction de l'indication et de l'âge.

Il est à souligner que l'indication de la desmopressine dans l'**énurésie** est réservée aux enfants de plus de 5 ans, or 4,3% des observations rapportées dans cette indication concernent des enfants de **moins de 5 ans**. Par ailleurs, la restriction d'âge à moins de 65 ans dans l'indication de **nycturie** n'est pas présente dans tous les pays, ce qui peut expliquer que 27/29 cas d'intoxication par l'eau dans cette indication soient décrits chez des patients de **plus de 65 ans.**

Dans l'indication de **diabète insipide**, la répartition en fonction de l'âge des cas d'intoxication par l'eau est de 24 enfants (dont 18 concernent des enfants de moins de 5 ans) et 25 adultes de moins de 65 ans. Cette répartition entre enfants et adultes est beaucoup plus homogène que celle observée dans l'indication énurésie où 109 observations d'effets indésirables graves sur 138 concernent des enfants.

Les cas concernant les **troubles de coagulation** sont assez équilibrés quant à la répartition par âge avec une forte représentation des très jeunes enfants de moins de 5 ans (30% de l'ensemble des cas).

Synthèse et discussion

L'incidence globale des effets indésirables notifiés sous desmopressine est estimée à **1,63 pour 10000 patients traités**. La proportion de notifications d'effets indésirables en rapport avec une **intoxication par l'eau** est importante puisqu'elle représente **51,7% des cas de la base nationale** de pharmacovigilance (**67,8% des effets graves**) et **51% des effets graves rapportés à la firme**.

La forme intra-nasale est le plus souvent en cause et représente 77,9% des cas français et 67,9% des cas internationaux d'intoxication par l'eau. Entre 1997 et 2002 en France, 4 fois plus de patients ont été traités par voie intra-nasale que par voie orale.

L'indication la plus souvent retrouvée dans les cas d'intoxication par l'eau sous desmopressine est **l'énurésie** (53,3% des cas français et 43,2% des cas internationaux).

Les observations d'intoxication par l'eau concernent en majorité des **enfants** de 0 à 16 ans (64,4% des cas français et 52% des cas internationaux).
L'analyse des **posologies** par indication, âge et voie d'administration montre une grande disparité avec des fourchettes de dose extrêmement importantes, ce qui illustre que la posologie n'est pas le seul facteur en cause dans ces observations.

Propositions :

- définir, si cela s'avère possible, des posologies initiales particulières (en µg/kg) :
  - chez le nourrisson pour le traitement du diabète insipide,
  - chez l'enfant de moins de 25 kg pour le traitement de l'énurésie
- insister sur la nécessité en cas d'énurésie de ne pas instaurer de traitements en dessous de 5 ans ;
- insister sur l'information donnée aux patients et à leur famille telle que la restriction hydrique, avec un ordre de grandeur du volume de boissons autorisé, identifier les situations à risque de déséquilibre, savoir reconnaître les éventuels symptômes d'une intoxication à l'eau, et insister sur les associations médicamenteuses à risque ;
- favoriser l'usage de la voie orale par rapport à la voie intra-nasale. Une forme sublinguale (Minirin® melt) permettrait de remplacer la voie intra-nasale.
- insister sur les risques lors d'une utilisation hors AMM ;
- harmoniser les différents RCP. L'ajout d'un tableau d'équivalences posologiques entre les différentes présentations et en particulier entre les formes orales et les formes intra-nasales pourrait être utile.

Le Comité technique estime par ailleurs que la ré-évaluation du rapport bénéfice/risque pourrait se justifier dans l'indication « énurésie ». Une présentation de cette enquête par domaines d'indication est prévue en Commission nationale de pharmacovigilance.

IV - ENQUETE OFFICIELLE : MIRTAZAPINE ET ARTHRALGIES ET MYALGIES, MIANSERINE ET MYALGIES

Le CRPV de Nantes a présenté les résultats de l'enquête officielle concernant d'une part la mirtazapine et les myalgies – arthralgies et d'autre part la miansérine et les myalgies. Cette enquête recense les observations notifiées du 1er septembre 1999 au 31 décembre 2003.

1/ mirtazapine (NORSET®) et myalgies – arthralgies

NORSET® est autorisé en France depuis 1997 et commercialisé depuis le 1er septembre 1999 par les laboratoires Organon. Il est indiqué dans les épisodes dépressifs majeurs.

Données des Centres Régionaux de Pharmacovigilance (CRPV)

221 observations ont été recensées avec la mirtazapine dont 7 cas d'arthralgie, 9 cas de myalgie et 3 cas possédant les deux items, soit 13 notifications correspondant à 16 effets indésirables. Ces observations, le plus souvent non graves, concernent une population à légère prédominance féminine, âgée de 30 à 60 ans. Le délai de survenue est variable (de une heure à un an) et dans 4 cas, la mirtazapine était administrée en monothérapie. Ces effets indésirables sont tous survenus à la posologie recommandée. Aucune utilisation hors autorisation de mise sur le marché (AMM) n'a été relevée.

Il s'agit dans ces observations de polyarthralgies concernant essentiellement les petites articulations (mains, poignets, coudes) et pouvant être associées à des oedèmes (face, membres inférieurs, mains), une prise de poids, une asthénie. Ces effets indésirables ne semblent pas dose-dépendants. L'évolution a été favorable dans la grande majorité des cas à l'arrêt de la mirtazapine. Un cas de réadministration positive a été observé.

A noter que les arthralgies sont déjà signalées dans le Résumé des Caractéristiques du Produit (RCP) de la miansérine qui appartient, comme la mirtazapine, à la classe des pipérazinoazépines.

Données des laboratoires Organon

330 dossiers d'arthralgie - myalgie ont été colligés par le laboratoire sur un total de 6492 cas au niveau mondial. 16 cas, correspondant à 18 effets indésirables ont été rapportés en France. Ces observations sont superposables à celles notifiées aux CRPV.

Données des essais cliniques

Sur une population de 2521 patients, 46 cas d'arthralgie (soit 1,8%) et 51 cas de myalgie (soit 2%) ont été rapportés. Ces cas présentent les mêmes caractéristiques que ceux décrits après la mise sur le marché.

Au total, 29 cas d'arthralgie – myalgie ont été notifiés en France (330 dans le monde) avec la mirtazapine, d'où une fréquence de cas notifiés de l'ordre de $0{,}23.10^{-6}$ (le nombre de traitements vendus en France du 1er septembre 1999 au 31 décembre 2003 étant de 743306). Il est probable que ces effets indésirables fassent l'objet d'une sous-notification, en raison de l'absence de gravité de ces cas, de la chronologie variable et de la sémiologie banale. Cependant, l'information mérite d'apparaître dans le RCP afin d'éviter un traitement symptomatique par AINS.

Le rapporteur a suggéré d'intégrer dans la rubrique 4.8 du RCP de la mirtazapine :
« Dans de rares cas, les effets indésirables suivants ont également été rapportés : arthralgies, myalgies ».

2/ Miansérine (ATHYMIL® et molécules génériques) et myalgies

ATHYMIL® est un antidépresseur commercialisé depuis 1979 par les laboratoires Organon et indiqué dans les épisodes dépressifs majeurs. 14 médicaments génériques ont à ce jour une Autorisation de Mise sur le Marché (AMM) et 11 sont commercialisés.

Données des CRPV

1879 observations ont été recensées avec la miansérine dont 13 cas de myalgie. Ces observations, le plus souvent non graves, concernent une population à prédominance féminine, âgée de 34 à 80 ans. Le délai de survenue est variable (de 3 jours à 2 ans) et dans 2 cas, la miansérine était administrée en monothérapie.

Il s'agit dans ces observations de myalgies associées à d'autres effets indésirables tels que asthénie, anorexie, élévations des transaminases, diarrhées, nausées, vertiges, ou augmentation des CPK.
L'évolution a été favorable dans la grande majorité des cas à l'arrêt de la miansérine. Un cas de réadministration positive a été observé.

Données des laboratoires
13 observations de myalgie rapportés avec ATHYMIL®, présentant les mêmes caractéristiques que celles décrites plus haut, ont été transmis par le laboratoire Organon (sur 649 notifications françaises). 60 cas de myalgie ont été signalés dans le monde.
Un cas supplémentaire australien a été transmis par le laboratoire Merck générique et concerne la spécialité MIANSERINE MERCK®.

Données de la littérature
L'analyse de la littérature a permis de retrouver un article issu du bulletin de pharmacovigilance des autorités de santé australiennes, l'ADRAC (Australian Adverse Drug Reactions Bulletin) de février 1984, recensant 14 cas de douleurs musculaires et articulaires sous miansérine.

Le rapporteur a suggéré d'intégrer dans la rubrique « Effets indésirables » 4.8 du RCP de la miansérine :
« Ont été signalés : de rares cas de myalgies ».

Le Comité technique a suivi l'avis du rapporteur, mais a proposé le terme « arthromyalgies » en remplacement de « arthralgie, myalgie ».
Le dossier sera présenté lors de la Commission nationale de janvier 2005.

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V - POINT SUR LES EFFETS CORONAIRES DES TRIPTANS

Le Centre Régional de Pharmacovigilance de Toulouse a présenté un point sur les effets indésirables coronaires des triptans. Ce point a été demandé par le Comité technique suite à la notification de 2 cas d'infarctus du myocarde chez des sujets jeunes (35 et 36 ans).
Les triptans sont des agonistes des récepteurs sérotoninergiques 5HT1B et 5HT1D, présents sur les artères intracrâniennes mais également sur les artères périphériques, comme les artères coronaires. Ces récepteurs déterminent, quand ils sont activés par un agoniste, un effet vasoconstricteur. Par ailleurs, les triptans inhibent l'extravasation des protéines plasmatiques.

A ce jour, 5 triptans sont commercialisés en France :

- *sumatriptan* (IMIGRANE® : comprimés pelliculés, solution injectable, solution pour pulvérisation nasale et IMIJECT® : solution injectable)
- *zolmitriptan* ZOMIG® (comprimés pelliculés) et sous forme de comprimés orodispersibles sous le nom de ZOMIGORO®
- *naratriptan* NARAMIG® (comprimés pelliculés)
- *almotriptan* ALMOGRAN® (comprimés pelliculés)
- *élétriptan* RELPAX® (comprimés pelliculés)

Ils sont indiqués dans deux indications :

- *« Traitement de la phase céphalalgique de la crise avec ou sans aura ».* La forme injectable est réservée *« au traitement de la crise de migraine sévère lorsque les autres traitements de la crise de migraine n'ont pas été efficaces au cours des crises précédentes ».*
- *« Traitement de la crise d'algie vasculaire de la face »* pour IMIGRANE® solution injectable et IMIJECT® solution injectable.

Analyse de la Base nationale de Pharmacovigilance :
Une interrogation de la Base Nationale de Pharmacovigilance en juin 2004, avec les mots clés « triptans » et « collapsus cardiovasculaire, troubles cardiaques, angine de poitrine, angine de poitrine compliquée, coronaropathie » a révélé 11 observations. Ces observations concernent 7 hommes et 4 femmes (le ratio homme/femme dans la migraine est de 1/3).

Dans 3 cas sur 11, le tableau a été qualifié de « non grave ». il s'agit de :

- 2 cas de précordialgie,
- un trouble visuel conduisant à la découverte de troubles de la repolarisation avec susdécalage du segment ST,

Dans les 8 autres cas, le tableau été qualifié de grave. Il s'agit de :

- un arrêt circulatoire avec fibrillation ventriculaire,
- quatre infarctus
- un angor spastique,
- deux spasmes coronariens.

Des facteurs de risque cardiovasculaire ont étè noté dans 8 cas sur les 11 rapportés.
L'évolution a été favorable dans tous les cas sauf un. Il s'agit d'un cas concernant un homme de 36 ans ayant présenté un arrêt circulatoire avec fibrillation ventriculaire. L'évolution s'est faite vers un coma et une encéphalopathie post-anoxique avec décès ultérieur.

Concernant les triptans imputés, il s'agissait :

- dans 5 cas, du *zolmitriptan* comprimés,
- dans 3 cas, du *naratriptan*,
- dans 2 cas, du *sumatriptan* injectable (IMIJECT°)
- dans 1 cas de la prise successive à 1 heure d'intervalle de zolmitriptan puis de spray de *sumatriptan*.

L'imputabilité a été jugée :

- douteuse (I1) dans 7 cas,
- plausible (I2) dans 1 cas,
- vraisemblable (I3) dans 2 cas,
- très vraisemblable (I4) dans 1 cas.

Dans un cas, a été notée l'association a de l'oxymétazoline (ATURGYL®) aux propriétés alpha stimulantes pouvant potentialiser les effets coronaroconstricteurs des triptans.
Dans 5 cas (45,5 %), une notion de mésusage a été retrouvée. Il s'agit dans 2 cas, d'interaction médicamenteuse et dans 3 cas, de non respect des posologies recommandées.

Analyse de la littérature :
Les symptômes thoraciques représentés par une impression d'oppression thoracique avec parfois une symptomatologie algique et observés très classiquement sous triptans, ont été exclus de ce travail.
La revue de la littérature réalisée au 3 septembre 2004 a permis de retrouvé 41 articles.
Concernant les cas rapportés dans ces articles, on note :

- Une dizaine d'accidents ischémiques myocardiques, coliques et cérébraux
- Des cas d'infarctus du myocarde, essentiellement rapportés avec le sumatriptan injectable
- De façon très anecdotique, la survenue d'infarctus du myocarde chez des patients sans pathologie cardiovasculaire préexistante
- Deux observations d'effets indésirables coronaires aprés utilisation de sumatriptan par voie orale.

Le « Groupe d'Experts de Sécurité Cardiovasculaire des Triptans » a publié ses résultats en 2004 (Doddick et al, Headache 2004, 44, 414-425). Ce groupe, travaillant au nom de l'American Headache Society, a conduit une revue générale de l'ensemble des données scientifiques et cliniques sur le risque cardiovasculaire associé aux triptans. Le groupe d'experts conclut que : « le risque d'effets indésirables cardiovasculaires sous triptans apparaît très faible chez les patients respectant les critères d'inclusion ou d'exclusion des essais cliniques ou recevant les triptans selon les recommandations officielles ». Ainsi, « les triptans peuvent être prescrits en confiance sans bilan cardiovasculaire préalable ».

Conclusion :
Les accidents coronaires graves sous triptans surviennent dans presque 50 % des cas en dehors de tout mésusage et peuvent apparaître en l'absence de tout antécédent cardiovasculaire connu. Ces accidents graves concernent non seulement le sumatriptan (injectable ou administré par voie orale) mais également les autres triptans disponibles par voie orale. Ces données conduisent à rappeler qu'il faut, avant la prescription de tout triptan, évaluer le terrain coronaire par un interrogatoire sur les facteurs de risque cardiovasculaires et l'existence ou non d'un comportement addictif (ou d'une tendance addictive). L'évaluation du risque cardiovasculaire doit être dynamique dans le temps : il convient donc de la renouveler régulièrement car l'âge est un facteur de risque en soi et le risque augmente donc au cours du temps.
L'information présente dans les résumés des caractéristiques des produits (RCP) des différents triptans mériterait d'être mieux présentée et surtout d'être mieux connue des prescripteurs. Des propositions pourront être faites dans ce sens au niveau européen, pour les produits enregistrées selon des procédures européennes. Les RCP des produits enregistrés en procédure nationale (ZOMIG® et IMIGRAN® solution pour pulvérisation nasale, solution injectable et comprimés) pourront être modifiés.
Par ailleurs, l'ajout, dans les RCP, de l'interaction avec les alpha-stimulants qui ne sont pas des dérivés de l'ergot de seigle (comme l'oxymétazoline) devra être discutée.

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VI – POINT SUR LES CEPHALEES PAR ABUS MEDICAMENTEUX

1 - POINT SUR L'ABUS DES TRIPTANS ET MIGRAINES AGGRAVEES

Le Centre régional de Pharmacovigilance (CRPV) de Dijon a présenté un point sur les migraines aggravées induites par abus de triptans. Ce point a été réalisé conjointement par le CRPV de Dijon et le Centre d'Evaluation et d'Information sur les Pharmacodépendances (CEIP) de Toulouse.
Ce point ne concerne que la classe des triptans même si l'abus dans la migraine est le plus souvent plurimédicamenteux. Les triptans sont des agonistes sélectifs des récepteurs $5HT_{1B}$ et $5HT_{1D}$ vasculaires. Il sont indiqués dans le traitement de la crise de migraine, avec ou sans aura et ne doivent pas être utilisés en traitement prophylactique.
Cinq spécialités sont commercialisées en France, sous des formes orales, injectables ou inhalées.

Définitions :
En 2004, l'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) a publié des recommandations concernant le diagnostic, et a précisé le rôle de l'abus médicamenteux dans ces circonstances et la prise en charge **des céphalées chroniques quotidiennes (CCQ)**. Les CCQ y sont définies comme : « un ensemble hétérogène défini par la présence de céphalées plus de 15 jours par mois et plus de 4 heures par jour en l'absence de traitement, depuis plus de 3 mois, sans *substratum* lésionnel ou symptomatique. Il s'agit le plus souvent d'une céphalée initialement épisodique (migraine ou céphalée de tension) qui évolue vers une céphalée chronique, sous l'influence notamment d'un abus médicamenteux et de facteurs psychopathologiques.»
Selon l'International Headache Society (IHS), **l'abus médicamenteux** se définit comme un usage excessif intentionnel, persistant ou sporadique, de médicaments, accompagné de réactions physiques ou psychologiques nocives et caractérisé par une prise médicamenteuse régulière et qui dure depuis plus de 3 mois et qui est présente plus de 15 jours par mois pour les antalgiques non opioïdes (AINS, aspirine, paracétamol) et plus de 10 jours par mois pour les autres traitements de la crise (opioïdes ergotés, triptans, spécialités antalgiques associant plusieurs principes actifs). L'abus médicamenteux serait à l'origine d'un tiers des CCQ dans la population générale.

Les céphalées par abus médicamenteux (CAM) sont définies par les 3 critères suivants :
- la céphalée est présente plus de 15 jours par mois
- la céphalée se développe ou s'aggrave lors de la surconsommation médicamenteuse
- la céphalée disparaît ou revient à son état initial dans les deux mois après l'arrêt de la surconsommation médicamenteuse.

La CAM répond à des caractéristiques cliniques dépendant du type de substance consommée. En cas de CAM liée à une prise excessive de triptans, la céphalée secondaire doit être à prédominance unilatérale, et /ou de nature pulsatile, et/ou d'intensité modérée à sévère, et/ou aggravée par les activités physiques usuelles, et/ou associées soit à des nausées, des vomissements, soit à une phono- et photophobie. L'aggravation clinique se traduit souvent par une augmentation de la fréquence des crises.
Les **céphalées de sevrage** surviennent aprés l'utilisation d'une dose importante de substance pendant plus de 3 mois, apparaissent dans les heures suivant son arrêt, sont soulagées par une réadministration et disparaissent dans les 14 jours après l'arrêt total.

Analyse de la Base Nationale de Pharmacovigilance :
La recherche des observations enregistrées dans la Base Nationale de Pharmacovigilance a été réalisée, pour chaque molécule de triptan en recherchant les effets indésirables suivants : céphalée, migraine, céphalée par abus médicamenteux, céphalalgie, aggravation des céphalées, abus médicamenteux. Chaque observation a ensuite été revue et ont été sélectionnées comme abus toutes celles pour lesquelles les critères de l'IHS étaient retrouvés :
- céphalée par abus médicamenteux : céphalées durant plus de 15 jours par mois, s'aggravant avec la consommation de triptans, cédant à l'arrêt de la surconsommation,
- surconsommation : prise de triptans pendant plus de 15 jours par mois et pendant au moins 3 mois,
- nécessité d'un ou plusieurs sevrages,
- indication d'abus (terme préférentiel), ou présence d'éléments tels que la falsification d'ordonnance.

La recherche, menée en juillet 2004, a permis d'identifier 49 observations, enregistrées depuis 1992, année de mise sur le marché du premier triptan. Ces observations concernent 43 femmes et 6 hommes, d'âge moyen 48 ans.

Pour ces 49 observations, le diagnostic de céphalées par abus médicamenteux a été objectivé par :
- une amélioration des céphalées aprés sevrage en triptans : 35 observations,
- une fréquence de prise trop importante d'aprés les critéres de l'IHS : 8 observations,
- une falsification d'ordonnance dans 1 observation,
- une prise chronique dans 2 observations,
- un abus probable mais difficile à objectiver par manque de renseignements dans 2 observations.

Dans 20 % des observations, un syndrome dépressif associé est indiqué.
Les triptans imputés sont :
- Zolmitriptan dans 30 cas (58%),
- Naratriptan dans 15 cas (30,6%),
- Sumatriptan dans 10 cas (20,4%) voie orale 6 fois, voie SC 2 fois, voie inhalée 2 fois,
- Almotriptan dans 1 cas (2%).

Dans 7 observations, une association de plusieurs triptans a été constatée. Une association aux autres traitements de la crise a été notée dans 61,2% des cas et aux antalgiques simples dans 12% des cas.
Dans les cas avec abus objectivé selon les critéres de l'IHS, les consommations vont de 10 jours par mois (limite inférieure pour parler d'abus) à 6 comprimés par jour tous les jours au maximum.
Un sevrage médical a été nécessaire dans 37 cas, dont 24 en milieu hospitalier.

Données des CEIP :
Ces données ont été obtenues en utilisant les outils des CEIP à savoir OSIAP (Ordonnances Suspectes, Indicateur d'Abus et de Pharmacodépendance), NOTS (Notifications Spontanées) et OPPIDUM (Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse). Vingt-sept cas d'abus ont été recensés grâce à ces outils.
Dans 22 cas sur 27, le triptan était associé à d'autres médicaments. Il s'agissait notamment d'antalgiques, dans 15 cas, de caféine dans 9 cas. Dans 1 cas, il y avait également consommation de substances illicites (héroïne, ectasy).
Treize des 27 cas ont été identifiés comme étant des doublons des observations de la base nationale de Pharmacovigilance.

Analyse de la littérature
Les céphalées chroniques induites par abus médicamenteux ne semblent survenir que chez des patients qui sont déjà céphalalgiques, le plus souvent migraineux.
Une étude portant sur la consommation de sumatriptan par la population danoise en 1994 et 1995 a montré une prévalence d'utilisation en 1994 à 7,8/1000, avec un sexe ratio F/H à 3,8.
L'analyse des délivrances de médicaments par les pharmacies au Danemark en 1995, représentant 46 500 patients, a montré le caractère inapproprié de la consommation de sumatriptan dans la population : 5% des patients consomment 40% des triptans. Trois grands groupes de consommateurs ont été définis : importants (plus de 60 unités par mois), intermédiaires (entre 30 et 59), et modérés (moins de 30 unités /mois). Dans chaque groupe la proportion de céphalées induites a été estimée respectivement à 86 %, 47% et 14%.
Une étude israélienne visant à documenter la relation entre consommation de sumatriptan et changement de la nature des migraines, a montré chez tous les patients une recrudescence des crises 3-4 semaines après introduction, des modifications des caractéristiques des céphalées et une augmentation de leur durée.
Concernant la prise en charge, le sevrage médicamenteux est indispensable, mais les protocoles thérapeutiques sont actuellement très hétérogènes et mal évalués. Les moyens non médicamenteux sont parfois déterminants. L'éducation du patient céphalalgique et le suivi régulier sont primordiaux pour éviter les rechutes. Des facteurs pronostiques ont été mis en évidence mais ne seraient pas déterminants à long terme. Le taux de réussite, actuellement évalué à 60% à 5 ans, et les bénéfices d'une prise en charge adaptée encouragent à détecter précocement ces céphalées induites encore largement sous-diagnostiquées

Information contenue dans les Résumés de Caractéristiques du Produit (RCP)
Il a été signalé qu'une information concernant le risque de céphalées chroniques induites par abus est mentionnée en section Mises en garde et précautions d'emploi pour tous les triptans commercialisés excepté pour Naramig, pour lequel une procédure de variation européenne est en cours à ce sujet, et Zomig, enregistré selon une procédure nationale. Une information est présente dans la section concernant les effets indésirables que pour Zomig.

2 - POINT SUR LES CEPHALEES PAR ABUS D'ANTALGIQUES

A la suite d'une alerte rapportée par deux médecins du centre de la douleur et de traitement des céphalées du CHU de Saint-Etienne en juin 2004, le CRPV de Saint-Etienne a souhaité présenter un point sur les céphalées par abus médicamenteux (CAM). Ce point a été réalisé en collaboration avec la Société Française d'Etudes des Migraines (SFEMC).
Après avoir rappelé les définitions de la CAM et de la surconsommation médicamenteuse, les données de la SFEMC ainsi que les cas de la base nationale de pharmacovigilance ont été présentés.

Données de la SFECM
Depuis le 1er juin 2002, cette société a créé un registre multicentrique de patients céphalgiques reçus dans 13 centres hospitalo-universitaires spécialisés dans la prise en charge des douleurs chroniques et/ou des céphalées.
Au 31 mars 2004, 20 628 patients étaient dénombrés, les conclusions suivantes pouvaient être dégagées :

- 1544 (7,5%) patients ont été identifiés comme souffrant de CAM
- les médicaments responsables se répartissent comme suit :
  - antalgiques non opiacés : 38,2%
  - triptans : 29,3%
  - antalgiques opiacés : 22,3%
  - ergotamine : 3,2%
  - associations : 4,3%
  - autres (sans précision) : 2,7%.

Par ailleurs, à la suite de ces premiers résultats, la SFEMC a instauré une étude épidémiologique observationnelle, transversale, multicentrique, réalisée auprès des centres hospitalo-universitaires spécialisés dans la prise en charge de patients céphalalgiques. L'objectif de cette étude est de décrire les caractéristiques sémiologiques des patients souffrant de CAM. Elle a débuté en juillet 2004 et doit inclure 500 patients au total.

Données de la base nationale de pharmacovigilance
Le recueil des données de la base nationale a été effectué sur une période identique (du 1er juin 2002 au 31 mars 2004) à celle de la SFEMC, afin de permettre une comparaison des résultats.
La recherche croisée de céphalalgie / migraine / abus de médicament / pharmacodépendance avec tous les principes actifs antalgiques ou antimigraineux appartenant aux listes « antalgiques » et « neurologie, antimigraineux, traitement de la crise » extraits du classement des médicaments par famille pharmacothèrapeutique (section jaune du Dictionnaire Vidal 2004), a permis de colliger 44 observations, contre 1544 pour la SFECM.
Les données comparatives peuvent être résumées de la façon suivante :

	REGISTRE SFECM	BNPV
Nombre de patients	1544	44
Abus d'antalgiques non opiacés	38,2%	32,1%
Abus de triptan	29,3%	18,3%
Abus d'antalgiques opiacés	22,3%	24,8%
Abus d'ergotamine	3,2%	9,1%
Autres	7%	15,7%

Information contenue dans les Résumés de Caractéristiques du Produit (RCP)
Après avoir revu l'ensemble des RCP concernés, il apparaît que le risque de CAM est de façon générale peu mentionné dans les RCP. En effet, seules les spécialités contenant de l'aspirine, du zolmitriptan ou de la dihydroergotamine comportent un libellé relatif au risque de CAM.

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Le CRPV de Saint-Etienne a l'issue de sa présentation a tiré les conclusions suivantes :

- La faible notification des cas de CAM, peut s'expliquer par la méconnaissance du problème des professionnels de santé et des patients eux-mêmes
- Le CRPV a rappelé la récente publication, par l'Agence Nationale d'Accréditation en Santé (ANAES)[1], de recommandations de prise en charge des céphalées chroniques quotidiennes.
- A la lumière de ces différentes données, le CRPV a souligné la nécessité de modification des RCP et des notices des produits concernés .

Par ailleurs, le CRPV de Saint-Etienne a fait part, lors de l'adoption du procès-verbal, de nouvelles informations : une étude concernant la surconsommation des triptans a été coordonnée par l'URCAM de la région Rhône-Alpes et certains neurologues. Le CRPV de Saint-Etienne est en attente des résultats.

CONCLUSION GENERALE

A la lumière de ces différentes données, le Comité technique a souligné la nécessité de modification des RCP et des notices des produits concernés.

Concernant les RCP, il a été rapporté qu'une NUI (Non Urgent Information) avait été demandée par le Danemark auprès de l'Europe en septembre 2004, concernant les CAM. 9 Etats Membres ont répondu (Irlande, Suède, Royaume-Uni, Lettonie, Portugal, Malte, Italie, Islande et France). Au total, les résultas français correspondent à la tendance européenne qui se dégage des réponses reçues.

Par ailleurs, une identification plus précise de la consommation des triptans dans la population française et le nombre d'abuseurs est nécessaire.

En accord avec le CRPV de Dijon, il a été conclu de centrer en premier lieu les actions sur les triptans. De plus, le CRPV de Dijon s'est engagé à finaliser le protocole d'une étude de suivi de consommations des triptans dans le région Bourgogne, en partenariat avec la Caisse d'Assurance Maladie.

[1] . Recommandations pour la pratique clinique. CCQ (Céphalées Chroniques Quotidiennes) : Diagnostic, rôle de l'abus médicamenteux, prise en charge. Septembre 2004. disponibles sur le site www.anaes.fr;

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VIII - QUESTIONS DIVERSES

Rappel des conditions de prescription d'ELSEP® (mitoxantrone) et de suivi des patients :

La spécialité ELSEP® (mitoxantrone) 2mg/ml a obtenu une autorisation de mise sur le marché en Octobre 2003 dans le traitement des formes agressives de sclérose en plaques de type récurrente/rémittente ou de type secondairement progressive. ELSEP®est agréé aux collectivités depuis le 4 Mai 2004. Ce médicament est en réserve hospitalière et sa prescription est limitée exclusivement aux neurologues des services spécialisés en neurologie.

En raison, notamment, des risques hématologiques (8 cas de leucémie rapportés) et cardiaques, liés à l'utilisation du produit, l'autorisation de mise sur le marché octroyée pour ELSEP prévoit :

- le recueil d'un accord de soins du patient avant l'initiation du traitement,
- une surveillance particulière et obligatoire de la pharmacovigilance, chez tous les patients traités, tout au long du traitement et pendant 5 ans après la fin de celui-ci.

Le 15 décembre 2004, une lettre d'information a été adressée par l'Afssaps aux neurologues hospitaliers exerçant en service de neurologie et aux pharmaciens hospitaliers concernés, afin de rappeler les conditions de prescription d'ELSEP® et de suivi des patients traités. Un communiqué de presse a également été diffusé sur le site internet de l'Afssaps. Il est rappelé dans ces documents que les patients traités par mitoxantrone dans le cadre d'une sclérose en plaques doivent impérativement recevoir la spécialité ELSEP et non NOVANTRONE, et ce afin de bénéficier du suivi de pharmacovigilance prévu. Les prix de ces deux spécialités sont aujourd'hui identiques.

Les Centres Régionaux de Pharmacovigilance ont demandé à disposer d'un exemplaire du classeur de suivi des patients traités par ELSEP, transmis aux prescripteurs pour toute initiation de traitement. Une demande en ce sens sera faite aux laboratoires Wyeth.

Exposition in utero à des hormones sexuelles, naturelles ou synthétiques et troubles psychiatriques ; cas recueillis par l'Association HHORAGES / CRPV de Bordeaux

Dans le cadre de l'étude des effets de l'exposition in utero au DiéthylStilbestrol et aux autres hormones stéroïdes naturelles ou de synthèse, un recueil de témoignages spontanés portés à la connaissance des associations de patients est effectué. L'association HHORAGES (Halte aux Hormones Artificielles pendant la Grossesse) s'intéresse tout particulièrement aux troubles psychiatriques induits. Cette association a collecté environ 525 témoignages, soit faits directement par les sujets exposés soit le plus souvent par l'intermédiaire des familles. Le Dr. F. Haramburu du CRPV de Bordeaux, membre du groupe de travail de l'Afssaps sur les conséquences de l'exposition au diéthylstilbestrol, a pris connaissance des cas transmis. Dans la majorité des cas, l'exposition est imprécise (nature, date d'exposition par rapport à la grossesse, durée de l'exposition, posologie) et la pathologie psychiatrique est vague, non médicalement confirmée. Soixante témoignages correspondant à 60 familles avec 74 enfants présentant des troubles psychiatriques (sur 89 exposés, pour un total de 144 enfants dans ces familles) ont été retenus. Si la nature de l'exposition est connue dans la plupart de ces cas, les autres caractéristiques de l'exposition sont le plus souvent imprécises ; il n'y a pas dans la majorité des cas de confirmation médicale des diagnostics psychiatriques retenus. Les tableaux cliniques présentés semblent très variés ; en revanche un certain nombre de cas correspondent indubitablement à des cas graves (hospitalisations, suicides, invalidité). Aussi, si ces témoignages représentent une source d'information intéressante et sans aucun doute un signal fort, ils ne peuvent pas constituer une base d'analyse pour l'évaluation d'une relation causale.

Suite à une étude pharmaco-épidémio-génétique « REGISCAR » des syndromes de Steven's Johnson et de Lyell, une copie des dossiers remplis par les investigateurs sera adressée par le centre de Paris–Henri-Mondor aux différents CRPV selon leur territoire d'intervention.

Annexe 3-46

l'Assurance Maladie
sécurité sociale
service médical de Saint-Etienne

1690

Contact Docteur WASSERSTROM
Téléphone 04 77 55 43 79

Réf. : MW/MC

Date 24 fev1997

Objet

Madame le Docteur CASTOT
Département de Pharmacovigilance
Agence du Médicament
143-147 Bd Anatole France
93285 SAINT DENIS CEDEX

Madame et Cher Confrère,

Je me permets de vous écrire de la part du Pr BECHTEL du CHU de BESANCON dans le cadre d'une étude que réalise le Service Médical de l'Assurance Maladie de Saint Etienne sur les prescriptions hors AMM concernant le benfluorex Mediator ®.

La pré-étude montre sur 309 prescriptions concernant le même prescripteur, 89 prescriptions de Mediator ® à la posologie de 300 à 450 mg/j (2 à 3 cp) pour une durée de 3 à 6 mois.

Il apparaît clairement que le benfluorex est utilisé dans la majorité des cas comme « coupe faim ou amaigrissant » chez des patients n'ayant ni hypercholestérolémie ni DNID.

Avez-vous connaissance de cas d'utilisation dans cette « indication » non officielle ?

A titre d'exemple, je vous fais part d'une observation concernant une jeune femme de 27 ans (née le 23/6/69) que je viens d'examiner ce matin :
Surcharge pondérale du post-partum (+ 26 kg pendant la grossesse) avec poids maximal de 83 kg pour 1m 70 (BMI=28,72) le 5.10.93 (1er accouchement).
Prise en charge par le médecin « étudié » en novembre 1995. Poids=75 kg pour 1m70 (BMI=25,95). Bilan initial négatif à l'exception d'une thyroïde asymétrique en euthyroïdie mais traité par 50 µg de Levothyrox. HGPO dans les limites de la normale mais prétexte à la prescription du Médiator à la posologie de 450 mg/j. Actuellement, la patiente a accouché d'une 2e enfant le 20.12.96. Elle avait semble t'il interrompu la prise de benzofluorex et de levo-thyroxine pendant sa grossesse. Elle reprend contact avec le prescripteur qui, le 27.1.97, reconduit in extenso sa prescription de Mediator et de Levothyrox. Actuellement, la patiente pèse 64 kg pour 1m 70 (BMI=22,14) à 2 mois de son 2e accouchement. Les glycémies pratiquées pendant la grossesse sont restées normales.
Que pensez-vous de ce cas clinique ?

3, avenue du Président-Emile-Loubet
42027 Saint-Etienne cedex
Tél. : 04.77.42.20.98
Fax : 04.77.42.21.07

Annexe 3-46

Avez-vous connaissance d'effets indésirables imputables au benfluorex qui ne soient pas mentionnés dans la monographie du VIDAL ? Le risque d'HTAP est-il connu ou possible (cf. Isoméride®) ?

Le Mediator ® benfluorex parait apparenté aux amphétaminiques anorexigènes : clobenzorex, méfénorex et fenfoprorex. Cette parenté est-elle établie au plan biochimique et pharmacologique ?

Je vous remercie de nous apporter votre éminent concours dans cette étude qui relève de la Santé Publique dans la mesure où, au moins, 89 personnes sont concernées.

Je vous prie de croire, Madame et Cher Confrère, en l'assurance de ma haute et confraternelle considération.

Docteur Marc WASSERSTROM
Médecin Conseil

PJ : documents anonymisés concernant le cas clinique décrit

Vue en Nov 91 1692

Annexe 3-46

Cher Ami,

J'ai eu l'occasion de voir à mon cabinet ta patiente Madame , née le 23 juin 1969.

Cette jeune femme est venue me consulter pour plusieurs problèmes :

1) celui d'un *diabète* ?
2) celui d'un *problème de thyroïde*,
3) elle présentait une *surcharge pondérale* de 75 kg pour 1 m 70.

Le bilan que j'ai réalisé montre quelques anomalies, c'est la raison pour laquelle je te passe ce courrier :

1) en ce qui concerne sa thyroïde, elle fonctionne normalement puisque :

* la TSH est normale,
* la recherche des anticorps antipéroxydases est négative,
* l'échographie montre une thyroïdie asymétrique mais non nodulaire,
* enfin la scintigraphie confirme la normalité de cette thyroïde avec simplement un lobe droit plus gros que le lobe gauche.

Je lui ai donc conseillé de prendre sous ta surveillance jusqu'à fin avril 1 comprimé par jour de [redacted] afin d'essayer d'empêcher ce goitre de grossir.

2) en ce qui concerne le diabète et donc le poids, j'ai fait réaliser une hyperglycémie sur 2 heures qui est anormale puisque sa glycémie atteint 1 g 87 à la 30ème minute, est encore à 1 g 70 à la 60ème minute, et encore à 1 g 23 à la 120ème minute. A cet état d'intolérance aux glycides, il existe également associé un hyperinsulinisme à environ 3 fois le taux habituellement rencontré.

.../...

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J'ai expliqué tout cela à [redacted] et je lui ai donc donné un régime diabétique standard associé à au [redacted] si cela est nécessaire. ajout du 31/12.

J'aimerais qu'elle atteigne à peu près 60 kg car l'insulinorésistance diminuerait alors et cela éloignera le moment où elle deviendra diabétique.

En attendant, je l'ai renvoyée à tes bons soins.

Bien amicalement.

Annexe 3-46

CHIMIE DU SANG

HYPERGLYCEMIE PROVOQUEE PAR VOIE ORALE

Apres absorption de 50 g de glucose

	GLYCEMIE (g/l)	GLYCEMIE (mmol/l)	GLYCOSURIE (g/l)
A JEUN	1.02	5.66	0.00
A 30 minutes	1.87	10.38	0.00
A 60 minutes	1.70	9.44	0.00
A 90 minutes	1.39	7.71	0.00
A 120 minutes	1.23	6.83	0.00

+

ANALYSE EN COURS (Institut Pasteur Strasbourg tel: 72.72.25.00)

HORMONOLOGIE

TSH (Ultrasensible) (42060)..... 3.56 mUI/l (N:0.25 - 5)

(Seuil de sensibilite : 0.04 mUI/L)

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ZEUS SAINT - ETIENNE

x 3 mois

1Type permis SD LETTRE BOX SD

MEDIATION 3 copies / jour

Saint-Etienne, le 13/03/96

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Saint-Etienne, le 27/01/97

MEDIATOR 3 cpés / jour

LEVOTHYROX 50 1Cpe par jour

x 4 mois

-70733
-284

PHARMACIE TIBERIER CHAUVEAU J.L.
Tél 42 2 02206 1
PLACE DE L'EUROPE

- 42000 SAINT - ETIENNE

BIOCHIMIE

1697

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		Normales	Antérieurs
GLYCEMIE POST-PRANDIALE. . . .	4,82 mmol/l 0,86 g/l	inf. à 7,00 inf. à 1,26	

Le Biologiste

Examen du 17/09/96 08h54

BIOCHIMIE

1698

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		Normales	Antérieurs
CREATININE	86 umol/l 9,7 mg/l	50 à 100 5,6 à 11,3	
ACIDE URIQUE	253,0 umol/l 42,5 mg/l	150,0 à 360,0 25,2 à 60,4	
GLYCEMIE à jeun.	5,85 mmol/l 1,05 g/l	3,90 à 5,80 0,70 à 1,04	

Le Biologiste

AGENCE DU MEDICAMENT
388
DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

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Saint-Denis le, 12 MARS 1997

Monsieur le Docteur WASSERSTROM
ASSURANCE MALADIE
Service Médical de Saint-Etienne
3, avenue du Président Emile-Loubet
42027 SAINT-ETIENNE cedex

Monsieur,

En réponse à votre courrier du 24 février 1997 relatif au Mediator® (benfluorex), je vous prie de bien vouloir trouver ci-joints ces quelques éléments d'information :

Le benfluorex est indiqué comme adjuvant du régime adapté dans les hypertriglycéridémies ou dans les diabètes asymptomatiques avec surcharge pondérale. Cette spécialité n'est donc pas indiquée dans la prise en charge de l'obésité et ses conditions de prescription et de délivrance ne sont pas actuellement soumises aux restrictions des médicaments coupe-faims.

En raison de sa parenté structurale, ce médicament fait l'objet d'un suivi de pharmacovigilance et son utilisation dans des préparations magistrales a été interdite (l'arrêté publié au JO du 31/10.95). Néanmoins les dérives d'utilisation sont difficiles à appréhender et nous sommes vivement intéressés par les résultats de votre enquête de prescriptions. En effet le suivi régulier des chiffres de ventes n'est pas suffisant pour identifier les reports de prescription. Aussi, nous examinons avec attention, les quelques signalements individuels que nous transmettent nos collègues pharmaciens .

Je vous conseille de joindre le Pr Ollagnier au Centre Régional de Pharmacovigilance de Saint-Etienne, pour répondre à vos questions relatives à la pharmacologie du produit et à sa parenté avec les amphétamines.

Restant à votre disposition pour tout complément d'information, je vous prie de recevoir Monsieur , mes meilleures salutations.

Le Chef de l'unité de Pharmacovigilance

Dr Anne CASTOT

Annexe 3-47

AGENCE
MEDICAMENT

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le 20 JUIL. 1998

NOTE A MONSIEUR FLEURETTE
Direction des Etudes et de l'Information Pharmaco-économiques

Objet : MEDIATOR® (benfluorex) et détournement d'usage

A la suite des mesures prises concernant la classe des médicaments anorexigènes, une enquête officieuse de pharmacovigilance sur le MEDIATOR® a été mise en place en 1995.
En effet, la métabolisation du benfluorex dans l'organisme entraîne la formation de norfenfluramine, métabolite apparenté à la fenfluramine, elle-même impliquée dans la survenue d'hypertensions artérielles pulmonaires. Par ailleurs, le risque de déviation d'utilisation du benfluorex comme anorexigène est à craindre.
Les premiers résultats de l'enquête ont été présentés au Comité Technique du 11 juillet 1995. Aucun cas d'hypertension artérielle pulmonaire d'allure primitive résultant d'une monothérapie n'a été rapporté et aucune déviation d'utilisation n'a été signalée. Il a alors été considéré que ce premier bilan était trop prématuré et qu'il fallait continuer à surveiller le profil de sécurité d'emploi.
Un second bilan des effets indésirables a été présenté au Comité Technique du 30 avril 1998. Le nombre d'effets indésirables observés n'a pas semblé plus important que celui rapporté en juillet 1995. Cependant, la possibilité d'une déviation de l'utilisation comme anorexigène ne peut être estimée au vue des seules données des centres régionaux de pharmacovigilance alors qu'il semble que des cas aient été identifiés, notamment par la Caisse Régionale d'Assurance Maladie de Bourgogne.
Compte-tenu de ce constat, le Comité Technique a demandé la mise en place d'une enquête officielle sous la responsabilité du Centre de Pharmacovigilance de Besançon afin d'obtenir les chiffres de vente et les observations du laboratoire.

Le Comité Technique a, par ailleurs, souhaité que l'Observatoire de la Prescription soit interrogé sur les conditions d'utilisation actuelles de cette spécialité et de leur évolution depuis ces dernières années. En conséquence, nous vous remercions vivement de nous communiquer les données d'utilisation disponibles concernant ce médicament.

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AGENCE MEDICAMENT

DIRECTION DES ETUDES ET
DE L'INFORMATION PHARMACO-ECONOMIQUES

Le Directeur

N/Réf : cg\n0998JMA

93 OCT. 1998

NOTE

- A l'attention de Monsieur Jean-Michel ALEXANDRE -

- Direction de l'Evaluation -

Objet : Evolution de la consommation et des prescriptions de MEDIATOR®

Les données dont dispose la DEIPE sur l'évolution des consommations et des prescriptions de MEDIATOR® au cours de ces dernières années ne permettent pas de mettre en évidence un détournement d'usage de ce médicament. Si MEDIATOR® a été - et est encore - prescrit comme anorexigène et, de façon plus large, comme médicament anti-obésité, la part des prescriptions dans ces indications hors AMM est modeste et - surtout - a décru au cours de la période étudiée. Ainsi, les prescriptions de ce médicament dans le traitement de l'obésité[1] étaient, selon le DOREMA, de 9 % en 1994 mais seulement de 5,1 % au cours de l'hiver 1997-1998.

Comme le montre le tableau joint en annexe, une tendance similaire peut être dégagée en ce qui concerne la prescription de MEDIATOR® comme amaigrissant ou comme anorexigène. En tout état de cause, si l'on admet que la rubrique "effets attendus" du DOREMA est correctement renseignée, les mesures prises en 1995 pour restreindre la prescription d'anorexigènes n'ont pas entraîné de reports en faveur de MEDIATOR®. Ce médicament demeure très largement prescrit comme hypocholestérolémiant et comme antidiabétique (80,2 % des prescriptions en 1997).

Quant à l'évolution globale du nombre de prescriptions de MEDIATOR®, si elle a été positive, elle est restée néanmoins modeste : + 5,6 % entre 1994 et 1997.

---

[1] Effet attendu : traitement de l'obésité

.../...

Il sera seulement indiqué le nombre de ventes en hausse augmentant de [illegible] progression plus importante que celle de l'ensemble des spécialités [illegible] Toutefois, cette progression aurait dû être encore beaucoup plus forte si les prescriptions d'anorexigènes s'étaient reportées de façon tangible sur MEDIATOR®. En effet, les ventes (en unités) d'anorexigènes s'élevaient en 1994 à 4,4 millions et, en 1995, à 2,8 millions.

Aussi, en conclusion, apparaît-il que le détournement d'usage de MEDIATOR®, s'il existe, ne pourrait être évalué qu'à l'aide de données beaucoup plus fines, et qui font actuellement défaut, sur la prescription de ce médicament.

Le Directeur des Etudes et de
L'Information Pharmaco-Economiques

Frédéric FLEURETTE

P.J. : Tableau sur l'évolution des ventes et des prescriptions de MEDIATOR®.

EVOLUTION DES VENTES ET DES PRESCRIPTIONS DE MEDIATOR

	1994	1995	1996	1997	Hiv. 97/98
Nbre de boîtes vendues (30 comp.)	4 809 905	5 159 845	5 283 371	5 588 203	
Nbre total de prescriptions	909 000	869 000	882 000	960 000	957 000
Nbre de prescriptions "anti-obésité"*	82 000	85 000	65 000	54 000	49 000
Part des prescriptions "anti-obésité"	9,02%	9,78%	7,37%	5,63%	5,12%

* Effet attendu

Parmi les prescriptions ayant pour effet attendu "Anti-obésité" :

	1994	1995	1996	1997	Hiv. 97/98
Nbre de prescriptions "amaigrissement"*	59 000	52 000	43 000	20 000	17000
Part des prescriptions "amaigrissement"	1,23%	1,01%	0,81%	0,36%	
Nbre de prescriptions "anorexigènes"*		19 000		17 000	15 000
Part des prescriptions "anorexigènes"		2,19%		1,77%	1,57%

* Effet attendu

Sources : "Taxe sur les spécialités" pour les données sur les ventes
"Doréma -EPPM" pour les données de prescriptions (automne, sauf pour hiver 97/98)

Annexe 3-48

FRS9333 4 CTF 0312 FRA /AFP-NF76
Santé-médicaments
Le Médiator, un médicament détourné de ses indications thérapeutiques

DIJON, 1er juil (AFP) - Le médicament appelé Médiator, classé parmi les amphétamines, est fréquemment détourné de ses indications thérapeutiques pour servir d'amaigrissant, révèle une étude menée par l'Union régionale des caisses d'assurance maladie (URCAM) de Bourgogne.

Le Médiator, classé par l'Organisation mondiale de la santé (OMS) parmi le groupe des amphétamines, mais non soumis en France à la législation qui s'y rapporte, est normalement prescrit comme adjuvant des traitements du diabète avec surcharge pondérale. Mais l'étude, menée sur 568 prescriptions du médicament présentées au remboursement en Bourgogne pendant 5 jours en avril 1997, montre qu'il est utilisé comme amaigrissant dans un tiers des cas.

L'URCAM de Bourgogne, jugeant les risques pour la santé importants, préconise le reclassement de ce médicament dans le groupe des amphétamines, ce qui implique une prescription restreinte. L'URCAM s'interroge également sur la légitimité à rembourser un médicament dont les indications thérapeutiques ne sont pas respectées. Le Médiator représente effectivement une dépense annuelle potentielle d'environ 4 millions de francs pour la seule Bourgogne.

Ce détournement du médicament lui semble d'autant plus grave que 66% des patients ne présentent pas d'obésité avérée. Deux patientes présentaient même un état de maigreur, indique le rapport de l'étude. De même, 20 % des médecins ne peuvent pas fournir d'information sur la taille et le poids du patient auquel ils ont prescrit ce médicament.

L'étude de cette structure régionale, créée début 97 pour être la pièce essentielle de la réforme de la Sécurité sociale, fait partie d'autres menées par les URCAM de France pour apprécier quels sont les médicaments utilisés de manière frauduleuse.

jms/tm
AFP 011308 JUL 98 @@@@

Reçu le 03/07/98

GS → JMB

Pour suite éventuelle à donner en Amont ?

et en Transparence

Merci d'avance SVP

6/7/98

cc DGS
DSS

Annexe 3-48

V - POINT BENFLUOREX (MEDIATOR®)

Le Centre Régional de Pharmacovigilance de Besançon a effectué une mise au point concernant les effets indésirables observés avec le benfluorex.

Le MEDIATOR® (chlorydrate de benfluorex) est commercialisé en France (depuis 1976) dans les indications suivantes :
- adjuvant du régime adapté dans les hypertriglycéridémies.
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex est inscrit depuis le 10 mai 1995, comme les anorexigènes, sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales.

Sur les 291 notifications rapportées avec le benfluorex, 152 ont été retenues au 30 avril 1998 (lors de la précédente mise au point de juillet 1995, 101 notifications avaient été rapportées).

● Les atteintes hépatiques : 16 cas
Les cas les plus souvent rapportés sont des hépatites et des perturbations de la biologie hépatique : élévation des transaminases. Ces effets ne sont pas mentionnés dans le RCP.

● Les atteintes digestives : 16 cas
Les cas les plus souvent notifiés sont les diarrhées. Cet effet indésirable est mentionné dans le RCP.

● Les atteintes hématologiques : 8 cas
Les effets les plus fréquents sont les thrombopénies. Il n'y a pas eu de nouveaux cas rapportés depuis juillet 1995.

● Les atteintes respiratoires : 8 cas
Les cas rapportés sont principalement des toux et des hypertensions pulmonaires (dans les 2 cas rapportés, il existe un traitement anorexigène associé).

● Les atteintes cardiovasculaires : 11 cas
Des cas d'hypertension artérielle, de tachycardie, d'extrasystoles ventriculaires et de syndrome de Raynaud sont le plus souvent notifiés.

● Les atteintes rénales : 9 cas
Parmi lesquelles on observe le plus souvent des dysuries, des pollakiuries.

● Les atteintes métaboliques : 3 cas
Une hyperlipémie, une hypothyroïdie et une crise de goutte ont été rapportées.

● Les atteintes cutanées : 38 cas
Des urticaires, des chocs anaphylactiques, des eczémas, des vascularires, des érythèmes ainsi que des purpuras sont les effets les plus fréquents. Ces effets indésirables ne sont mentionnés pas dans le RCP.

Annexe 3-48

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Jean Minjoz 25030 BESANCON Cedex

MEDIATOR (benfluorex)
Effets indésirables

Mise au point

Comité Technique du 30 Avril 1998

Confidentiel

M.DAVII
P.BECHTE

Le MEDIATOR (chlorhydrate de benfluorex) est commercialisé en France depuis 1974 sous forme de comprimés, dosés à 150 mgL La posologie recommandée est : 3 comprimés par jour.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène.
(Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Une enquête officieuse a été ouverte, suite à la première mise au point des effets indésirables du benfluorex, présentée lors du Comité Technique du 11 juillet 1995.

Pharmacocinétique humaine du chlorhydrate de benfluorex :

L'absorption gastro-intestinale du chlorhydrate de benfluorex est complète et rapide, avec une concentration plasmatique maximale entre 1h et 2 h après l'administration.
Le volume de distribution est faible : 0,37 ± 0,03 l/Kg chez l'homme (1,4 l/Kg chez le rat, 1,6 l/Kg chez le chien,0.36l/Kg chez le singe et 0,31 l/Kg chez le babouin.
Le chlorhydrate de benfluorex est métabolisé rapidement dans le foie. Au niveau tissulaire, il n'y a aucune accumulation ou rétention de métabolites.

Les métabolites principaux retrouvés dans l'urine sont :
- le 1-(3-trifluorométhylphényl)-2-N-(carboxyméthyl)amino propane : 65% de la dose
- le 1-(3-trifluorométhylphényl)-2-N-(2-hydroxyéthyl)amino propane : 22% de la dose

- la 3-trifluorométhylphényl)-1 -hydroxy-propanone-2 sous forme conjuguée (5% de la dose)
- la Nor-fenfluramine : 2% de la dose.

Les métabolites principaux retrouvés dans le plasma sont :
- le 1-(3-trifluorométhylphényl)-2-N-(carboxyméthyl)amino propane
- le 1-(3-trifluorométhylphényl)-2-N-(2-hydroxyéthyl)amino propane

On ne retrouve pas de benfluorex inchangé dans le plasma.,

A. BILAN GLOBAL :

Parmi 291 notifications dans lesquelles le MEDIATOR est présent, et qui sont rapportées aux Centres Régionaux de Pharmacovigilance, 152 notifications ont été retenues.

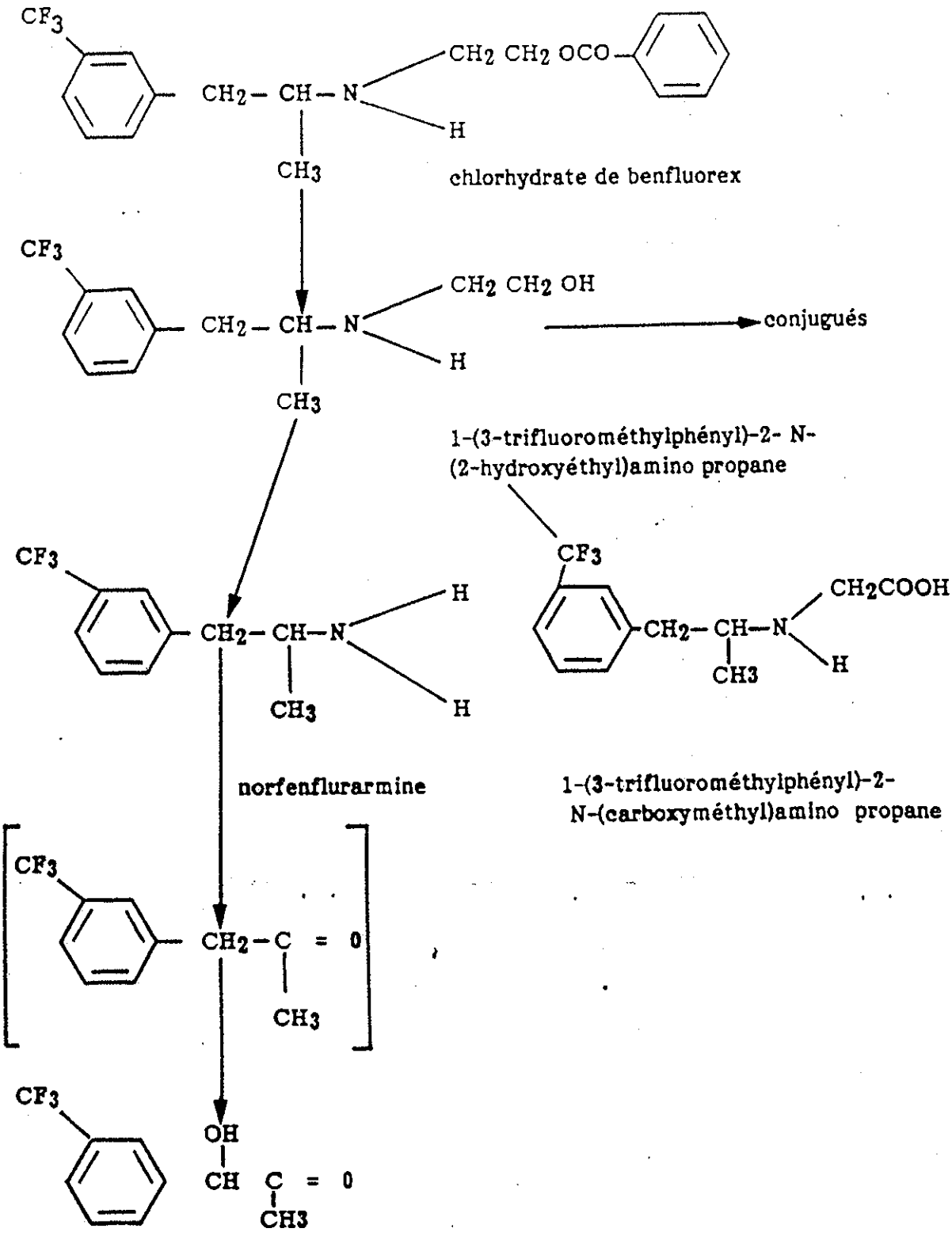
Elles concernent 54 hommes et 97 femmes (1 sexe non précisé), dont l'age moyen est de :
- 57 ans pour les hommes (N = 54)
- 55,6 ans pour les femmes (N = 92)

Pour les notifications reçues jusqu'à 1995 , l'age moyen est de :
- 55,4 ans pour les hommes (N = 45)
- 56,7 ans pour les femmes (N = 66)

Pour les notifications reçues après 1995 , l'age moyen est de :
- 64,7ans pour les hommes (N = 9)
- 52,8 ans pour les femmes (N = 26)

Annexe 3-48

SCHEMA DU METABOLISME



3-trifluorométhylphényl-1-hydroxypropanone-2

2. bis

Annexe 3-48

Répartition des notifications par année de déclaration aux CRPV

- 1985 : 3
- 1986 : 6
- 1987 : 7
- 1988 : 13
- 1989 : 9
- 1990 : 6
- 1991 : 11
- 1992 : 9
- 1993 : 21
- 1994 : 10
- 1995 : 21
- 1996 : 7
- 1997 : 26
- 1998 : 3

Répartition par classe-organe des effets indésirables notifiés au CRPV :

APPAREIL	Nombre de Notifications au 30 juin 1995	Nombre de Notifications au 30 avril 1998	
FOIE	9	16	7
APP. DIGESTIF (sauf foie)	13	16	3
HEMATOLOGIE	8	8	-
APPAREIL RESPIRATOIRE	4	8	4
CARDIO-VASCULAIRE	5	11	6
APPAREIL URINAIRE	7	9	2
PEAU - ALLERGIE	25	38	13
EURO-PSYCHIATRIE	19	27	8
VERTIGES	9	16	7
METABOLISME	2	3	1
TOTAL	101	**152**	51

N.B : les nouvelles notifications par rapport à la mise au point de Juillet 1995, sont imprimées «en **gras** » dans les tableaux suivants.
Dans la colonne, « traitement associé », le médicament est souligné, lorsque l'imputabilité bibliographique est supérieure au MEDIATOR.

Annexe 3-48

I. ATTEINTES HEPATIQUES :

Dans 14 cas sur 26 cas d'hépatites ou perturbations de la biologie hépatique notifiés aux CRPV, le MEDIATOR est le seul suspect ou d'imputabilité égale ou supérieure aux médicaments associés.

Dans la majorité des dossiers, le délai de survenue est de ≅ 3 mois.

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
Hépatite mixte						
RE8600098	M,82	1 mois	C2,S1	CORVASAL, DIAMICRON TADENAN	A	
DJ9300271	F,50	8 jours	C2,S2	Amfépramone, C2,S2	A	
Hépatite cytolytique						
NY8804047	M,47	3 mois	C2,S2		A	
DJ9100164	M,61	3 ans	C2,S2	RENITEC, C2,S2 DOGMATIL	A	
Hépatite cholostatique						
NC9200360	F,85	3 mois	C2,S1	TENSTATEN, C2,S1	A	
Biologie hépatique perturbée						
NC9600020	**F,39**	**8 mois**	**C2,S2**		**A**	**ALAT↑**
MA9700402	**F,47**	**12 sem.**	**C2,S1**		**A**	**ALAT↑**
MA9400451	F,57	3 mois	C1,S1	Amfépramone, C1,S1	U	ALAT↑
BX9700611	**F,51**	**6 j**	**C2,S1**	**LUTERAN, C2,S1** **LEVOTHYROX , C2,S1** **TENORMINE, C2,S1**	**F**	**ALAT↑**
PA9803765	**F,66**	**3 mois**	**C1,S1**	**LAROXYL** **GLUCOR** **TEATROIS** **TEALINE...**	**U**	**ALAT↑** **Prep.Magistr.**
PB9300028	M,60	15 j	C1,S1	Prep. magistrale: 15 j Yohimbine Dexfenfluramine Metformine, 2 ans ANAFRANIL, 2 ans	A	ALAT↑
NY9608618	**F,36**	**4 mois**	**C2,S2**		**A**	**ALAT+Bil↑**
PA8851623	M,61	3 ans	C2,S1	(Myocoril,C1,S1)	F	ALAT+P.A↑
BX9700024	**F,59**	**4sem.**	**C2,S2**	**LOXEN,C2,S2** **ACUILIX, C2,S2**	**A**	**ALAT+P.A↑**

- **AUTRES ATTEINTES HEPATIQUES**

CIRRHOSE						
BX8800309	M,57	13 ans	C1,S1	ZYLORIC,13 ans, C1,S1 VISKEN,13 ans,C1,S1	U	autre étiologie
STEATOSE						
LY9500598	**F,59**			**EQUANIL** **LEVOTHYROX** **LOXAPAC** **ANAFRANIL** **ROHYPNOL**	**U**	**dossier succinct**

II. AUTRES ATTEINTES DIGESTIVES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DIARRHEE						
LY8600250	F,70	6 j	C2,S1		A	
MP8600156	M,60	2 mois	C3,S2	MODUCREN, C1,S1	A	
LY8700109	M,71	21 j	C2,S2	DIGOXINE	A	
BX8800223	M,40	3 j	C3,S2		A	
LY8800383	F,72	10 mois	C1,S1		F	
LY8800202	F,58	18 j	C2,S1		A	
MA9000721	F,29	3 j	C2,S2	DININTEL,C1,S2	A	
NC9200041	F,42	3 ans	C2,S2		A	
BR9300084	F,63	1 j	C2,S1	ZOCOR,C1,S1 ZYLORIC, C1,S1 ARMOPHYLLINE, C1,S1 DIAMICRON, C1,S1 BRICANYL, C1,S1	A	
NC9300212	M,75	47 j	C2,S2	DIACTANE, C1,S1	A	
DJ9400277	F,81	7 mois	C1,S2		U	
NC9500365	**F,70**	**2 sem.**	**C2,S2**	**BEFIZAL, C1,S2**	**A**	
CF9700156	**F,62**	**3 sem.**	**C2,S1**		**A**	
PANCREATITE						
MA9000382	M,40	6m	C2,S1	ISOMERIDE ,C2,S1	A	
MA9700296	**F,54**	**8j**	**C2,S1**		**A**	**autre étiologie!**
EPIGASTRALGIE						
LY8600060	M,72	13j	C2,S1		A	

Dans les 13 cas de diarrhée rapportés, le MEDIATOR est utilisé en monothérapie, ou son imputabilité est supérieure aux médicaments associés.

Cet effet indésirable est mentionné dans les RCP.

III. ATTEINTES HEMATOLOGIQUES

- Dans toutes les observations, il existe un traitement associé, qui peut être responsable de l'effet indésirable.
- Aucun nouveau cas n'a été rapporté depuis la mise au point de Juillet 1995

-Ils concernent 3 hommes (Age moyen = 60,7 ans) et 5 femmes (Age moyen = 55,6 ans)

Annexe 3-48

N°	S / Age	Durée TTT	Imput MEDIATOR	TTT associé / Imputabilité	Evol.	
THROMBOPENIE						
LY8500365	M,51	3 mois	C1,S1	RISORDAN, 4 ans, C1,S1 SECTRAL, 4 ans, C1, S1 TILDIEM, 7 mois, C1S1	U	
SE9100183	F,64	2 mois	C1,S1	TENSTATEN, 2m, C1S1 EFFERALGAN, C1S1	U	
PS9400301	F,61	?	C1,S1	GERIMAX, C1,S1 OROCAL, C1,S1 LEVOTHYROX, C1,S1	A	
NC9400153	F,19	2 mois	C2,S1	DOXYCLINE, 5j, C2,S1 ALDACTONE, 2m, C2,S1	A	
LEUCOPENIE						
MA8801234	F,58	2 mois	C1,S1	LIPUR, 2ans, C2,S1	A	
LYMPHOPENIE						
DJ8800131	F,76	6 j	C1,S1	DIGOXINE, C1,S1 CALCIPARINE, C1,S1 RYHTMPODAN, C1,S1	A	somnolence
MA9100793	M,59	8 j	C1,S1		A	hyperthermie
NEUTROPENIE + THROMBOPENIE						
NC8900022	M,72	2 ans	C1,S1	HEMIDAONIL, 6 ans, C1S1	A	

IV. ATTEINTES RESPIRATOIRES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION PULMONAIRE						
PP8990081	F,42	1 an	C1,S1	DININTEL, 5ans, C1,S1 Tenuate Dospan,5ans,C1,S1 FRINGANOR, 5ans, C1,S1	U	
NC9300007	M,48	4 ans	C1,S1	ISOMERIDE, 3 ans, C1,S1 ZYLORIC, 6 ans, C1,S1	F	
TOUX						
MA9000654	F,60	2 ans	C1,S1	ARTEX, 1 an, C1,S1 GLUCINAN, 2 ans,C1,S1	U	
NC9500265	**F,48**	**10mois**	**C1,S1**	**EUTHYRAL, 2mois, C1,S1**	**A**	
MA9600518	**F,63**	**8 mois**	**C1,S1**	**MONOTILDIEM, 1 an, C1,S1** **KARDEGIC, 1 an, C1,S1** **ADANCOR, 1 an, C1,S1**	**U**	
SYNDROME HEMORRAGIQUE INTRA-ALVEOLAIRE						
MP9500482	**F,45**	**1 mois**	**C1,S1**	**PONDERAL, 1 mois, C1,S1**	A	
TUBERCULOME						
SE9400175	F,46	2 mois	C1,S1	ISOMERIDE, 2 mois, C1,S1 DININTEL, 2 mois, C1,S1	A	autre étiologie !
FIBROSE INTERSTITIELLE						
NT9800036	**M,69**	**10 ans**	**C1,S1**	**DETENSIEL, C1,S1** **JOSIR, C1,S1** **LEXOMIL, C1,S1**	F	

Dans les 2 cas d'hypertension pulmonaire, il existe un traitement anorexigène associé : ISOMERIDE ou DININTEL, TENUATE DOSPAN et FRINGANOR.

Annexe 3-48

V. ATTEINTES CARDIOVASCULAIRES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERTENSION ARTERIELLE						
NC9100093	F,51	1an	C2,S2	RENITEC, C1S1 LOPRESSOR, C1S1	A	
CF9300241	F,73	6j	C2,S1		A	
SYNCOPE						
PP9010597	F,37	1j	C1,S2	Amfepramone, C1,S2 LUMITENS, C1,S2	A	
TACHYCARDIE						
GR9500235	**F,52**	**?**	**C1,S1**	**SOTALEX, C1,S1**	**A**	
NC8900097	F,60	1j	C2,S2	CERVOXAN, C1,S1 DIGOXINE, C1,S1	A	
FIBRILLATION AURICULAIRE						
LY9700643	**F,25**	**9 m**	**C2,S3**	**MODERATAN ,C2,S3 CANOL, C2,S3 TEALINE, C2,S3**	**A**	**Terrain dépressif**
EXTRASYSTOLES VENTRICULAIRES						
CN9500150	**F,?**		**C2,S1**		**A**	**dossier succinct**
CN9500151	**F,?**		**C1,S1**		**U**	**dossier succinct**
ACCIDENT VASCULAIRE CEREBRAL						
LL9700372	**F,39**	**3 mois**	**C2,S1**	**SPIRONONE, 3 mois, C2,S1**	**A**	
SYNDROME DE RAYNAUD						
PC9300059	M,63	3 mois	C1,S1	MINIDIAB, 2ans, C1,S1	F	
PC9700170	**F,30**	**2 sem.**	**C2,S2**		**A**	

VI. ATTEINTES RENALES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
DYSURIE						
BR9100053	F,42	?	C3,S1	VARNOLINE,C1,S1	A	
NC9300208	M,78	5 mois	C2,S2		A	
SE9700347	**F,?**	**2 j**	**C2,S1**		**A**	
POLYURIE						
BX8700115	F,40	7 mois	C2,S1		A	
POLLAKIURIE						
NC8800144	M,62	4 mois	C3,S1		A	
NC9300297	F,67	16 j	C2,S2		A	
ANURIE						
MA8900044	M,79	2 mois	C1,S1	ARTEX, 2mois, C1,S1 ZYLORIC, 2 mois, C1,S1 HEMIDAONIL, 2 mois, C1,S1 ALDACTAZINE, 2 mois,C1,S1	N	dossier succinct, non informatif

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GLOMERULONEPHRITE						
LY8700356	M,52	5 mois	C1,S1	ZYLORIC, C1,S1 DIAMICRON, C1,S1	U	
SYNDROME NEPHROTIQUE						
BX 9700689	**F,71**	**?**	**C1,S1**	**TROLOVOL, C1,S1** **LASILIX,C1,S1** **MONOTILDIEM, C1,S1** **TRINITRINE, C1,S1** **GLUCOPHAGE, C1,S1** **DAONIL, C1,S1** **VOLTARENE, C1,S1** **CYTOTEC, C1,S1** **AZANTAC, C1,S1**	F	

VII. ATTEINTES METABOLIQUES :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
HYPERLIPEMIE						
BX8600168	?,55	15j	C1,S1		U	
HYPOTHYROIDIE						
BS9600267	**F,86**	**?**	**C1,S1**	**DAONIL, C1,S1** **SERMION, C1, S1** **LIPANTHYL,C1,S1** **VASTAREL, C1,S1**	A	
GOUTTE						
LY8500568	M,71	8j	C2,S1	LASILIX, C3,S2	U	

Annexe 3-48

VIII. ATTEINTES CUTANEES et REACTIONS ALLERGIQUES :

Elles concement 13 hommes (Age moyen = 51,2 ans) et 23 femmes (Age moyen = 53,8 ans)

1 . Allergie, eczema :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
URTICAIRE						
CF8500013	M,50		C1,S2	LEXOMIL, C1,S2	A	
LY8700092	F,69	15 j	C3,S1		A	
TO9100366	M,34	7 j	C2,S2		A	
NC9400046	F,38	1 j	C3,S2		A	
MA9500024	M,45	3 mois	C3,S1	MAXEPA, C3,S1	U	
NY9507878	**M,61**	**2 mois**	**C2,S1**		**A**	
MA9700146	**F,50**	**1 j**	**C2,S2**		A	
OEDEME DE QUINCKE						
PA9200399	F,41	1 j	C2,S1	GLUCINAN, C2,S1	A	
MA9500231	F,56	1 j	C3,S1		A	
CHOC ANAPHYLACTIQUE						
DJ9200119	F,73	2 j	C3,S2		A	
MA9300967	F,50	8 j	C3,S2		A	
MA9400018	F,?	1 j	C3,S2		A	
MA9700036	**F,60**	**1j**	**C2,S2**		**A**	
ALLERGIE						
LY9300329	F,53	12j	C3,S2		A	
ECZEMA						
NC9300394	F,?	3 ans	C1,S2		F	
MA9500621	**F,68**	**2 ans**	**C2,S2**		**A**	
NY9809751	**M,70**	**10 mois**	**C1,S1**	**MOPRAL, C1,S1** **GLUCOR, C1,S1**	**F**	
SUDATION EXCESSIVE						
PA9240186	F,79		C1,S2	DIAMICRON, C1,S2 MEDIATENSYL, C1,S2 BRUFEN, C1,S2	A	

Parmi les réactions allergiques, on note:

- **7 cas d'urticaire**
- **2 oedèmes de Quincke**
- **4 chocs anaphylactiques**
- **1 allergie cutanée**

Le délai de survenue est le plus souvent ytrès rapide (1 jour).

Parmi les 3 cas d'eczéma, l'évolution est favorable dans un seul cas!

Annexe 3-48

2. Eruption, vascularite, purpura

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Ev.	
ERUPTION						
DJ9100155	M,31	10j	C3,S2		A	éruption érythémateuse
MP9300201	F,36	1 mois	C1,S1	DOLIPRANE, 1j,C1,S1 CLARADOL, 1j, C1,S1	A	éruption érythémateuse, prurit
PA9333879	F,54	5 sem.	C1,S1	GLUCOPHAGE,3 sem,C1,S1	U	prurit
MA9500227	**M,38**	**16j**	**C3,S1**		**A**	**éruption prurigineuse**
LY9700381	**F,56**	**11 sem.**	**C2,S1**	**LIPANTHYL, 11 SEM, C2S1**	**A**	**éruption**
MA9300723	F,41	1 cp	C2,S1	HEXALYSE,1cp, C2,S1	A	éruption maculopapul.
LY9400078	F,46	1 mois	C2,S1	TOCO 500, C1,S1 CYCLO 3, C1S1 CONFLICTAN, C1,S1 LEXOMIL, C1,S1	A	éruption maculeuse, prurit
LM9100055	M,56	1 an	C1,S1	DETENSIEL, C1,S2 DIDRONEL, C1,S1	U	prurigo
NC9100505	F,48	1 mois	C2,S2	SOPROL, 1 mois, C2S2	A	éruption pustuleuse
NC9100194	M,60	15 j	C2,S1	EUPRESSYL, C2,S1	A	érythème polymorphe
MA9700614	**F,50**	**3 mois**	**C1,S2**	**TANAKAN, C1,S2** **MEGAMAG, C1,S2**	**U**	**érythème polymorphe**
NY9300951	M,68	6 mois	C2,S1		A	érythème polymorphe
MP9700134	**F,58**	**6 j**	**C1,S1**	**SECTRAL** **BOP** **LEVOTHYROX**	**F**	**vascularite**
RE9420042	M,41	4 j	C1,S1	SORBITOL	A	vascularite
MA9700957	**F,50**	**8 ans**	**C1,S1**	**STAGID, 8 ANS, C1,S1**	**A**	**vascularite**
PP8990384	F,75	3 sem.	C2,S1	DAONIL, C1,S1 STAGID, C1,S1 TILDIEM, C1,S1 NATIROSE, C1,S1	A	purpura
CF9200106	F,67		C2,S2	VASTAREL, C2,S2 DAFALGAN, C2,S2 ELISOR, C2,S2	A	purpura
PO9700410	**M,47**	**2 sem.**	**C1,S1**	**ATHYMIL,C1,S1**	**F**	**purpura rhumatoide**
PA9739366	**M,65**	**8 mois**	**C1,S1**	**COZAAR, 5 j, C1,S1** **DAONIL, 8 mois, C1,S1** **GLUCOPHAGE, 8 m., C1,S1** **ZYLORIC, 33 mois, C1,S1** **LOXEN, 33 mois, C1,S1**	**A**	**lichen plan**
NC9400417	F,20	1 mois	C1,S2		F	acné

Annexe 3-48

Les éruptions cutanées sont variées

- 3 cas d'érythème polymorphe, avec une évolution favorable à l'arrêt du MEDIATOR, chez 2 hommes agés de 60 et 68 ans.

- 3 notifications de vascularite aigue leucocytoclasique:
  - dans 1 cas, l'évolution est favorable à l'arrêt du MEDIATOR (RE9420042)
  - dans 1 cas, l'évolution est favorable sans arrêt du MEDIATOR , mais avec un traitement corticoïde (lorsque la corticothérapie est arrêtée, 4 moisplus tard, survient un érythème polymorphe :MA9700957)
  - dans le troisième cas (MP9700134), l'évolution n'est pas complète malgré l'arrêt du MEDIATOR et une corticothérapie.

- 3 cas de purpura:
  - purpura des membres inférieurs avec un oedème apparu une semaine après le début du traitement par MEDIATOR (PP8990384)
  - purpura des membres inférieurs, s'étendant aux membres supérieurs, disparaissant 1 semaine après l'arrêt du traitement (CF9200106)
  - purpura rhumatoïde survenant après 2 semaines de traitement, l' évolution est inconnue (PO9700410)

IX. ATTEINTES NEURO-PSYCHIATRIQUES :

Elles concernent 18 hommes (Age moyen : 54,5 ans) , 25 femmes (Age moyen : 58,7 ans)

1. Asthénie, Somnolence, Impuissance :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
ASTHENIE						
LM8600219	M,56	2 ans	C2,S2		A	
TO8900326	M,49	1 mois	C1,S1		F	
MA9300480	F,45	6 mois	C2,S1	PRAXINOR, 1 mois, C2,S1 PONDERAL, C1,S1	A	
LY9600435	**F,53**	**8 sem.**	**C2,S1**	**GLUCOPHAGE, 8 sem., C2,S1** **PROZAC**	**A**	
SOMNOLENCE						
DJ8800131	F,76	?	C2,S2		A	+ lymphopénie
TO9200397	F,64	6 j	C3,S2		A	
MA9300577	F,42			ISOMERIDE		
RE9510102	**F,69**	**4 j**	**C2,S1**	**LASILIX, C1,S1** **PREVISCAN, C1,S1** **COVERSYL, C1,S1** **INSULATARD, C1,S1**	**A**	
IMPUISSANCE						
NC9500466	**M,55**	**3 j**	**C3,S2**		**A**	

Dans la plupart des observations:
- soit le délai de survenue semble long : 2ans (LM8600219) ou inconnu (DJ8800131)
- soit le traitement associé peut être responsable de tels effets: PROZAC, GLUCOPHAGE...

Cet effet indésirable est mentionné dans les RCP.

Annexe 3-48

2. Troubles psychiatriques :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
TROUBLES PSYCHIATRIQUES						
LY9600963	**M,45**	**1 mois**	**C1,S1**	**LEXOMIL, C2,S1**	**A**	**agressivité**
NC9700094	**F,74**	**6 j**	**C2,S2**		**A**	**agressivité**
MA8900523	F,40		C1,S1	ISOMERIDE, 1j, C2,S1	A	agitation
NC9300347	M,39	11 mois	C2,S2		A	irritabilité
NC9500171	F,50	1 cp	C3,S2		A	nervosité
NC9300349	M,50	9 mois	C2,S2	LOPRIL, C1,S1	A	dépression
MA9100069	M,40	1 j	C2,S2		A	angoisse
TS9500338	**F,69**	**8 j**	**C2,S1**	**DAONIL, C1,S1** **ALPRESS** **BITILDIEM** **DIAMICRON...**	A	**stupeur**
LY8900392	M,52	20 j	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1	A	cauchemars
SE9500017	F,41	84 j	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1	A	confusion
CF9000137	F,79		C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2	A	désorientation
RN9500096	**F,59**	**73 j**	**C1,S2**	**LIPANTHYL, C1,S2** **PILOSURYL, C1,S2** **CANOL, C1,S2** **OLIVIASE, C1,S2** **Amfépramone, C1,S2**	A	**délire**
GR8700216	M,45	16 j	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1	A	délire

Les troubles psychiatriques sont divers : la responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue.

3. Troubles neurologiques :

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
CONVULSION						
PA9223988	M,60	?	C2,S1	TENSIONORME, C2,S1 DIFFU K	A	
NEUROPATHIE						
MA8700716	M,73	9 ans	C1,S1	HEMOCLAR TORENTAL	U	autre étiologie!
PARESTHESIE						
BX8800193	M,36	8 j	C1,S1	PRAXINOR, 8j, C1,S1	F	
LM9500090	M,61	4 j	C2,S1		A	
MA9700170	**F,42**	**1 j**	**C2,S2**	**TAMIK, C1,S1**	**U**	

Annexe 3-48

X. TROUBLES DE L'EQUILIBRE, VERTIGES

Ils concernent 5 hommes (Age moyen: 64 ans) et 11 femmes (Age moyen : 60,5 ans)

N°	S / Age	Durée TTT	Imput. MEDIATOR	TTT associé / Imputabilité	Evol.	
VERTIGE, TROUBLE DE L'EQUILIBRE						
BX9500092	M,34	3 mois	C3,S2		A	
MA8800356	F,60	1 j	C2,S2		A	
MA8800929	F,47	1 cp	C2,S2	DAFLON, C1,S1	A	
NC9000297	F,58	15 j	C3,S2		A	
LL9200133	F,63	2 j	C1,S1		U	
NY9306790	F,77	2 j	C1,S2		A	
LM9500091	F,84		C2,S1	SOTALEX, C1,S1 LOXEN, C1,S1 ALDACTONE, C1,S1 CORDIPATCH, C1,S1 PREVISCAN, C1,S1	U	
TS9600227	**F,64**	**4 sem.**	**C3,S1**	**RENITEC, C1,S1** **LIPANTHYL, C1,S1**	**A**	
BX9701040	**M,74**	**4 sem.**	**C2,S1**	**PREVISCAN, C1,S1** **DAONIL, C1,S1** **CAPTOLANE, C1,S1** **GLUCOPHAGE, C1,S1**	**A**	
BX9701041	**M,78**	**10 j**	**C2,S1**	**DAONIL** **CORDARONE** **ASPEGIC** **GLUCOR**	**A**	
NC8900097	F,60	1 cp	C2,S2		A	
MA8700143	F,66	?	C1,S1	FLUVERMAL, C1,S1	F	
BX9701023	**F,63**	**9 sem.**	**C2,S1**	**AVLOCARDYL** **DAFLON** **DAONIL** **LASILIX** **GLUCOR** **TRANXENE** **IMOVANE**	**A**	
BX9700381	**M,63**	**4 sem.**	**C2,S1**	**DAONIL**	**A**	
BX9700301	**M,71**	**6 sem.**	**C2,S1**	**LOPRIL** **CORDARONE** **VASTAREL** **PRAXILENE** **EUGLUCAN**	**A**	
BX971022	**F,24**	**7 mois**	**C2,S1**	**DIAMICRON** **MOPRAL** **TILDIEM** **ALDACTAZINE** **LYSANXIA**	**A**	

16 cas ont été notifiés: il s 'agit de patients agés,en général, avec une pathologie lourde : diabète, insuffisance cardiaque...

Cet effet indésirable est mentionné dans les RCP.

Annexe 3-48

VIDAL 1992

☆ MEDIATOR®

benfluorex

FORMES et PRÉSENTATIONS

Comprimé enrobé (blanc) : Boîte de 30.

Modèle hospitalier : Boîte de 100, sous plaquette thermoformée unidose.

COMPOSITION

	p cp	*p boîte*
Benfluorex chlorhydrate	150 mg	4,5 g

Excipients : amidon de maïs, carmellose sodique, cire d'abeille blanche, éthylcellulose, stéarate de magnésium, oléate de glycérol, polysorbate 80, povidone, silice colloïdale, saccharose, bicarbonate de sodium, talc, dioxyde de titane.

DC INDICATIONS

- Adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable.
- Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.

Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

DC POSOLOGIE et MODE D'ADMINISTRATION

3 comprimés par jour.

Cette posologie peut être prescrite d'emblée ou atteinte progressivement :

- 1 comprimé la première semaine au dîner,
- 2 comprimés la deuxième semaine : 1 au déjeuner, 1 au dîner,
- 3 comprimés à partir de la troisième semaine : 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

Par la suite, la posologie peut être ramenée à 2, parfois 1 comprimé par jour, en fonction des résultats biologiques.

Coût du traitement journalier : 1,43 à 4,29 F.

En association avec le régime, Mediator constitue un traitement symptomatique devant être très prolongé et régulièrement surveillé.

DC CONTRE-INDICATIONS

Pancréatites chroniques avérées.

DC MISES EN GARDE et PRÉCAUTIONS D'EMPLOI

Mises en garde :

Les troubles métaboliques relevant d'un traitement par Mediator sont essentiellement observés chez l'adulte. La prescription de Mediator n'est donc pas justifiée chez l'enfant.

Précautions d'emploi :

Si, après une période d'administration de quelques mois (3 à 6 mois), une réduction satisfaisante des concentrations sériques de lipides n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

DC GROSSESSE et ALLAITEMENT

Grossesse : Les résultats des études réalisées chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence de données dans l'espèce humaine, ces résultats expérimentaux ne permettent pas de préjuger un effet malformatif. Cependant, par mesure de prudence, ne pas prescrire pendant la grossesse.

Allaitement : En l'absence de données sur le passage dans le lait maternel, l'allaitement est déconseillé pendant la durée du traitement.

DC EFFETS INDÉSIRABLES

Les effets secondaires suivants ont été observés : digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.

DC SURDOSAGE

Conduite à tenir en cas d'absorption massive : le traitement sera purement symptomatique : lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience, des fonctions respiratoire et cardiaque.

PP PHARMACODYNAMIE

Hypolipémiant :

Il agit sur plusieurs facteurs liés au risque athérogène.

- Actions de Mediator sur le métabolisme lipidique :
  - Mediator diminue l'absorption intestinale des triglycérides (rat). Cet effet, confirmé chez l'homme en pharmacologie clinique, repose sur la diminution d'activité de la lipase pancréatique.
  - Il réduit la synthèse hépatique des triglycérides et du cholestérol in vitro et in vivo (rat).
  - Il diminue la stéatose hépatique induite par des régimes riches en lipides, en glucides chez le rat obèse et au cours du diabète expérimental (rat).
  - Il limite l'incorporation du cholestérol dans la paroi artérielle (lapin).

  Ce mode d'action est susceptible d'expliquer la diminution du cholestérol et des triglycérides chez l'homme.
- Actions de Mediator sur le métabolisme glucidique :
  - Il facilite la pénétration et l'utilisation cellulaires du glucose (rat).
  - Il diminue l'hyperglycémie du rat diabétique (insulinoprive ou non) et l'aire d'HPO chez le lapin.
  - Dans le diabète asymptomatique chez les patients obèses, il entraîne une baisse de la glycémie postprandiale et une amélioration de la courbe d'HPO supérieure à celle qu'on obtient avec un régime identique associé à un placebo.

  Mediator, n'ayant pas d'action sur l'insulinosécrétion, ne peut pas provoquer d'hypoglycémie.
- Effet complémentaire de Mediator :

  Chez des patients obèses hyperuricémiques traités par Mediator et régime, une baisse de l'uricémie d'environ 14 % a été observée.

Aucune interférence indésirable de Mediator avec les traitements associés au cours des études n'a été constatée.

Mediator :

- ne potentialise pas les anticoagulants,
- ne provoque pas d'hypoglycémie,
- n'interfère pas avec la fonction thyroïdienne.

PP PHARMACOCINÉTIQUE

- Absorption gastro-intestinale rapide et totale avec un pic maximal survenant entre 1 et 2 heures après l'administration.
- Élimination rapide et totale par voie urinaire : en 8 heures, une excrétion moyenne d'environ 74 % de la dose administrée est constatée.

  L'élimination se fait en 2 phases :
  - une première phase rapide (60 % en 3 ou 4 heures),
  - une deuxième phase lente, se terminant en 36 heures environ.

LISTE I

AMM 317 557.9 (1974, validée 1987) 30 comprimés.
317 559.1 (1974, validée 1987) 100 comprimés.

PRIX : 42,90 F (30 comprimés).

Remb Séc soc à 65 %. Collect.

BIOPHARMA
Information médicale :
29, rue du Pont. 92200 Neuilly-sur-Seine
Tél : 01 46 41 60 00
Les Laboratoires Servier
22, rue Garnier. 92200 Neuilly-sur-Seine

l'Assurance Maladie
des salariés - sécurité sociale
caisse nationale

1722

Annexe 3-49

Service Médical

Date 11 SEP. 1998

Madame la Ministre
Ministère de l'Emploi et
de la Solidarité
8 avenue de Ségur
75350 PARIS CEDEX 07 SP

A l'attention de Mr le Pr Joël MENARD
Direction Générale de la Santé

Réf : 1948/98

Objet : Prescription du MEDIATOR

Je vous prie de trouver ci-joint, copie du courrier que j'adresse à Monsieur Jean-René BRUNETIERE, Directeur Général de l'Agence du Médicament, au sujet de la prescription du MEDIATOR.

Vous en souhaitant bonne réception.

Le Médecin Conseil National Adjoint

Dr Alain ROUSSEAU

Direction Générale de la Santé
14 SEP. 1998

PJ : 2

COURRIER ARRIVÉ LE
14 SEP. 1998
DIRECTION GÉNÉRALE
DE LA SANTÉ

CNAMTS
66, avenue du Maine
75694 Paris Cedex 14 Télécopie : 01.43.21.48.19

C.N.A.M.T.S
66 avenue du Maine
75694 PARIS CEDEX 14

C.A.N.A.M.
1723Centre Paris-Pleyel
93521 SAINT-DENIS CEDEX

C.C.M.S.A.
8 rue d'Astorg
75380 PARIS CEDEX 08

Annexe 3-49

11 SEP. 1998

Mr Jean-René BRUNETIERE
Directeur Général
Agence du Médicament
143 - 147 Bd Anatole France
93285 SAINT-DENIS CEDEX

Objet : Prescription de MEDIATOR.

Monsieur le Directeur Général,

L'Union Régionale des Caisses d'Assurance Maladie (URCAM) de Bourgogne a réalisé une étude[1] portant sur les modalités d'utilisation de la spécialité MEDIATOR® (Benfluorex).

Il est constaté qu'un nombre important de cas (environ 1/3) correspond à des prescriptions médicales se situant hors du champ des indications thérapeutiques prévues par l'Autorisation de Mise sur le Marché (adjuvant du régime dans les hypertriglycéridémies ou traitement du diabète asymptomatique avec surcharge pondérale), notamment dans le cadre de traitements à visée amaigrissante.

En conséquence, il nous est apparu nécessaire de vous transmettre les résultats de cette étude même si, en l'absence de données issues du codage pharmacie, ceux-ci ne peuvent être exhaustifs.

Face aux constats établis par les praticiens conseils, il nous apparaîtrait particulièrement opportun de procéder à une réévaluation de l'utilité du MEDIATOR dans la stratégie thérapeutique de la maladie diabétique et dans celle des hyperlipidémies.

D'autre part, il nous semble également utile d'alerter l'Agence du médicament sur l'utilisation non contrôlée d'un produit de structure amphétaminique, dans un but anorexigène. Il est en effet, assez paradoxal de constater que la prescription de MEDIATOR est tout à fait libre tandis que celle des médicaments du groupe des amphétamines est strictement encadrée depuis mai 1995.

[1] 2 documents joints en annexe.

Enfin, il convient de rappeler que la présente démarche relève d'une volonté de promouvoir la qualité des soins qui s'inscrit dans le cadre des missions de santé publique dévolues aux organismes d'assurance maladie.

Nous vous prions de croire, Monsieur le Directeur Général, à l'assurance de nos sentiments distingués.

Le Médecin Conseil National de la C.N.A.M.TS.

Pr Hubert ALLEMAND

Le Médecin Conseil National de la C.A.N.A.M.

Pr Claudine BLUM-BOISGARD

Le Médecin Conseil National de la M.S.A.

Pr Patrick CHOUTET

Annexe 3-49

MINISTERE DE L'EMPLOI ET DE LA SOLIDARITE

SECRETARIAT D'ETAT A LA SANTE
8, Avenue de Ségur - 75007 PARIS
☎ : 01.40.56.60.00

Expéditeur	:	Monsieur Gilles DUHAMEL
Fonction	:	Conseiller Technique
☎	:	01.40.56.49.88
Fax	:	01.40.56.73.47

Destinataire	:	**Mme E. MENGUAL** **Adjoint au Directeur Général de la Santé**
Fax	:	646 74
Nb de Pages	:	1 + 1

POUR REMISE IMMEDIATE

Paris, le 1er/07/88

OBJET

Dépêche AFP a/s du Médiator

Pour information

Merci de nous consulter en cas de mauvaise réception au numéro indiqué

Copie faite à PM

Annexe 3-49

FRS0333 4 GTF 0312 FRA /AFP-NF76
Santé-médicaments

Le Médiator, un médicament détourné de ses indications thérapeutiques

DIJON, 1er juil (AFP) - Le médicament appelé Médiator, classé parmi les amphétamines, est fréquemment détourné de ses indications thérapeutiques pour servir d'amaigrissant, révèle une étude menée par l'Union régionale des caisses d'assurance maladie (URCAM) de Bourgogne.

Le Médiator, classé par l'Organisation mondiale de la santé (OMS) parmi le groupe des amphétamines, mais non soumis en France à la législation qui s'y rapporte, est normalement prescrit comme adjuvant des traitements du diabète avec surcharge pondérale. Mais l'étude, menée sur 568 prescriptions du médicament présentées au remboursement en Bourgogne pendant 5 jours en avril 1997, montre qu'il est utilisé comme amaigrissant dans un tiers des cas.

L'URCAM de Bourgogne, jugeant les risques pour la santé importants, préconise le reclassement de ce médicament dans le groupe des amphétamines, ce qui implique une prescription restreinte. L'URCAM s'interroge également sur la légitimité à rembourser un médicament dont les indications thérapeutiques ne sont pas respectées. Le Médiator représente effectivement une dépense annuelle potentielle d'environ 4 millions de francs pour la seule Bourgogne.

Ce détournement du médicament lui semble d'autant plus grave que 66% des patients ne présentent pas d'obésité avérée. Deux patientes présentaient même un état de maigreur, indique le rapport de l'étude. De même, 20 % des médecins ne peuvent pas fournir d'information sur la taille et le poids du patient auquel ils ont prescrit ce médicament.

L'étude de cette structure régionale, créée début 97 pour être la pièce essentielle de la réforme de la Sécurité sociale, fait partie d'autres menées par les URCAM de France pour apprécier quels sont les médicaments utilisés de manière frauduleuse.

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PH

G 1-7

GS → JRB

Pour suite éventuelle à donner

en Assu ?

et en Transparence

Me Fleur informée SVP

G 1/7/98

cc DGS
DSS

Union régionale des Caisses d'Assurance Maladie
URCAM Bourgogne

Faut-il revoir les conditions de prises en charge du MEDIATOR ?

Etude sur le respect des indications thérapeutiques

Dossier de présentation

14, rue Jean Giono
21000 Dijon
tél : 03.80.78.80.16
télécopie : 03.80

17/11 2010 10:10 IFAX Date:10:09:01 17/11/2010 De:CPAM COTE D'OR fax:0380593763 ID:43428 page :3 /12 0002/0011

MARS 1998

Sommaire

1. Analyser la réalité de la prescription d'une spécialité pharmaceutique
2. Quelle est l'utilité médicale du Médiator ?
3. Pourquoi le Médiator n'est-il pas classé comme anorexigène ?
4. Le Médiator est utilisé associé à des traitements à visée amaigrissante
5. Le Médiator : un enjeu économique
6. Faut-il reconsidérer les conditions de mise sur le marché du Médiator ?

- Fiche signalétique de l'étude réalisée en Bourgogne sur la prescription du Médiator
- L'URCAM de Bourgogne : agir ensemble pour la santé.

MARS 1998

Analyser la réalité de la prescription d'une spécialité pharmaceutique

L'Union régionale des caisses d'Assurance Maladie de Bourgogne a choisi en 1997 d'étudier la prescription du Médiator dans les quatre départements de la région.
Le Médiator est un adjuvant des traitements du diabète asymptomatique avec surcharge pondérale et des hypertryglycéridémies.
Or, les praticiens conseils des organismes d'assurance maladie ont détecté cette spécialité dans des traitements à visée amaigrissante.
Par ailleurs, le Médiator dont le principe actif est le Benfluorex fait en réalité partie du groupe des amphétamines, mais de part ses indications thérapeutiques, n'est pas soumis à la législation qui s'y rapporte.

Au delà des aspects de « santé publique » liés à des prescriptions inutiles voire dangereuses pour la santé, le constat d'une utilisation du Médiator en dehors du champ des indications reconnues et validées, pose également une question d'ordre économique. L'Assurance maladie doit-elle prendre en charge des prescriptions qui ne répondent pas à une utilité médicale ?

Aussi, l'URCAM de Bourgogne a décidé d'analyser plus précisément le réel respect des indications du Médiator et de rechercher les détournement éventuels de ce médicaments pour des traitements à visée amaigrissante.

Toutes les ordonnances accompagnant les feuilles de soins présentées au remboursement ont ainsi été analysées pendant une semaine avril 1997/

Parallèlement à la démarche de l'URCAM de Bourgogne, des interrogations se sont fait jour sur l'utilité médicale réelle du Médiator. Ainsi, deux articles sont parus en mai et en décembre 1997 dans La Revue ***Prescrire***.
Ainsi, il est estimé que « *l'on ne sait toujours pas à quoi sert ce médicament administré au diabétique* [1] » et « *qu'il n'y a actuellement aucune raison de traiter les patients ayant une hypertriglycéridémie avec le Benfluorex* » [2].
La Revue ***Prescrire*** va jusqu'à conclure que « *le maintien sur le marché et la prise en charge par l'assurance maladie de ce médicament doivent être reconsidérés* » [1][2]

Les deux réflexions motivaient donc une étude précise de l'utilisation réelle du Médiator.

[1] tome 17 N°173 page 328
[2] tome 17 °179 page 809

MARS 1998

Quelle est l'utilité réelle du Médiator ?

Le Médiator a comme indications thérapeutiques actuellement inscrites à l'autorisation de mise sur le marché :

« Adjuvant du régime adapté dans les hypertriglycéridémies, la poursuite du régime étant toujours indispensable.
Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale »

Il est également remarqué dans ces indications que « *l'efficacité du Médiator pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.* »

Différentes analyses médicales ont été menées récemment sur le Médiator, notamment par la revue ***Prescrire*** (N° de mai et de décembre 1997).
Leurs conclusions amènent à s'interroger sur l'utilité du Médiator tant pour le traitement des diabétiques asymptomatiques que chez les patients atteints d'hypertriglycéridémie.

En effet, le dossier d'évaluation clinique du Médiator apparaît de mauvaise qualité méthodologique :

- les essais versus placebo n'ont pas apporté la preuve convaincante d'un éventuel effet.
- les essais versus autre molécules pharmacologiques sont ininterprétables.

Par ailleurs, actuellement on ne connaît pas de donnée claire et indépendante sur les effets indésirables du Médiator.

MARS 1998

Pourquoi le Médiator n'est-il pas classé comme anorexigène. ?

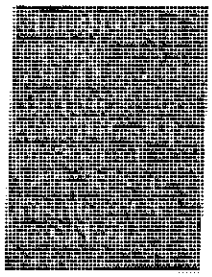
« Le principe actif du Médiator est le benfluorex, proche de substances anorexigènes. D'ailleurs, son suffixe en « orex » est attribué aux dénominations communes internationales des substances anorexigènes par l'Organisation Mondiale de la Santé. Dans le Vidal 1997, le Benfluorex figure dans le groupe des « amphétamines et autres excitants » (*Revue Prescrire*)

Ainsi, bien que faisant partie d'une liste de substances anorexigènes (arrêté du 25 octobre 1995 Journal Officiel) qui ne doivent être incorporées dans des préparations magistrales, le Médiator ne fait pas l'objet d'une prescription restreinte.

On ne peut que s'étonner de cet état de fait qui prend une dimension particulière lorsque l'on pose parallèlement la question de l'utilité réelle du Médiator sur un plan médical.

MARS 1998

Le Médiator est utilisé dans le cadre de régimes à visée amaigrissante



Parallèlement aux analyses médicales sur l'utilité du Médiator, l'URCAM de Bourgogne a entrepris une étude sur le respect de ses indications thérapeutiques .

Dans les quatre départements de la région, un échantillon de 568 prescriptions de Médiator présentées au remboursement pendant 5 jours en avril 1997 a été analysé.

Dans 35 % des cas, les indications thérapeutiques ne sont pas respectés. Ce taux monte à 43 % chez les patients de sexe féminin. Or 69 % des prescriptions concernent des femmes.

En fait, près de la moitié des cas de non respect de l'indication thérapeutique du Médiator concernent des personnes polymédicamentées à visée amaigrissante. Ce taux atteint 86 % des prescriptions délivrées à la population de sexe féminin.

De surcroît, l'étude de l'indice de Masse Corporelle montre que dans le cadre de traitements à visée amaigrissante, 20 % des médecins ne peuvent pas fournir d'information sur le poids et la taille de leur patient.
45 % ne retrouvent pas, ne possèdent pas ou n'ont pas fait réaliser de bilan biologique et enfin 66 % des patients ne présentent pas d'obésité avérée (IMC < 30) ou tout au moins ne justifient pas de tels traitements. Par ailleurs, deux patientes présentent un état de maigreur (IMC <20).
On peut alors s'interroger sur les raisons qui ont poussé le médecin à prescrire en dehors de l'indication thérapeutique...

MARS 1998

Le Médiator : un enjeu économique

Au delà des aspects médicaux, l'analyse économique des ordonnances étudiées dans le cadre de l'étude de l'URCAM de Bourgogne permet d'estimer que le coût annuel des prescription de Médiator pour l'Assurance maladie est d'environ 4 millions de francs par an sur la seule région, soit envoi 2 % des dépenses remboursées annuellement en Côte d'Or.

Ainsi bien qu'adjuvant d'un traitement, le Médiator n'en a pas moins de réelles implications économiques. Porté sur l'ensemble des régions, l'enjeu financier n'est pas négligeable.

MARS 1998

[redacted]aut-il reconsidérer les conditions de mise sur le marché du Médiator ?

L'étude réalisée sur le respect des indications du Médiator conjuguée aux différentes analyses médicales sur l'utilité de cette spécialité amène à s'interroger sur la pertinence de son classement thérapeutique, mais aussi de son remboursement à 65 % par l'Assurance maladie.

Ainsi, un reclassement dans le groupe des amphétamines avec la législation qui s'y rapporte (prescription restreinte) apparaît être la mesure de premier niveau nécessaire .
Au -delà, on peut s'interroger sur la légitimité à rembourser un médicament dont les indications thérapeutiques ne sont pas respectées et ne répondent donc pas à un souci de qualité, de sécurité et d'efficacité.

MARS 1998

Etude du respect des Indications thérapeutiques du Médiator en Bourgogne

Fiche signalétique de l'étude

Le médecin est tenu de signaler sur l'ordonnance le cas où il prescrit un médicament en dehors de l'indication thérapeutique pour laquelle le produit a été admis au remboursement.

Une étude du Médiator a été réalisée pendant 5 jours en avril 1997 dans les quatre département de Bourgogne. Toutes les prescriptions de Médiator présentées au remboursement par les malades pour l'ensemble des praticiens de Bourgogne ont été concernées par l'enquête. Les praticiens conseils de l'Assurance maladie ont pu ainsi estimer la pratique médicale des prescriptions en évaluant les écarts retrouvés entre les motifs des prescriptions et les indications thérapeutiques du Médiator.
Outre les données d'ordre administratif tels que le sexe du patient, la date de prescription, les données médicales comme le poids, la taille, les résultats des examens biologiques réalisés, les traitements amaigrissants associés ont également été analysés.

Pourquoi une étude sur le Médiator ?
Deux raisons :

- la connaissance du terrain par les praticiens conseils de l'Assurance maladie a permis de détecter le Médiator dans certaines prescriptions à visée amaigrissante, en dehors de ses indications thérapeutiques;
- le Médiator est un traitement adjuvant, donc non majeur, dont les indications sont claires et facilement vérifiables.
  Par ailleurs, c'est la seule molécule qui bien que faisant partie du groupe des amphétamines » n'est pas soumise à la législation de ces spécialités pharmaceutiques.

Qualité de l'échantillon.
568 ordonnances ont été saisies manuellement lors du traitement des dossiers présentés au remboursement sur une période de 5 jours. Si une déperdition a eu lieu, elle est par définition involontaire, liée au hasard et n'influence pas les structures de l'étude.
On note toutefois que quelque soit le régime d'assurance maladie (régime général, mutualité sociale agricole ou assurance maladie des professions indépendantes), la structure de l'échantillon est la même.

L'Indice de masse corporelle (IMC) n'a pu être calculée pour 264 patients. Leurs poids et leur taille n'ont pas pu être fournis par le médecin traitant. Il n'a pas été choisi de convoquer les malades dans le cadre d'une étude. Les avis par rapport à l'IMC ont donc concernés 304 dossiers.

Les avis sur le respect ou non des indications thérapeutiques ont été cependant donnés sur l'échantillon complet.

Choix de l'IMC pour définir l'obésité;
Ce choix a été fait après analyse de la littérature et semble le plus objectif pour apprécier la pertinence de traitement à visée amaigrissante.

MARS 1998

URCAM de Bourgogne : Agir ensemble pour la santé

Pièce essentielle de la Réforme de la sécurité sociale inscrite dans les Ordonnances de 1996 et concrétisée par le décret d'octobre 1997, la mise en place des Unions régionales des caisses d'assurance maladie marque une étape décisive dans la déclinaison d'une véritable politique de santé, conjuguant l'amélioration constante de la qualité et de l'efficience du système de soins et la régulation des dépenses de soins de ville.

En Bourgogne, comme dans les autres régions, l'Union régionale est un lieu de concertation et d'analyse des données médicales et de santé pour permettre une meilleure efficacité des actions des caisses, tous régimes confondus, et de leurs services de médecin-conseil.

L'activité de l'Union régionale se centrera sur deux pôles essentiels :

- la santé publique : l'URCAM sera le lieu où s'élaborera la politique de prévention et d'éducation pour la santé qui permettra à l'Assurance Maladie de répondre aux priorités arrêtées par les conférences nationale et régionale de santé.

- l'analyse et l'expertise en matière de comportements et de pratiques médicales : l'URCAM proposera à ses partenaires, que sont notamment l'Agence Régionale de l'hospitalisation et l'Union régionale des médecins libéraux , de mener ensemble des actions pour une meilleure prise en charge des malades.

Petite structure de 8 personnes et forte d'un conseil d'administration représentant les assurés sociaux et les employeurs bourguignons, l'URCAM ne se substitue pas aux caisses locales qui restent les interlocuteurs de proximité des professionnels de santé et des assurés. Elle vient fédérer leurs actions.

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Directeur : Vincent Ravoux

Annexe 3-49

Médiator

Contrôle du respect de l'indication thérapeuthique

998

es médicaux des Régimes d'Assurance Maladie

MALE DES CAISSES D'ASSURANCE MALADIE
RCAM
Bourgogne

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UNION NATIONALE DES CAISSES D'ASSURANCE MALADIE
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Annexe 3-49

RESUME

OPPORTUNITE DE L'ETUDE

- les ordonnances du 24/04/1996 créant les URCAM.
- mise en place en Bourgogne d'un comité opérationnel régional de gestion du risque dans l'attente de celle officielle de l'URCAM.
- le domaine d'intervention sur le poste pharmacie a été dégagé comme prioritaire par le comité opérationnel régional.
- les indications thérapeutiques sur le MEDIATOR sont précises et claires avec des indicateurs objectifs.
- des anomalies ont été constatées lors de contrôles antérieurs (régimes amaigrissants).

OBJECTIFS

- vérifier le respect des indications thérapeutiques du MEDIATOR pour lesquelles cette molécule a été admise au remboursement .
- rechercher les détournements de ce médicament à usage de régime à visée amaigrissante et cibler les médecins coutumiers de ce fait.
- Vérifier le respect des règles de délivrance.
- Cette étude doit se dérouler selon deux modalités :
  - une première phase pédagogique, sous la forme d'une enquête collective dont les résultats sont présentés ci-dessous
  - et une seconde phase normative sous la forme de contrôles individuels ciblés à l'issue de l'enquête initiale.

La première phase s'est faite à partir des prescriptions de MEDIATOR reçues sur une semaine de liquidation au printemps 1997 par l'ensemble des caisses d'Assurance Maladie de la BOURGOGNE. Une communication des résultats à l'ensemble des prescripteurs sera faite à l'issue de cette première analyse.

METHODOLOGIE

Dans la phase collective, l'avis du médecin conseil sur le respect de l'indication thérapeutique du MEDIATOR et sur l'existence d'un traitement associé à visée amaigrissante est donné sur un questionnaire papier après demande de renseignements auprès du prescripteur concerné.

Outre des données d'ordre administratif (identification prescripteur, sexe du patient, date de la prescription), il est relevé sur ce questionnaire des données médicales telles que les poids et taille du patient avec calcul de l'Indice de Masse Corporelle, les résultats des examens biologiques passés, les traitements amaigrissants associés.

Les questionnaires sont regroupés afin d'être saisis puis analysés.

Les informations recueillies sont retournées aux services concernés pour informer les prescripteurs des résultats de cette première phase d'étude et se préparer à la phase de contrôle des plus déviants aboutissant si nécessaire à des actions contentieuses.

RESULTATS

L'échantillon recueilli est composé de 568 prescriptions

- l'utilisation du MEDIATOR apparaît être très variable selon les départements :
  - 48 % des prescriptions proviennent de Côte d'Or
  - 28 % ..... de Saône et Loire
  - 20 %..... de l'Yonne
  - et 5 % ..... de la Nièvre

Comparativement à la structure démographique, la Côte d'Or est sur-représentée et la Nièvre sous-représentée.

- La population du régime général représente 87 % des prescriptions
- le régime agricole 12 %
et - le régime des travailleurs non salariés à peine 1 %

- les prescriptions concernant les patients de sexe féminin représentent 69 % des ordonnances

- dans 93 % des cas, le prescripteur est un généraliste
et dans 6 % des cas, le prescripteur est un endocrinologue

- il est constaté 35 % de prescriptions pour lesquelles l'indication thérapeutique du MEDIATOR n'est pas respectée soit 197 cas.

Ce taux de non respect est de.... - 43 % chez les patients de sexe féminin
et... - 17 % chez les patients de sexe masculin.

- ventilé selon la spécialité médicale, le taux de non respect de l'indication thérapeutique est de 55 % chez les spécialistes
contre 33 % chez les généralistes

- 7 médecins ont précisé "NR" (non remboursable) sur leurs prescriptions appliquant ainsi les nouvelles dispositions, mais il est à noter que dans 3 cas le traitement rentrait effectivement dans les indications thérapeutiques et que dans tous les cas, le pharmacien a présenté la dépense au remboursement.

- sur les 197 prescriptions ne respectant pas l'indication thérapeutique du MEDIATOR, on retrouve 98 prescriptions associées à des traitements à visée amaigrissante. Ces prescriptions sont essentiellement destinées à des patients de sexe féminin : 86 %.

- au surplus, l'étude de l'indice de masse corporelle de cette population (lorsqu'il est connu : 3 cas sur 4), montre que 2 patients sur 3 reçoivent du MEDIATOR alors que l'IMC n'est pas véritablement perturbé (<30), 2 patientes présentant même un état de maigreur (IMC<20).

Il s'agit là d'un détournement manifeste des indications thérapeutiques du MEDIATOR, avec des risques majeurs en terme de santé publique.

DISCUSSION - CONCLUSION

Cette étude est intéressante à divers titres :

- elle montre, si besoin était, que le travail en inter régime et à l'échelle de la région est possible dans une bonne coordination avec des résultats que seule la région permet d'espérer en terme de puissance d'étude. Les actions de communication à l'égard des professionnels de santé n'en ont que plus de poids.

- elle est importante en terme de Santé Publique, puisqu'au regard des résultats, on observe des traitements à visée amaigrissante chez des personnes qui n'en ont pas l'indication. Elle a permis de retrouver des polymédicamentations dont certaines présentent un caractère de dangerosité.

- elle a également permis d'identifier des médecins prescripteurs ne respectant pas l'indication thérapeutique du MEDIATOR de façon coutumière. Ces médecins feront l'objet de la deuxième phase de l'étude.

Ce travail dont l'objectif premier était d'apporter un éclairage sur l'utilisation réelle d'une spécialité en l'occurrence MEDIATOR, permet en fait de s'interroger sur le problème général du bon usage des spécialités pharmaceutiques dans le cadre de leurs indications thérapeutiques reconnues et validées.

Annexe 3-49

SYNTHESE

1. INTRODUCTION

L'ordonnance N° 96-344 du 24 avril 1996 relative à la maîtrise médicalisée des dépenses de santé a créé, dans son titre V, les Unions Régionales des Caisses d'Assurance Maladie (URCAM)

Dans l'attente de leur mise en place officielle et sous l'impulsion commune des services médicaux et administratifs de l'ensemble des régimes d'assurance maladie de la région BOURGOGNE, un comité régional de gestion du risque a été organisé.

L'analyse médico-administrative des postes de dépense a permis de dégager comme domaine d'intervention prioritaire LE POSTE PHARMACEUTIQUE.

A la demande du Comité Régional, une analyse sur le respect des indications thérapeutiques de cinq molécules, dont le MEDIATOR dans un premier temps, est diligentée.

Cette analyse doit se dérouler selon deux modalités.

- une première phase pédagogique, sous la forme d'une enquête collective.

et - une seconde phase normative sous la forme de contrôles individuels.

A l'issue de la première phase, devra être réalisé un ensemble d'actions systémiques validées par le Comité Régional opérationnel de coordination.

Les vecteurs choisis sont :

- Les instances conventionnelles
- Les journaux professionnels
- les supports d'information des caisses

Parallèlement à ces actions à visée systémique, seront effectués des ciblages des professionnels les plus déviants, et tout particulièrement lès responsables des prescriptions du MEDIATOR dans le cadre des régimes amaigrissants.

Ces praticiens feront l'objet de contrôles individuels spécifiques et seront à ce titre concernés par la seconde phase de ce travail sur le respect des indications thérapeutiques.

Pour le service médical du contrôle médical du régime général, chef de projet, les objectifs de ce travail sont les suivants.

- mesurer globalement à l'échelle des 4 départements bourguignons et des 3 régimes d'assurance maladie, le respect de la réglementation : Articles L 162-4 et L 315-3 du code de sécurité sociale.

- appréhender en terme de santé publique, l'incidence de ce non respect, et tout particulièrement dans le cadre des prescriptions à visée amaigrissante.

- cibler les professionnels les plus déviants.

Les résultats présentés ci-après concernent la première phase.

2. MATERIEL ET METHODES

2.1. Champ de l'enquête

L'étude porte sur l'ensemble des prescriptions de MEDIATOR tous praticiens confondus : omnipraticiens et spécialistes, et liquidées par les caisses d'Assurance Maladie de Bourgogne : Régime Général dont les sections locales mutualistes, Mutualité Sociale Agricole, régime des travailleurs non salariés.

2.2. Echantillon

L'individu statistique ciblé par l'enquête est la prescription de MEDIATOR.

L'échantillon est constitué par la totalité des ordonnances présentées au remboursement au cours d'une période de 5 journées consécutives située entre le 01 avril 1997 et le 30 avril 1997.

La période de 5 jours était, pour des raisons d'organisation interne et de charge de travail, laissée à l'appréciation de chacune des caisses d'assurance maladie concernées par l'enquête.

Chaque service administratif avait pour responsabilité la saisie des prescriptions de MEDIATOR, par tri manuel au fil de l'eau et de les transmettre aux services médicaux.

L'échantillon ainsi composé comporte 568 prescriptions de MEDIATOR.

Cependant, compte tenu de l'impossibilité que nous avons de valider cet échantillon de par l'absence du codage pharmacie, nous ne pouvons pas considérer cet échantillon comme représentatif.

2.3. Les modalités de recueil de l'information

Le recueil de l'information par les médecins conseils (30 praticiens) s'est fait sur un questionnaire spécifique à l'enquête (Annexe 1).

Tous les individus statistiques ont fait l'objet d'un questionnaire.

L'origine des informations recueillies sur les questionnaires papier est le dossier médical du service médical, les renseignements fournis par les médecins prescripteurs et si nécessaire l'examen du malade.

S'agissant du versant pédagogique de l'analyse du respect des indications thérapeutiques, il était prévu un grand nombre d'échanges avec les praticiens libéraux. Un fort effet psychologique était attendu de cette démarche.

L'opportunité de l'examen clinique des patients était laissée à l'appréciation des médecins conseils en fonction de la situation, mais dans le strict respect du décret n° 96-786 du 10 septembre 1996.

Le recueil de l'information concernait :

- des éléments d'identification : département, régime...
- des données médicales : poids, taille, résultat des examens biologiques...
- l'avis des praticiens conseils.

Le questionnaire a été retranscrit sur une grille de saisie informatique rigoureusement anonyme établie sous EPI-INFO version 5.

2.4. L'exploitation des données

Compte tenu des réserves pouvant être exprimées sur la représentativité statistique de l'échantillon :

- saisie manuelle sans source de contrôle (absence de codage)
- 5 jours en flux continu sans possibilité de validation

Nous ne parlerons pas d'analyse statistique mais d'exploitation des données.

Cependant compte tenu de la qualité de l'échantillon, il est fort probable mais non certain que la réalité corresponde aux résultats qui vont être ci-dessous développés.

Il est par ailleurs important de préciser qu'il n'existe aucune possibilité de lien entre les questionnaires papier et la base de données informatiques sous EPI-INFO.

Les logiciels utilisés pour l'exploitation sont
- EPI-INFO version 5
et - SPSS version 6-1-2

Enfin, les questionnaires papier seront détruits après la diffusion des conclusions de cette étude.

3. RESULTATS

L'échantillon est composé de 568 prescriptions de MEDIATOR.

Les résultats seront présentés en huit parties :

- résultats globaux : répartition par département
- les prescripteurs
- les patients
- analyse des indices de masse corporelle
- les bilans biologiques
- le respect des indications thérapeutiques
- les traitements à visée amaigrissante

3.1. Résultats globaux répartition par département et par régime

Tableau I Par département

Département	Observations	Pourcentages	Structure démographique
Côte d'or	268	47,2	32,2
Nièvre	25	4,4	13,6
Saône et Loire	160	28,2	33,9
Yonne	115	20,2	20,3
BOURGOGNE	568	100	100

Comparativement à leur poids structurel, la Côte d'Or est sur-représentée, et la Nièvre sous-représentée. La différence qui existe dans la répartition de l'âge des populations ne peut pas à elle seule expliquer ce constat.

Tableau II Par regime

Régime	Echantillon = répartition %	Bénéficiaires = Répartition BOURGOGNE %
Regime général	87,6	82,7
MSA	12	11,2
TNS	0,4	6,1

La part des TNS "semble" sous représentée, mais il est à noter que pour ce régime, aucun dossier n'a été recueilli dans trois départements.

3.2. Les prescripteurs

3.2.1. *Répartition*

Tableau III

Spécialité	Observation	Pourcentage
Omnipraticiens	527	92,8
Endocrinologue	36	6,4
Autres	5	0,8

La part des omnipraticiens prédomine très largement.

La part des prescriptions des endocrinologues est de 10 %. Elle est nulle ou négligeable pour certains départements : Saône et Loire et Yonne.

3.2.2. *Signalement de l'indication non remboursable*

L'article 162-4 du code de sécurité sociale précise que les médecins qui prescrivent une spécialité pharmaceutique en dehors des indications thérapeutiques ouvrant droit au remboursement ou à la prise en charge par l'assurance maladie, sont tenus de le signaler sur l'ordonnance.

Parmi les 568 prescriptions recueillies, 7 fois (1,2 %) la mention NR (Non Remboursable) a été indiquée. Tous les cas concernent des généralistes et seuls 2 départements sont intéressés.

Il est par ailleurs intéressant de signaler que les 7 cas ont fait l'objet d'un remboursement, le MEDIATOR ayant été facturé comme remboursable par le pharmacien.

Dernier constat : dans 3 des 7 cas, l'indication thérapeutique était en fait respectée.

Il y a manifestement une méconnaissance totale des textes.

3.3. Les patients - Répartition

Tableau IV

Sexe	Nombre	Pourcentage
Hommes	178	31,3
Femmes	390	68,7

La répartition par département oscille autour de ces valeurs.

Au plan régional nous connaissons la répartition des diabètes non insulino-dépendant (enquête ALD 30 de 1995) exonérés du ticket modérateur. Les populations sont très certainement très différentes mais la logique voudrait que globalement les répartitions ne soient pas très éloignées.

Or la répartition des DNID est : femme 53 %, hommes 47 % - valeurs à rapprocher de la répartition de notre échantillon : 69 % - 31 %

Le MEDIATOR, traitement adjuvant au traitement des diabètes asymptomatiques avec surcharge pondérale et des hypertriglycéridémies trouve très probablement, du moins chez la femme, des indications autres.

3.4. Les indices de masse corporelle - les bilans biologiques

Compte tenu des indications du MEDIATOR "avec surcharge pondérale", et des indications détournées connues du service médical, c'est-à-dire les traitements à visée amaigrissante, les indices de masse corporelle de la population ont été étudiés.

Pour cela la formule suivante a été appliquée :

$$IMC = \frac{Poids}{(Taille)^2} \quad (en\ kg/m^2)$$

Tableau V N = 304 observations

Observations	Nombre	Pourcentage
IMC < 20	2	0.6
20 IMC 24,9	55	18,1
25 IMC 29,9	109	35,8
30 IMC 39,9	118	38,9
IMC 40	20	6,6

Ce tableau objective les résultats globaux y compris les cas "avoués" de régimes amaigrissants.

La bibliographie parle d'obésité moyenne pour un IMC supérieur à 27,8 pour un homme et 27,9 pour une femme, et d'obésité massive à partir de 31,1 et 32,3.

Tableau VI Type d'obésité : N = 304

	Hommes	Femmes	Total
pas de surcharge pondérale	6	51	57
surcharge modérée	27	38	65
Obésité moyenne	18	67	85
Obésité massive	34	63	97
Total	85	219	304

La méthodologie prévoyait l'interrogation du médecin prescripteur sur l'existence d'un bilan biologique, la date du dernier bilan et les résultats. Il nous est donc possible d'étudier, pour chaque classe d'IMC, le contenu des bilans biologiques et le comportement des prescripteurs.

3.4.1. *Population "pas de surcharge pondérale"(IMC <25), bilans biologiques et prescripteurs* : N = 57

3.4.1.1. *Le bilan biologique : répartition par sexe*

Tableau VI Existence retrouvée d'un bilan et le sexe

Bilan	Hommes	Femmes	Total
Non	0	23	23
Oui	6	28	34
Total	6	51	57

Dans 23 cas, il n'a pas été retrouvé d'examen biologique notamment la glycémie et la triglycéridémie

3.4.1.2. *Le bilan biologique : les résultats*

Tableau VII **Dosage des triglycérides si réalisation d'un bilan biologique**
Hommes Nle = 0,26 à 1,6 g/l - femmes Nle = 0,22 à 1,27 g/l

TRIGLYCERIDES	Hommes	Femmes	Total
Non dosés	0	4	4
Normaux	1	10	11
Elevés	5	14	19
Total	6	28	34

L'absence de surcharge pondérale, compte tenu des indications thérapeutiques, rend la prescription de MEDIATOR justifiée par l'élévation des triglycérides soit 19 cas sur 57 (33 %)..., les autres dossiers étant injustifiés de par :

- l'absence d'une surcharge pondérale
- l'absence d'un bilan biologique
- l'absence d'une élévation des triglycérides

Tableau VIII **Dosage de la glycémie, réalisation d'un bilan biologique**

Glycémie	Observations
Non dosée	5
Inférieure ou égale à 1 g	18
Comprise en 1 g et 1,4 g	7
Elevée	4
Total	34

4 patients ont présenté un véritable diabète = glycémie > 1,4 g
et 7 patients ont présenté une glycémie comprise en 1 g et 1,4 g

Il n'existait pas chez ces patients de surcharge pondérale. Ceux-ci ne justifiaient donc pas, au regard des indications thérapeutiques, une prescription de MEDIATOR.

L'ancienneté moyenne des examens de biologie, lorsqu'ils ont été réalisés (34/57), est d'une année pour la triglycéridémie et d'une dizaine de mois pour la glycémie.

Cette ancienneté est de 10 mois lorsqu'il existe une élévation de la triglycéridémie et sans changement pour l'élévation de la glycémie.

3.4.1.3. *Le bilan biologique : les prescripteurs*

Au sein de cette population qui ne présente pas de surchage pondérale, examinons le comportement des professionnels.

Tableau IX Prescripteurs et réalisation d'un bilan biologique

Spécialités	Pas de bilan	Bilan	Total
Omnipraticien	21	31	52
Endocrinologue	2	3	5
Total	23	34	57

Tableau X Respect des indications thérapeutiques

Spécialités	Non Précisé	Non	Oui	Total
Omnipraticien	1	31	20	52
Endocrinologue	0	4	1	5
Total	1	35	21	57

Tableau XI Traitements à visée amaigrissante associés au MEDIATOR

Spécialités	Non Précisé	Non	Oui	Total
Omnipraticien	1	27	24	52
Endocrinologue	0	3	2	5
Total	1	30	26	57

La part de prescription des endocrinologues est faible, ce qui, compte tenu des indications du MEDIATOR, peut s'expliquer.

On constate néanmoins que pour les patients avec un IMC normal leur pratique vis à vis de cette molécule est identique à celle des omnipraticiens pour ce qui concerne :

- la part de traitement sans examens retrouvés

- la part de traitement en dehors des indications thérapeutiques
- la part de traitement à visée amaigrissante associé

3.4.2. *Population "surcharge pondérale modérée", bilan biologique et prescripteurs*

Critères retenus IMC compris entre 25 et 27,8 pour l'homme
et IMC compris entre 25 et 27,9 pour la femme

3.4.2.1. *le bilan biologique : répartition par sexe*

Tableau XI **Existence d'un bilan biologique et le sexe**

Bilan	Hommes	Femmes	Total
Non	3	6	9
Oui	24	32	56
Total	27	38	65

Dans 9 cas sur 65 il n'a pas été signalé de bilan biologique ce qui, proportionnellement, est inférieur aux résultats retrouvés lors d'IMC normal (23/57).

On pourrait penser que le bilan biologique ne dépend pas de la prescription de MEDIATOR mais de l'état du patient.

3.4.2.2. *le bilan biologique : résultats*

Tableau XII **Dosage des triglycérides si réalisation d'un bilan biologique**
Hommes N = 0,26 à 1,6 g/l - femmes N = 0,22 à 1,27 g/l

Triglycérides	Hommes	Femmes	Total
non dosée	4	2	6
Normaux	11	16	27
Elevés	9	14	236
Total	24	32	56

Tableau XIII Dosage de la glycemie si réalisation d'un bilan biologique

Glycémie	Hommes	Femmes	Total
non dosee	0	4	4
Inférieure ou égale à 1 g	5	17	22
Compnse entre 1 g et 1,4 g	11	8	19
Elevée	8	3	11
Total	24	32	56

Dans 9 cas, il n'y a pas eu d'examen, et ce, malgré la légère surcharge pondérale : rien ne justifie donc le traitement.
De même comment expliquer le traitement de deux patients pour lesquels la glycémie n'a pu être retrouvée et qui présentent par ailleurs une triglycéridémie normale.

L'ancienneté moyenne des examens biologiques est d'une année pour la triglycéridémie et d'une dizaine de mois pour la glycémie. Ces données sont identiques à la classe des patients avec IMC normal.

3.4.2.3. le bilan biologique : le respect des indications thérapeutiques

Tableau XIV Respect des indications et existence d'un bilan biologique

	Bilan biologique	Pas de bilan	Total
Respect	33	0	33
Non respect	23	9	32
Total	56	9	65

Tableau XV Traitement à visée amaigrissante associé au MEDIATOR et existence d'un bilan biologique

	Bilan biologique	Pas de bilan	Total
Visée amaigrissante	6	7	13
Pas de visée amaigrissante	50	2	52
Total	56	9	65

Sur les 9 dossiers sans bilan biologique fourni qui ne respectent pas les indications thérapeutiques, 7 correspondent à des prescriptions de MEDIATOR avec des traitements à visée amaigrissante associés : 3/3 chez l'homme et 4/6 chez la femme.

Tableau XVI Respect des indications thérapeutiques, traitement à visée amaigrissante associé au MEDIATOR, si existence d'un bilan biologique

	Respect	Non respect	Total
Visée amaigrissante	0	6	6
Pas de visée amaigrissante	33	17	50
Total	33	23	56

Les 6 patients recevant un traitement à visée amaigrissante associé présentent :

- un IMC très peu augmenté à 26-27,
- une glycémie normale ou proche de la normale,
- des triglycérides non dosés, normaux ou peu augmentés.

3.4.2.4. le bilan biologique : les prescripteurs

Au sein de cette population qui présente une surchage pondérale modérée, examinons le comportement des professionnels

Tableau XVII Prescripteurs et réalisation d'un bilan biologique

Spécialités	Pas de bilan	Bilan	Total
Endocrinologues	1	8	9
Omnipraticiens	8	48	56
Total	9	56	65

Tableau XVIII Respect des indications thérapeutiques

Spécialités	Non	Oui	Total
Endocrinologues	6	3	9
Omnipraticiens	26	30	56
Total	32	33	65

Tableau XIX Traitement à visée amaigrissante associé au MEDIATOR

Spécialités	Non	Oui	Total
Endocrinologues	8	1	9
Omnipraticiens	44	12	56
Total	52	13	65

La part des prescriptions faites par les endocrinologues diabétologues est faible se situant autour de 10 %, tout comme pour le groupe des patients avec un indice de masse corporelle normal.

Concernant les anomalies, il semblerait que quelles que soient les spécialités, les tendances soient les mêmes.

3.4.3. *Population "obésité moyenne", bilans biologiques et prescripteurs*

Critères retenus :
IMC compris entre 27,8 et 31,1 pour l'homme
et 27,9 et 32,3 pour la femme

3.4.3.1. *le bilan biologique : répartition par sexe*

Tableau XX Existence d'un bilan et le sexe

Bilan	Hommes	Femmes	Total
non	5	18	23
oui	13	49	62
Total	18	67	85

Dans 23 cas sur 85, alors que ces patients présentent une obésité moyenne et qu'un traitement est prescrit, il n'a pas été possible au médecin traitant contacté par le médecin conseil, de présenter les résultats d'examens de biologie notamment : triglycéridémie et/ou glycémie.

3.4.3.2. *le bilan biologique :les résultats*

Tableau XXI Dosage des triglycérides si réalisation d'un bilan biologique
Hommes - N : 0.26 à 1.60 g/l
Femmes - N : 0.22 à 1.27 g/l

Triglycérides	Hommes	Femmes	Total
non dosés	3	6	9
normaux	7	21	28
élevés	3	22	25
Total	13	49	62

Tableau XXII Dosage de la glycémie, si réalisation d'un bilan biologique

Glycémie	Hommes	Femmes	Total
non dosée	0	3	3
< ou = a 1 g/l	2	11	13
> 1 g/l < 1.40 g/l	3	24	27
élevée	8	11	19
Total	13	49	62

On remarque que les 3 patientes chez lesquelles on ne retrouve pas de dosage de la glycémie, présentent, pour 2 d'entre elles, un dosage de la triglycéridémie rigoureusement normal. Il s'agit de prescriptions de MEDIATOR avec un traitement à visée amaigrissante associé.

De même, parmi les 9 patientes sans bilan des triglycérides, 2 d'entre elles présentent un bilan glycémique normal. Il s'agit, dans les deux cas, de prescriptions de MEDIATOR avec un traitement à visée amaigrissante associé.

L'ancienneté moyenne des examens est de 7 à 8 mois autant pour la triglycéridémie que pour la glycémie. Il semble que la fréquence des examens ait tendance à augmenter avec l'importance de l'IMC.

3.4.3.3. le bilan biologique : le respect des indications thérapeutiques

Tableau XXIII Respect des indications et existence d'un bilan biologique

	Bilan biologique	Pas de bilan	Total
Respect	41	1	42
Non respect	21	22	43
Total	62	23	85

Tableau XXIV Traitement à visée amaigrissante associé au MEDIATOR et existence des indications et existence d'un bilan biologique

	Bilan biologique	Pas de bilan	Total
non précisé	1	0	1
à visée amaigrissante	10	12	22
pas de visée amaigrissante	51	11	62
Total	62	23	85

Sur les 23 dossiers sans bilan biologique fourni, 12 correspondent à des prescriptions associées à des traitements à visée amaigrissante : 1 fois chez l'homme et 11 fois chez la femme.

Tableau XXV Non respect et traitement à visée amaigrissante, si existence d'un bilan biologique

	Respect	Non respect	Total
Non précisé	1	0	1
Visée amaigrissante	0	10	10
pas de visée amaigrissante	40	11	51
Total	41	21	62

Les 10 patientes recevant un traitement à visée amaigrissante associé présentent un bilan biologique normal. Dans 2 cas, le dosage des triglycérides n'a pas été retrouvé.

3.4.3.4. le bilan biologique : les prescripteurs

Au sein de cette population qui présente une obésité moyenne, examinons le comportement des professionnels

Tableau XXVI Prescripteurs et réalisation d'un bilan biologique

Spécialités	Pas de bilan	Bilan	Total
Endocrinologue	3	5	8
Homéopathe	0	1	1
omnipraticien	20	55	75
Total	23	62	85

Tableau XXVII Respect des indications therapeutiques

Spécialités	Non	Oui	Total
Endocrinologue	5	3	8
Homéopathe	1	0	1
omnipraticien	36	39	75
Psychiatre	1	0	1
Total	43	42	85

Tableau XXVIII Traitement à visée amaigrissante associé au MEDIATOR

Spécialités	Non précisé	Non	Oui	Total
Endocrinologue	0	5	3	8
Homéopathe	0	0	1	1
omnipraticien	1	57	17	75
Psychiatre	0	0	1	
Total	1	62	22	85

Au total : 50 % de non respect dont 25 % de prescriptions associées à des traitements à visée amaigrissante.
Les femmes sont très largement concernées, 21/22 dans les cas de traitement à visée amaigrissante associé.

Quel que soit le prescripteur, la proportion d'anomalies est sensiblement constante.

3.4.4. *population "obésité massive", bilans biologiques et prescripteurs*

Critères retenus :
IMC supérieur à 31.1 pour les hommes
et 32.3 pour les femmes.

3.4.4.1. *Le bilan biologique : répartition par sexe*

Tableau XXIX Existence d'un bilan et le sexe

Bilan	Hommes	Femmes	Total
Non	3	8	11
Oui	31	55	86
Total	34	63	97

Au sein de cette population le nombre de traitements sans bilan biologique réalisé ou retrouvé par le médecin traitant est, "semble-t-il", beaucoup plus faible que dans les autres classes d'IMC - (11/97).
Compte-tenu des réserves émises sur la représentativité de notre échantillon, ceci ne peut être qu'un constat.

3.4.4.2. le bilan biologique : les résultats

Tableau XXX Dosage des triglycérides si réalisation d'un bilan biologique
Hommes - N : 0,26 à 1,60 g/l
Femmes - N : 0,22 à 1,27 g/l

Triglycérides	Hommes	Femmes	Total
non dosés	4	12	16
normaux	14	11	25
élevés	13	32	45
Total	31	55	86

Tableau XXXI Dosage de la glycémie si réalisation d'un bilan biologique

Glycémie	Hommes	Femmes	Total
Non dosée	1	2	3
Inférieure ou égale à 1 g	8	11	19
Comprise entre 1 g et 1,4 g	13	28	41
Elevée	9	14	23
Total	31	55	86

Parmi les 16 patients qui n'ont pas eu de dosage des triglycérides, 4 d'entre eux présentent une glycémie normale ne justifiant pas à priori le traitement par MEDIATOR.

Par contre, parmi les 3 patients n'ayant pas eu de dosage de la glycémie, tous présentent des valeurs élevées de la triglycéridémie.

L'ancienneté moyenne des examens biologiques est de l'ordre de 8 mois environ. Il n'y a pas de différence avec la classe précédente.
Néanmoins, la tendance retrouvée précédemment sur un raccourcissement des délais entre les deux examens semble confortée.

3.4.4.3. le bilan biologique : le respect des indications thérapeutiques

Tableau XXXII Respect des indications thérapeutiques et existence d'un bilan biologique

	Bilan biologique	Pas de bilan	Total
Respect	63	1	64
Non respect	23	10	33
Total	86	11	97

Tableau XXXIII Traitement à visée amaigrissante associé au MEDIATOR et existence d'un bilan biologique

	Bilan biologique	Pas de bilan	Total
Non précisé	1	0	1
Visée amaigrssante	10	4	14
Pas de visée amaigrissante	75	7	82
Total	86	11	97

Sur les 11 dossiers sans bilan biologique retrouvé, 4 correspondent à des prescriptions associées à des traitements à visée amaigrissante :

- 1 fois chez l'homme

et - 3 fois chez la femme.

La proportion est la même que dans la classe d'IMC précédente.

Tableau XXXIV Non respect des indications thérapeutiques, traitement à visée amaigrissante associé au MEDIATOR, si existence d'un bilan biologique

	Respect	Non respect	Total
Non précisé	0	1	1
Visée amaigrissante	1	9	10
Pas de visée amaigrissante	62	13	75
Total	63	23	86

Parmi les 9 patients recevant le MEDIATOR en vue d'un régime amaigrissant, tous présentent un bilan normal ou peu modifié. Par contre, le patient dont le traitement est associé à un traitement à visée amaigrissante, présente une élévation importante des triglycérides.

En admettant "l'indication thérapeutique du MEDIATOR dans les régimes amaigrissants" retenue, il est fort étonnant que le médecin traitant ne s'enquière pas d'un minimum d'indicateurs biologiques avant de mettre en place ce type de traitement puisque dans 52 % (39/75) des cas, il n'est pas retrouvé de bilan biologique.

3.7. Le respect des indications et les prescripteurs

La part des prescriptions des spécialistes est de 7,2 % (41/568) qui sont endocrinologues - diabètologues dans 36 cas (36/41).

Il n'existe pas de différence dans la réalisation ou la connaissance des résultats d'un bilan biologique entre les spécialistes et les omnipraticiens.

Par contre la connaissance du poids et de la taille, donc de l'IMC est de meilleure qualité chez les spécialistes.

Tableau XXXXI Respect des indications thérapeutiques

Spécialités	Non précisé	Non	Oui	Total
Omnipraticiens	18	175	334	527
Endocrinologues	0	20	16	36
Autres spécialités	1	2	2	5
Total	19	197	352	568

Avec beaucoup de prudence sur le résultat du test, il semble qu'il y ait une différence significative entre le respect chez les omnipraticiens et chez les endocrinologues.

Ces derniers respectent moins souvent les indications thérapeutiques (55 % contre 33 %) ; par contre la part due aux prescriptions de MEDIATOR associées au traitement à visée amaigrissante est identique : 19 % contre 17 %.

Lorsque nous étudions l'ensemble des dossiers, tous prescripteurs confondus, nous retrouvons :

- non respect des indications thérapeutiques .....33 %
- Traitement à visée amaigrissante associé .....15 %

Ces deux valeurs sont probablement les plus proches de la réalité.

3.8. Analyse spécifique des prescriptions associées à des traitements à visée amaigrissante

98 traitements sont associés à des traitements à visée amaigrissante parmi lesquels les médecins conseils ont justifié 7 prescriptions au regard des résultats des bilans biologiques.

Tableau XXXXII Répartitions des IMC si traitement amaigrissant associé (si IMC connu)
N =75 (23 dossiers sans information sur l'IMC)

	Homme	Femmes	Total	Pourcentages
IMC < 20	0	2	2	2.7
20 IMC 24,9	1	23	24	32
25 IMC 29,9	4	20	24	32
30 IMC 39,9	5	18	23	30.6
IMC 40	0	2	2	2.7
Total	10	65	75	100

Plusieurs questions:

- *Comment expliquer la nette prédominance de la population féminine* : 65 dossiers sur 75 ?
- *Comment expliquer les prescriptions de MEDIATOR associées à des traitements dits à visée amaigrissante sans connaissance précise du poids et de la taille soit 23 dossiers sur 98 ?*
- *Comment expliquer les prescriptions associées à des traitements dits à visée amaigrissanté sans bilan biologique préalable* : 45 dossiers sur 98 (36 dossiers sur 75 lorsque l'IMC est connu) ?
- *Comment expliquer un traitement à visée amaigrissante associé au MEDIATOR chez des patients*
  - en état de maigreur ..... 2 = IMC < 20
  - de poids normal ..... 24 = IMC > 20 et < 25
  - avec un surpoids léger ..... 24 = IMC > 25 et < 30
    soit plus de 66 % des patients ?
- *Comment expliquer un traitement dit "amaigrissant"associé au MEDIATOR chez des patients présentant une obésité, voire une obésité massive ?*
  - sans bilan biologique connu, on retrouve 10 dossiers.
  - avec un bilan biologique non perturbé, 15 dossiers. Où sont la place du régime et celle du suivi diététique ?

Autant de questions qui en terme de santé publique mériteraient une réponse.

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4. AU TOTAL

Le MEDIATOR a comme indications thérapeutiques actuellement inscrites à l'autorisation de mise sur le marché :

- "Adjuvant du régime adapté dans les hypertriglycéridémies, la poursuite du régime étant toujours indispensable.
- Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale".
- le laboratoire déclare que ce produit n'a jamais fait la preuve de son efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose.
  Ce produit est actuellement remboursé à 65 %.

Compte tenu du fait que dans un tiers des cas les indications thérapeutiques ne sont pas respectées,

Compte tenu du fait que dans 15 à 20 % des cas le but avoué est une prescription associée à un traitement à visée amaigrissante alors que cette molécule n'a pas cette indication thérapeutique,

Compte tenu du fait que dans les traitements déclarés à visée amaigrissante associés

- plus de 20 % des médecins ne peuvent pas fournir d'information sur le poids et la taille de leur patient
- 45 % ne retrouvent pas, ne possèdent pas ou n'ont pas fait réaliser de bilan biologique
- 66 % des patients ne présentent pas d'obésité avérée IMC < 30 (si IMC connu).

(On peut s'interroger sur les raisons qui ont poussé le médecin à prescrire en dehors de l'indication thérapeutique, est-ce par manque d'information ?)

Compte tenu du fait que l'étude de la bibliographie et tout particulièrement celle la revue PRESCRIRE de mai 1997 (tome 17 N° 173) **et décembre 1997** (tome 17 n° 179) **où sont retrouvées les conclusions suivantes :**

" Après 20 ans de commercialisation du BENFLUOREX (Médiator), on ne sait toujours pas à quoi sert ce médicament aux diabétiques... Le seul essai comparant le BENFLUOREX à la METFORMINE est ininterprétable... Le maintien sur le marché et la prise en charge par l'assurance maladie de ce médicament doivent être reconsidérés".

Il semble évident que les conditions de prise en charge de ce médicament doivent être reconsidérées.

Annexe 3-49

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- Hyperglycémie provoquée par voie orale P 411

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ANNEXE I — QUESTIONNAIRE PAPIER

RESPECT DES INDICATIONS THERAPEUTIQUES : MEDIATOR

1 Département

2 Régime

3 N° de centre ou mutuelle (MSA et TNS code 000)
Si autre mutuelle (Cf. table) préciser en clair.....

4 N° de fiche (bien suivre la notice de remplissage pour remplir cet item)

PATIENT - ORDONNANCE - PRESCRIPTEUR

5 Prescripteur (en clair).....

6 Spécialité (en clair).....

7 N° de CO (4 derniers chiffres)

8 L'indication "Hors indication thérapeutique" Art L 612-4 est-elle précisée Oui = 1 Non = 2

9 Nom de l'assuré.....

10 Nom du Bénéficiaire.....

11 Prénom.....

12 Sexe Homme = 1 Femme = 2

13 Date de prescription

14 Recueil de l'information

RECUEIL MEDICAL

15 Poids

16 Taille

Si l'examen n'a pas été réalisé coder : date 00-00-00 Résultat = 0

		Examen	Date du dernier examen	Résultat
17	Hypertriglycéridémie	Triglycérides		g/l
18	Diabète asymptomatique	Glycémie à jeun		g/l
19		Glycémie post-prandiale		g/l
20		HGPO		Résultat pathologique Oui = 1 Non = 2
21		HB A_1		%
22		HB A_{1C}		%
23	Autre(s) examen(s) spécifique(s) (en clair)			

AVIS DU MEDECIN CONSEIL

24 L'indication thérapeutique de MEDIATOR est elle respectée Oui = 1 Non = 2

25 Existe t-il un traitement associé à visée amaigrissante Oui = 1 Non = 2

Si OUI, préciser le traitement en clair et transmettre le dossier au pharmacien-conseil pour étude complémentaire

.....

.....

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis le,

Madame le professeur BLUM-BOISGARD
Monsieur le Professeur ALLEMAND
Monsieur le Professeur CHOUTET

Objet : prescription de Médiator®

Madame, Messieurs

Je vous remercie de m'avoir communiqué les résultats de l'étude portant sur les modalité s d'utilisation de la spécialité Médiator® qui ont été examinés avec attention.

En réponse aux différents points que vous avez soulevés dans votre courrier, je souhaite vou s appportez ces quelques informations suivantes :

- Les conditions de prescription de cette spécialité n'ont pas été restreintes puisque c e médicament n'est pas indiqué dans la prise en charge de l'obésité. Toutefois, en raison de sa parenté structurale avec les amphétaminiques, l'Agence du Médicament conscient e du risque de report de prescription, a décidé dès les mesures prises à l'encontre de s anorexigènes,en Octobre 1995,la mise en place d'une enquête de pharmacovigilance et d'un suivi des chiffres de vente de cette spécialité.

-sur le plan de la Pharmacovigilance, cette spécialité commercialisée depuis 1974 n'a pas fait l'objet d'une alerte particulière.

Les conditions d'utilisation de cette spécialité apparaissent également comme une préoccupatio n européenne, aussi une enquête a t-elle été mise en place sous la repsonsabilité de l'Italie. L'Agence du Médicament maintient donc la surveillance attentive de cette spécialité dan s l'attente des données Européennes.

Nous vous tiendrons informés de la suite de ce dossier.

Restant à votre disposition pour tout complément d'information, je vous prie de croi re Madame, Messieurs à l'assurance de nos sentiments distingués

Annexe 3-51

CHU MONTPELLIER
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page de garde

Destinataire : Dr R. Maria

Adresse : Agence du Médicament

Numéro de Fax : 01 55 87 35 32

Transmission : 3 Nombre de pages du document (y compris la page de garde).

Chère Nicole,

Ce médecin nous a écrit plusieurs fois par ce problème que lui reproche-t-on actuellement ? Pourrais-tu me donner la position de l'Agence ?

Amitié

JPB

Diplômé de la Faculté de Montpellier

MÉDECINE GÉNÉRALE

LECTEUR ÉMÉRITE
DE LA REVUE PRESCRIRE
DEPUIS 1996

Diplôme de Gériatrie

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1773

5/12/98

Consultations :
• 10 h à 12 h
• Sur rendez-vous : 14 h à 16 h
• 16 h à 19 h

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Dr D. HILLAIRET-BUYS
Pr J.P. BLAYAC
Hôpital St Charles
34 295 Montpellier
Fax : 04.67.33.67.51.

Mon cher confrère,

J'ai bien reçu votre réponse à mes inquiétudes concernant le benfluorex.

Je note bien que l'Agence du médicament ne classe pas le benfluorex parmi les amorexigènes ce qui contredit l'Organisation mondiale de la Santé qui classe le benfluorex dans la liste "anorexigenic agents".(1)

La question me semble suffisamment grave pour que vous interrogiez les experts de l'OMS sur les effets indésirables potentiels de ce médicament. A défaut, pouvez-vous me donner leurs coordonnées afin que je les interroge moi-même ?

Je confirme l'utilisation massive, dans AOM, comme amorexigène en ville. Cette utilisation m'inquiète, pourquoi ne vous inquiète-t-elle pas ?

Inquiète-t-elle ou pas l'Agence du Médicament ?

28, rue des Jacinthes
11100 NARBONNE
Tél. : 04 68 65 23 91

Le sujet me paraît grave c'est pourquoi je demande toute votre vigilance et (utilisation comme anorexigène en pratique, Antidiabétique, anti hyperthyroïdie en théorie) et de tirer tout cela au clair avec les experts de l'OMS.

Je vous remercie et vous prie de croire à mes sentiments les meilleurs.

Gutierrez

du mois de 1990.

Annexe 3-52

CENTRE HOSPITALIER ET UNIVERSITAIRE DE BESANÇON
SERVICE DE PHARMACOLOGIE CLINIQUE
CENTRE REGIONAL DE PHARMACOVIGILANCE
Professeur Pierre BECHTEL
Höpital Jean Minjoz - 25030 BESANÇON CEDEX
Tél. : 03.81.66.83.00 Fax : (33) 03.81.66.84.83

Martine DAVID - LAROCHE, Pharmacien
Tel. direct : 03.81.66.82.99

Besançon, 23 septembre 1998

Madame le Docteur Anne CASTOT
Unité de Pharmacovigilance
Agence du Médicament

Chère amie,

Je te prie de trouver ci-joint , pour information,le rapport que nous avons rédigé pour le GT du 2 octobre concernant MEDIATOR, et que je t'ai déjà faxé.

Je te prie de recevoir mes amicales salutations.

Martine DAVID-LAROCHE

P.S. : je te joins d'autre part, les données du DOREMA concernant MEDIATOR, qui seront présentées au Comité Technique de décembre 1998.

CENTRE REGIONAL DE PHARMACOVIGILANCE DE FRANCHE COMTE
CHU Jean Minjoz 25030 BESANCON Cedex

Analyse des données de Pharmacovigilance relevées lors des études cliniques de benfluorex (MEDIATOR), réalisées en vue de la validation du produit dans l'indication : diabète de type 2

Experts:
P.R. BECHTEL
M. DAVID - LAROCHE

Annexe 3-52

Le présent rapport est établi à partir de l'analyse des dossiers fournis par l'Agence du Médicament, Direction de l'Evaluation intitulée :

- Etude d'efficacité du Benfluorex versus placebo (analyse principale) volume 1/13 et 2/3

- Efficacité du Benfluorex par voie orale chez 500 patients diabétiques de type 2, mal contrôlés par le régime seul, volume 1/29 et 2/29.

Dans les faits, l'ensemble des données se trouvant dans les volumes 1/29 et 2/29 et afin éviter toute erreur liée à une redondance entre les deux dossiers, le présent rapport est essentiellement basé sur les volumes 1/29 et 2/29.

Introduction.

Cette étude de pharmacovigilance concerne un essai clinique randomisé en aveugle portant sur 722 malades traités, soit par Benfluorex (294 malades), Metformine (284 malades) ou placebo (144 malades).

L'âge moyen était de 56 ans+/- 9 ans avec comme extrême : 33 ans -72 ans.

La majorité des malades présentait des pathologies associées au diabète de type 2 avec les thérapeutiques correspondantes.

Nous distinguerons dans notre analyse :

-des événements indésirables liés soit au diabète, à la pathologie associée ou au traitement.

- des événements indésirables émergents : événements indésirables qui sont apparus après la mise en route du traitement, objet de l'étude. Ces événements indésirables n'étaient pas rapportés à S0 (début de la période de traitement) ou présents à S0, ils se sont aggravés au cours de l'étude.

- DES EFFETS INDÉSIRABLES, tous émergents, en relation avec le traitement, objet de l'étude. Après vérification nous avons accepté les imputations telles qu'elles étaient faites dans les dossiers.

Annexe 3-52

1°) Evènements et/ou effets indésirables apparus au cours de l'étude. (tableau I)

Sur le total des 722 malades traités, 178 (24,7%) ont présenté au moins un évènement indésirable.
Le nombre de malades ayant présenté au moins un évènement indésirable sont répartis de la façon suivante :

- placebo : 30 (20,8%)

- benfluorex : 73 (24,8%)

- metformine : 75 (26,4%)

Le nombre de malades ayant présenté au moins un évènement indésirable émergent est de 153 (21,2%).
La répartition entre les traitements étant de :

- placebo : 24 (16,7%)

- benfluorex : 64 (21,8%)

- metformine : 65 (22,9%)

Quel que soit le type d'évènement indésirable il n'y a pas de différence entre benfluorex et metformine

Le nombre total d'évènements indésirables émergents est de 592 réparti comme suit:

- placebo : 96

- benfluorex : 224

- metformine : 272

Le nombre total **d'effets indésirables émergents** est de 223 réparti entre les trois groupes de la façon suivante :

- placebo : 32

- benfluorex : 80

- metformine : 111

Parmi les évènements indésirables émergents, 64 ont été classés comme étant sévères :

- placebo : 15 (16%)
- benfluorex : 19 (8%)
- metformine : 30 (11%)

Parmi ceux-ci, 34 sont des **effets indésirables émergents** en rapport avec le traitement :

- placebo : 8
- benfluorex : 5
- metformine : 21

Les 5 **effets indésirables émergents** sévères attribués à benfluorex sont :

- un trouble de l'équilibre
- un vertige
- deux diarrhées
- un ballonnement abdominal

Les investigateurs ont de plus caractérisé comme étant des effets indésirables **émergents graves,** sans hospitalisation, mais en rapport avec le traitement par benfluorex :

- un vertige à la 13e semaine
- une urticaire à la 5e semaine.

De plus des évènements indésirables graves ou assimilés graves (tableau II) ont été rapportés dans le groupe traité par benfluorex.

Ces événements sont réputés sans relation avec le traitement.

2°) Evènements indésirables émergents les plus fréquents. (tableau III)

Il s'agit d'évènements indésirables, dont certains peuvent être qualifiés **d'effets indésirables car en rapport avec le traitement** qui pour la plupart sont des manifestations de type gastro-intestinal :

- diarrhées
- nausées
- douleurs abdominales

avec une prédominance des diarrhées (Benfluorex: 15 malades (5,1%), Metformine: 39 malades (13,7%)..

Les autres évènements indésirables dont certains peuvent être qualifiés d'effets indésirables avec le traitement concernent des désordres de l'état général (asthénie, vertige) et le système ostéo-articulaire (myalgie, douleurs lombaires).

L'ensemble de ces effets indésirables sont cités dans les RCP et correspondent aux effets indésirables du benfluorex, qui fait l'objet actuellement d'une enquête de Pharmacovigilance.

On notera par ailleurs qu'aucun effet de type atteinte hépatique, atteinte des lignées sanguines, atteinte rénale n'a été observé au cours de cet essai clinique.

CONCLUSION.

1°) Tous les effets indésirables rapportés au traitement sont des effets connus.

2°) Les effets indésirables les plus fréquents concernent la sphère digestive avec notamment des diarrhées, ce qui est également parfaitement conforme avec ce que la Pharmacovigilance connnait de ces médicaments.

3°) La comparaison entre benfluorex et metformine n'est pas facile. Il semblerait que dans cette série de malades traités les effets indésirables, identiques pour les deux produits, aient été un peu moins fréquents dans le groupe benfluorex que dans le groupe metformine.

4°) On notera un nombre non négligeable "d'effets indésirables" dans le groupe placebo, notamment ceux concernant le système gastro-intestinal (15 effets indésirables, soit 10,4%).

Tableau des événements et effets indésirables au cours de l'étude

	Placebo	Benfluorex	Metformine	TOTAL
Nb patients inclus	144	294	284	722
Nb patients avec Evénements indésirables ≥ 1	30 (20.8%)	73 (24.8%)	75 (26.4%)	178 (24.7%)
Nb patients avec Evénements indésirables émergents ≥ 1	24 (16.7%)	64 (21.8%)	65 (22.9%)	153 (21.2%)
Nb patients hospitalisés *(Evénements indésirables sans rapport avec le traitt)*	3	10	7	20
Nb patients avec Evénement indésirable grave sans hospitalisation	1	2	1	4
Nb Evénements indésirables émergents	96	224	272	592
Nb Effets indésirables émergents (en relation avec le trtt.)	**32**	**80**	**111**	223
Nb Evénements indésir. ⇒ arrêt du traitement	6	14	16	36
Nb Evénements indésirables sévères	15 (16%)	19 (8%)	30 (11%)	64
Nb Effets indésirables sévères (en relation avec le trtt)	**8**	**5**	**21**	34

TABLEAU I

-Patient n°1 :

Vertiges* : à la 13° semaine

H,48 ans,
Diabète NID depuis 18 mois,
HTA, coronaropathie, hypercholestérolémie
Traitement associé : céliprolol, fénofibrate

-Patient n°2:

Urticaire : à la 5° semaine

H, 36 ans
Diabète type 2 depuis 7 mois

Evénements indésirables graves ou assimilés graves (traitement : benfluorex)

(S= durée de traitement en semaines)

-Evénements émergents en relation avec le traitement : 2 *(cf ci-dessus)*

- Vertiges S13
- Urticaire S5

-Evénements émergents sans relation avec le traitement : 10

- Appendicite S3
- Calcul rénal S3
- Hystérectomie S5
- Papillome paupière S3
- Hernie inguinale S21
- Arthroscopie du genou S29
- Luxation de l'épaule S29
- Intervention cataracte S5
- Hernie discale S5
- AVC S13

-Evénements non émergents sans relation avec le traitement : 2

- Malaise vagal S 0
- Cystocèle S -4

TABLEAU II

Patients	Placebo (N=144)				Benfluorex (N=294)				Metformine (N=284)			
	nb tot.	% tot.	nb R	% R	nb tot.	% tot.	nb R	% R	nb tot.	% tot.	nb R	% R
Syst.gastro-intestinal (NP)	*15*	*10*			*39*	*13*			*72*	*25*		
Syst. gastro-intestinal (NEI)	*22*		***15***	***10.4***	*48*		*30*	***10.2***	*105*		*73*	*25.8*
Diarrhée (NP)	2	1.4	**2**	**1.4**	20	6.8	**15**	**5.1**	40	14.1	**39**	**13.7**
Nausées (NP)	3	2.1	**2**	**1.4**	2	0.7	**2**	**0.7**	12	4.2	**11**	3.9
Douleurs abdominales (NP)	4	2.8	**4**	**2.8**	4	1.4	**2**	**0.7**	10	3.5	**5**	1.8
Asthénie (NP)	-	-	-	-	8	2.7	**5**	**1.7**	3	1.1	**2**	**0.7**
Vertiges (NP)	1	0.7	**0**	-	9	3.1	**3**	**1**	2	0.7	**1**	**0.3**
Syst.Musculosquelettique (NP)	*8*	*5.5*	-	-	*22*	*7.5*	***3***	***1***	*23*	*9.4*	***0***	-
Myalgies (NP)	1	0.7	**0**	-	7	2.4	**2**	**0.7**	2	0.7	**0**	-
Douleurs lombaires (NP)	1	0.7	**0**	-	3	1	**1**	**0.3**	4	1.4	**0**	-
Infection virale (NP)	-	-	-	-	7	2.4	**1**	**0.3**	3	1.1	**0**	-
Bronchite (NP)	-	-	-	-	6	2	**1**	**0.3**	7	2.5	**0**	-
Rhinite (NP)	4	2.8	**0**	-	3	1	**0**	-	6	2.1	**0**	-
Pharyngite (NP)	3	2.1	**0**	-	1	0.3	**0**	-	7	2.5	**0**	-

N = nombre de patients inclus
NP = nombre de patients avec événements ou effets indésirables
NEI = nombre d'effets indésirables
R = en relation avec le traitement

TABLEAU III

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1785

REPARTITION DES PRESCRIPTIONS DE MEDIATOR EN FONCTION DES INDICATIONS

Source : DOREMA Médicaments - Printemps - Cumuls 12 mois

INDICATIONS	Juin 94 à Mai 95		Juin 95 à Mai 96			Juin 96 à Mai 97			Juin 97 à Mai 98		
	Prescriptions	Répart. %	Prescriptions	Répart. %	evol. an-1	Prescriptions	Répart. %	evol. an-1	Prescriptions	Répart. %	evol. an-1
Total Prescriptions	893 000	100,0%	821 000	100,0%	-8,1	897 000	100,0%	9,3	948 000	100,0%	5,7
Diabète et apparentés*	389 000	43,6%	407 000	49,6%	4,6	376 000	41,9%	-7,6	420 000	44,3%	11,7
Lipides (Diag. 272)	151 000	16,9%	174 000	21,2%	15,2	248 000	27,6%	42,5	268 000	28,3%	8,1
Obésité (Diag. 278)	212 000	23,7%	124 000	15,1%	-41,5	123 000	13,7%	-0,8	100 000	10,5%	-18,7

* Diag. 250-259 + 277 + 790-2

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1786

REPARTITION DES PRESCRIPTIONS DE MEDIATOR EN FONCTION DES EFFETS ATTENDUS

Source : DOREMA Médicaments - Printemps - Cumuls 12 mois

EFFETS ATTENDUS	Juin 94 à Mai 95		Juin 95 à Mai 96			Juin 96 à Mai 97			Juin 97 à Mai 98		
	Prescriptions	Répart %	Prescriptions	Répart %	evol. an-1	Prescriptions	Répart. %	evol. an-1	Prescriptions	Répart. %	evol. an-1
Total Prescriptions	893 000	100,0%	821000	100,0%	-8,1	897 000	100,0%	9,3	948 000	100,0%	5,7
ANTIDIABETIQUE	463 000	51,8%	424 000	51,6%	-8,4	438 000	48,8%	3,3	449 000	47,4%	2,5
LIPOTROPE	265 000	29,7%	247 000	30,1%	-6,8	303 000	33,8%	22,7	313 000	33,0%	3,3
REGULATEUR METAB.	29 000	3,2%	63 000	7,7%	117,2	62 000	6,9%	74,2	108 000	11,4%	74,2
ANTIOBESITE	101 000	11,3%	45 000	5,5%	-55,4	74 000	8,2%	-28,4	53 000	5,6%	-28,4

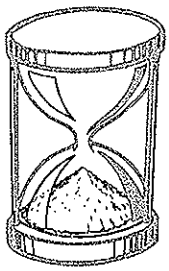
VENTES UNITAIRES DE MEDIATOR

SOURCES	1991	1992		1993		1994		1995		1996		1997		Juillet 1998*	
	Unités (000)	Unités (000)	evol. an-1	Unités (000)	evol. an-1	Unités (000)	evol. an-1	Unités (000)	evol. an-1	Unités (000)	evol. an-1	Unités (000)	evol. an-1	Unités (000)	evol. an-1
IMS - Eisipharm - LMP	3 279	3 767	14,9	4 135	9,8	4 794	15,9	5 157	7,6	5 164	0,1	5 555	7,6	5 625	3,1
GERS	3 147	3 605	14,6	4 223	17,1	4 792	13,5	5 141	7,3	5 253	2,2	5 531	5,2	5 666	4,8

Entre 1992 et 1997 : Cumuls 12 mois de janvier à décembre

* Pour 1998 : Cumul 12 mois de août 1997 à juillet 1998 (évolution par rapport au cumul à juillet 1997)

Annexe 3-53



Avec plus de recul

benfluorex antidiabétique ?

MEDIATOR°

comprimés

• 150 mg
de benfluorex (chlorhydrate)
par comprimé
30 comprimés (blancs) ..42,90 F

Séc. Soc. 65 % et collect.
Liste I

Lab. Biopharma (Servier)

antidiabétique ?

Le *benfluorex*, Mediator° des laboratoires Servier, est commercialisé en France depuis 1976, sous forme de comprimés dosés à 150 mg (**a**). Chimiquement, le *benfluorex* est proche d'autres substances anorexigènes dont la *fenfluramine* (Pondéral°, Isoméride° pour la forme dextrogyre, du même groupe Servier) (**b**)(1). Une de ses indications officielles, « *adjuvant au régime dans le diabète asymptomatique avec surcharge pondérale* » fait l'objet depuis de nombreuses années d'une campagne promotionnelle récurrente (**c**)(2). Pour répondre à la demande de lecteurs qui nous interrogent régulièrement sur l'intérêt éventuel du *benfluorex* chez les diabétiques, et sur les affirmations de certains visiteurs médicaux tendant à faire croire que le *benfluorex* serait aussi efficace que la *metformine* (Glucinan°, Glucophage°, Stagid°), nous avons recherché les données disponibles dans le dossier d'évaluation clinique (**d**).

Le traitement des diabétiques devrait avant tout prévenir les complications cliniques, et réduire la mortalité. Sur ces critères, l'intérêt des divers antidiabétiques oraux actuellement commercialisés est mal établi (3,4). Le *benfluorex* occupe-t-il une place privilégiée dans ce lot ?

Indication officielle dans le diabète :
« adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale ».

Quelques effets, modestes et à court terme (3 mois), sur des paramètres biologiques

L'essentiel des essais cliniques comparatifs recensés dans une brochure d'information des laboratoires Servier (5) est publié.

Essais versus placebo. Nous avons identifié 6 essais cliniques *benfluorex* versus placebo réalisés en double aveugle chez des patients atteints de diabète non insulino-dépendant (5à10). Ces essais ont été menés selon des méthodologies très proches : après une phase de pré-inclusion (de 1 mois en général) sous placebo, destinée à vérifier la stabilité du diabète, les patients ont reçu durant 3 mois en double aveugle, soit un placebo, soit du *benfluorex*

a- En Europe, le benfluorex est également commercialisé en Espagne, en Grèce, en Italie, au Luxembourg, au Portugal et en Suisse (réf. 5). Le benfluorex n'est commercialisé dans aucun pays anglosaxon ou du nord de l'Europe.

b- En France, le benfluorex est bizarrement classé. Il n'est pas officiellement classé parmi les anorexigènes pour ce qui concerne les spécialités : de ce fait, Mediator° ne fait pas l'objet d'une prescription restreinte. Cependant, une circulaire de la Direction générale de la santé en date du 25 octobre 1995 (Journal Officiel du 31 octobre 1995, page 15937) inclut le benfluorex dans la liste des anorexigènes, et précise qu'il ne doit pas être incorporé dans des préparations magistrales. Par ailleurs, la dénomination "benfluorex" est incluse dans la liste des anorexigènes par l'Organisation mondiale de la santé (OMS).

c- L'autre indication officielle est « adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable ». Nous étudierons cette indication dans un autre article. Les deux indications officielles du benfluorex datent de 1974. En application de la directive européenne 75/319/CEE visant les spécialités pharmaceutiques enregistrées avant le 1er décembre 1976, les indications officielles du benfluorex ont fait l'objet d'une procédure de validation en 1987.

d- Notre recherche documentaire a reposé sur le suivi prospectif continu des sommaires des principales revues internationales et des Current Contents, ainsi que sur la consultation systématique d'ouvrages de référence en pharmacologie clinique (Martindale The Extra Pharmacopoeia, etc.). Nous avons également consulté sur CD-Rom les bases de données Medline (1996-mars 1997), Embase Drugs and Pharmacology (1991-décembre 1996) et Cochrane (1996 issue 3), et interrogé par Minitel, pour la dernière fois le 26 mars 1997, les bases de données Pascal et EMC. Par ailleurs, les laboratoires Servier nous ont communiqué divers documents publiés et non publiés. Deux membres de l'ISDB (International Society of Drug Bulletins), le Boletin Terapeutico Andaluz et Informazion sui Farmaci nous ont aussi communiqué les documents en leur possession.

(450 mg/jour par voie orale). L'efficacité a été jugée uniquement sur des critères biologiques (lire tableau page 330). Un essai a été réalisé chez des patients soumis seulement à un régime hypocalorique, sans autre médicament antidiabétique (6) ; 3 essais ont été réalisés chez des patients obèses recevant par ailleurs de l'insuline (5,7,8,9) ; 2 essais ont été réalisés chez des patients recevant par ailleurs un sulfamide hypoglycémiant (5,10).

Selon l'American Diabetes Association, le but du traitement antidiabétique est de ramener la glycémie à jeun à 6,7 mmol/litre (environ 1,2 g/litre) et l'hémoglobine glyquée à 7 % (11). Dans deux essais sur six seulement, le *benfluorex* a eu un effet supérieur à celui du placebo sur la glycémie à jeun, et la glycémie moyenne n'a été ramenée à 6,7 mmol/litre que dans un seul essai (7). Si dans les cinq essais où la comparaison est possible, l'effet du *benfluorex* sur l'hémoglobine glyquée est statistiquement supérieur à celui du placebo, c'est seulement dans un essai que le taux moyen d'hémoglobine glyquée a été ramené au-dessous de 7 % (7). À l'exception d'un essai (7), le *benfluorex* n'a pas modifié l'insulinémie à jeun par rapport au placebo. Sur les trois essais réalisés chez des patients traités par insuline, le *benfluorex* n'a permis une réduction statistiquement significative des besoins quotidiens en insuline que dans un essai (9). Aucun de ces essais cliniques versus placebo ne mentionne un effet du *benfluorex* sur des critères de morbimortalité ; ils n'ont d'ailleurs pas été conçus pour cela (e).

Essai versus metformine. Un essai comparatif *benfluorex* versus *metformine*, réalisé chez 121 patients a été publié (12). Cet essai est ininterprétable en raison de sources de biais importantes. Les patients du groupe *metformine* avaient, lors de l'inclusion, une glycémie post-prandiale et une aire sous la courbe d'hyperglycémie provoquée statistiquement inférieures à celles du groupe *benfluorex*. Or, le critère d'évaluation principal était l'évolution de la glycémie au cours d'une épreuve d'hyperglycémie provoquée par voie orale. Par ailleurs, l'essai n'a pas été réalisé en aveugle.

En somme. Les essais disponibles montrent que le *benfluorex* a des effets, au moins à court terme (3 mois), sur certains critères permettant d'évaluer l'équilibre glycémique, hémoglobine glyquée notamment. Cependant, ces effets sont modestes, et faute de comparaisons, on ne sait pas s'ils sont voisins ou non de ceux des antidiabétiques oraux actuellement commercialisés. Aucune donnée relative à l'éventuel effet du *benfluorex* sur la morbimortalité du diabète n'est disponible.

Quid des effets indésirables ?

Compte tenu de l'absence de données indépendantes, il est impossible de connaître avec précision le profil des effets indésirables du *benfluorex*. Selon les laboratoires Servier, « *les effets indésirables le plus souvent observés avec benfluorex sont des effets digestifs (nausées, vomissements, gastralgies, diarrhées) mais aussi asthénie, somnolence ou état vertigineux. Toutefois, ils s'observent aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles* » (5). Ces affirmations ne reflètent pas les données de quatre essais cliniques au cours desquels le *benfluorex* a été utilisé à la dose de 3 comprimés par jour (450 mg) et au cours desquels ces mêmes effets indésirables ont été observés (10,13,14,15). D'après ces essais de petite taille, réalisés avec la dose thérapeutique de 450 mg/jour, une somnolence ▶▶

MEDIATOR°

DCI	Belgique	Suisse
benfluorex	–	MEDIAXAL°
dexfenfluramine	ISOMERIDE°	ISOMERIDE°
fenfluramine	PONDERAL°	PONFLURAL°
metformine	GLUCOPHAGE°	GLUCOPHAGE°

Quelques essais comparatifs à court terme (3 mois) montrent que le *benfluorex* n'a, au mieux, que des effets limités sur la glycémie à jeun et l'hémoglobine glyquée des patients diabétiques non insulinodépendants, sans effet démontré sur la morbimortalité. Les effets indésirables du *benfluorex* sont fort mal connus. Au terme de 20 ans de commercialisation, il n'y a toujours aucune raison de prescrire le *benfluorex* chez les diabétiques.

e- Par ailleurs, certains de ces essais ne sont pas exempts de sources de biais qui peuvent rendre aléatoire leur interprétation. Par exemple, dans un essai, la dose quotidienne d'insuline et le taux d'hémoglobine glyquée étaient statistiquement supérieurs dans le groupe benfluorex lors de l'inclusion (réf. 9).

1- "Benfluorex°" Micromedex 31/03/1996 ; **87** : 9 pages.
2- "Mediator° activité ou non ?" *Rev Prescr* 1986 ; 6 (58) : 42.
3- Noiry JP et Boissel JP "À quoi servent les antidiabétiques oraux ?" *Rev Prescr* 1996 ; **16** (164) : 541-547.
4- "acarbose-Glucor°" *Rev Prescr* 1996 ; **16** (165) : 593-596.
5- Institut de recherches internationales Servier "S780 - benfluorex - brochure pour investigateur" Version n° 1 du 30 mai 1996 (non publié) : 80 pages.
6- Velussi M et coll. "Therapeutic effect of benfluorex in type II diabetic patients on diet regimen alone" *J Diab Complications* 1996 ; **10** (5) : 261-266.
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9- Leutenegger M et coll. "Intérêt de l'adjonction du benfluorex à l'insuline chez des patients diabétiques insulino-traités ayant un surpoids" *Diab Metab* 1996 ; **22** : P43 : 2 pages.
10- Stucci N et coll. "Therapeutic benefit of benfluorex in type II diabetic patients treated with sulfonylrureas" *J Diab Complications* 1996 ; **10** : 267-273.
11- In : Bailey CJ et coll. "Metformin" *N Engl J Med* 1996 ; **334** : 574-579.
12- Brun JM "Efficacité antidiabétique du benfluorex. Données cliniques" *Presse Med* 1992 ; **21** (28) : 1344-1352.
13- Sommariva D et coll. "Effects of benfluorex on serum lipoproteins in diabetic and non-diabetic hypertriglyceridemic patients" *Curr Ther Res* 1986 ; **39** (3) : 281-287.
14- Giustina A et coll. "Effects of benfluorex on glucose tolerance, metabolic control, beta-cell secretion, and peripheral sensitivity to insulin in obese type II diabetic patients on a body weight-maintaining diet" *Curr Ther Res* 1989 ; **45** (1) : 33-42.
15- Cavallo-Perin P et coll. "Benfluorex and blood glucose control in non insulin-dependent diabetic patients" *J Endocrinol Invest* 1991 ; **14** : 109-113.

Essais cliniques comparatifs en double aveugle benfluorex (B) versus placebo (P)

Réf.	Nombre patients	Traitement associé	Résultats après 3 mois de traitement			
			glycémie à jeun (mmol/l)	Hb glyquée (%)	insulinémie à jeun (mU/l)	Autres résultats
5,6	32	non	B -1,3 (±1,0) P -0,5 (±1,3) NS	B -0,6 (±1,0) P +0,3 (±1,1) p=0,024	B -4,9 (±4,3) P -2,7 (± 5,0) NS	
5,7	20	insuline	B -3,0 (±1,9) P -1,6 (±3,3) NS	B -0,6 (±0,6) P +,03 (±1,0) p<0,001	B -0,3 (±5,8) P +10,1 (± 10,1) p=0,02	pas de différence sur les besoins en insuline
5,8	30	insuline	B -0,5 (±2,5) P +1,7 (±3,0) NS	B -2,2 (±1,6) P -0,5 (± 0,9) p=0,006	B -10,2 (±12,7) P -5,0 (±6,8) NS	pas de différence sur les besoins en insuline
9	76	insuline	B -1,45 (±5,28) P +0,15 (±3,88) NS	non similaire lors de l'inclusion	résultat non connu	baisse des besoins en insuline dans le groupe benfluorex
5 (*)	25	sulfamide	B -1,6 (±1,9) P +0,2 (±2,3) p=0,046	B -0,5 (±1,0) P +1,2 (±2,1) p=0,023	B -4,8 (±4,7) P -0,7 (±9,6) NS	
5,10	68	sulfamide	B -1,4 (±?) P -0,3 (±?) p=0,009	B -0,66 (±1,14) P -0,14 (±1,04) p=0,007	B -0,8 (±4,0) P -1,3 (±5,6) NS	

* Étude Louvet.

MEDIATOR°

► peut être notée chez 7 à 10 % des patients sous *benfluorex* (1), et une diarrhée a été observée chez 25 % des patients dans un essai non comparatif (13). Dans un autre essai, 5 patients sur 34 ont arrêté le *benfluorex* pour effets indésirables (contre 2 patients sur 34 sous placebo) (10).

Conclusion

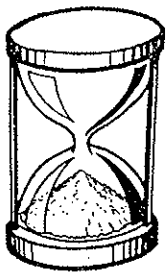
Après 20 ans de commercialisation du *benfluorex* (Mediator°), on ne sait toujours pas à quoi sert ce médicament administré aux diabétiques. Aucun essai au long cours, prenant en compte la morbimortalité du diabète n'est disponible.

Quelques essais comparatifs versus placebo réalisés à court terme (3 mois) chez des diabétiques non insulinodépendants montrent que le *benfluorex* en monothérapie ou en association avec l'insuline ou avec un sulfamide hypoglycémiant réduit l'hémoglobine glyquée. Une réduction de la glycémie à jeun n'a été observée que dans deux essais sur six. Ces effets sont cependant modestes, permettant rarement de ramener la valeur de ces paramètres dans les limites considérées comme la normale. Le seul essai comparant le *benfluorex* à la *metformine* (Glucinan°, Glucophage°, Stagid°) est ininterprétable.

Le *benfluorex* a des effets indésirables, à la dose officiellement recommandée de 450 mg/jour : somnolence et diarrhée, entre autres. Mais ni le profil d'effets indésirables du *benfluorex*, ni leur fréquence ne sont connus avec précision.

Il n'y a actuellement aucune raison de traiter les diabétiques non insulinodépendants avec le *benfluorex*. Le maintien sur le marché et la prise en charge par l'assurance maladie de ce médicament doivent être reconsidérés.

Annexe 3-53



Avec plus de recul

benfluorex pour quoi faire ?

Le *benfluorex*, Mediator° des laboratoires Biopharma (du groupe Servier), est commercialisé en France depuis 1976, sous forme de comprimés dosés à 150 mg (a). Chimiquement, le *benfluorex* est proche d'autres substances anorexigènes (b)(1). En France, le *benfluorex* possède deux indications officielles. Nous avons revu récemment, "avec plus de recul", son dossier d'évaluation dans l'indication "traitement adjuvant du diabète avec surcharge pondérale", pour conclure que ses effets limités (sur des critères intermédiaires) ne justifiaient pas sa prescription chez les diabétiques (2).

La deuxième indication officielle du *benfluorex* concerne les hypertriglycéridémies (lire en encadré ci-contre). Elle suscite régulièrement des demandes de la part de lecteurs de la revue, parfois soumis par certains visiteurs médicaux à une promotion intensive. En réalité, la question primordiale qui se pose est la suivante : chez les patients atteints d'hypertriglycéridémie, est-il démontré que le *benfluorex* possède des effets bénéfiques sur les seuls critères cliniquement pertinents, la morbidité cardiovasculaire et la mortalité, chez les patients sans antécédents (prévention primaire) et/ou avec antécédents cardiovasculaires (prévention secondaire) ?

Une conférence de consensus aux États-Unis d'Amérique a été consacrée à l'hypertriglycéridémie (3). Selon cette conférence, seules les hypertriglycéridémies importantes justifient une prise en charge thérapeutique ayant pour but non seulement de réduire l'hypertriglycéridémie, mais surtout de diminuer les taux de LDL-cholestérol et d'augmenter ceux de HDL-cholestérol ; les liens de causalité entre fractions du cholestérol et morbidité cardiovasculaire étant mieux établis que pour la triglycéridémie. Le traitement de première intention d'une hypertriglycéridémie est fondé sur l'hygiène de vie (suppression du tabac et de l'alcool, lutte contre la sédentarité) et le régime alimentaire (apport plus important en poissons gras). Selon cette conférence de consensus américaine, les médicaments ne sont utiles qu'en seconde intention (3).

Les hypolipémiants permettant une réduction marquée des hypertriglycéridémies sont les fibrates, les dérivés de l'acide nicotinique et l'huile de chair de poisson (Maxepa°) (c)(3,4). Le *gemfibrozil* (Lipur°), un fibrate, est le seul de ces médicaments pour lequel un effet préventif, sur des critères cliniques, ait été démontré lors d'un essai ▶▶

a- En Europe, le benfluorex est également commercialisé en Espagne, en Grèce, en Italie, au Luxembourg, au Portugal et en Suisse (réf.1). Le benfluorex n'est commercialisé dans aucun pays anglosaxon et du Nord de l'Europe.

***b-** En France, le benfluorex est bizarrement classé. Il n'est pas officiellement classé parmi les anorexigènes pour ce qui concerne les spécialités : de ce fait, Mediator° ne fait pas l'objet d'une prescription restreinte. Cependant, un arrêté du 25 octobre 1995 (Journal Officiel du 31 octobre 1995 : 15 937) inclut le benfluorex dans une liste de substances qui ne doivent pas être incorporées dans des préparations magistrales et cette liste ne comporte que des anorexigènes. Par ailleurs, le suffixe "orex" est attribué aux dénominations communes internationales des substances anorexigènes par l'Organisation mondiale de la santé (OMS) (réf. 1), et le benfluorex figure dans la liste des substances dopantes, dans le groupe des "amphétamines et autres excitants" (Dictionnaire Vidal édition 1997, page 6).*

***c-** Les inhibiteurs de l'HMG-CoA réductase (alias statines) ont un effet modeste sur la triglycéridémie.*

1- "Benfluorex°" Micromedex 31/03/1996 ; 87 : 9 pages.
2- "Benfluorex antidiabétique ?" *Rev Prescr* 1997 ; **17** (173) : 326-328.
3- NIH consensus development panel on triglyceride, high-density lipoprotein, and coronary heart disease "Triglyceride, high-density lipoprotein, and coronary heart disease" *JAMA* 1993 ; 269 (4) : 505-510.
4- "Lipid regulating agents". In : "Martindale - The Extra Pharmacopoeia" 31ème ed., The pharmaceutical Press, London 1996 : 1299-1302.

MEDIATOR°

comprimés

150 mg de *chlorhydrate de benfluorex* par comprimé
30 comprimés (blancs)..42,90 F

Séc. Soc. 65 % et collect.
Liste I

Lab. Biopharma

hypolipémiant ?

Indication officielle dans les dyslipidémies :
« Adjuvant du régime adapté dans les hypertriglycéridémies. La poursuite du régime est toujours indispensable. Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée ».

Posologie officielle recommandée :
« 3 comprimés par jour ».

Annexe 3-53

évaluant les effets du *benfluorex* sur des critères cliniques.

Nous avons souligné dans un article récent, l'absence de données claires et indépendantes sur les effets indésirables du *benfluorex* (1). Nous n'avons pas recueilli d'éléments nouveaux susceptibles de modifier ce constat.

Conclusion : aucune estimation sérieuse du rapport bénéfices/risques

Le *benfluorex* (Mediator°) est chimiquement apparenté à certains anorexigènes. Son dossier d'évaluation clinique dans les hypertriglycéridémies est pauvre. Aucun essai clinique n'a été réalisé avec des critères d'évaluation cliniques de morbi-mortalité. Les essais versus placebo sont de petite taille, généralement de mauvaise qualité méthodologique, et leurs résultats sur la triglycéridémie sont contradictoires. Aucun des trois essais *benfluorex* versus fibrate n'est interprétable en raison de problèmes méthodologiques.

Ni le profil des effets indésirables du *benfluorex*, ni leur fréquence ne sont connus avec précision.

Il n'y a actuellement aucune raison de traiter les patients ayant une hypertriglycéridémie avec le *benfluorex*. Le maintien sur le marché et la prise en charge de Mediator° par l'assurance maladie doivent être reconsidérés.

9- Ranquin R "Effects of benfluorex on patients with endogenous hypertriglyceridemia" *Curr Med Res Opin* 1987 ; 10 : 521-526.
10- Di Martino G et coll. "Effects of benfluorex in obese patients with metabolic disorders" *Br J Clin Pract* 1989 ; 43 (6) : 201-208.
11- Bianchi R et coll. "Effects of benfluorex on insulin resistance and lipid metabolism in obese type 2 diabetic patients" *Diabetes Care* 1993 ; 16 (4) : 557-559.
12- Balestreri R et coll. "Effet thérapeutique comparé du benfluorex et du clofibrate dans les troubles métaboliques" *Gaz Med de France* 1982 ; 89 (14) : 1636-1644.
13- Di Perri T et Guerrine M "Etude comparative du benfluorex et du clofibrate dans les hyperlipoprotéinémies de type IIa, IIb, IV" *Acta Therapeutica* 1981 ; 7 : 335-343.
14- Sommariva D et coll. "Differential effects of benfluorex and two fibrate derivatives on serum lipoprotein patterns in hypertriglyceridemic type 2 diabetic patients" *Curr Ther Res* 1996 ; 40 (5) : 859-870.

DCI	Belgique	Suisse
benfluorex	–	MEDIAXAL°
bézafibrate	CEDUR° EULITOP°	CEDUR°
clofibrate	ATROMIDIN°	REGELAN°
dexfenfluramine	ISOMERIDE° (1)	ISOMERIDE° (1)
fenfluramine	PONDERAL° (1)	PONDERAL° (1)
fenofibrate	LIPANTHYL°	LIPANTHYL°
huiles de poisson (type Maxepa°)	–	TIMLIC° (2)

1- Spécialité aujourd'hui retirée du marché.
2- Avec le statut de complément alimentaire mais pas de médicament.

MINI-INDEX 1997

L'index complet 1997 ne paraissant qu'en février 1998, cet index résumé permet le repérage des spécialités analysées dans le Rayon des Nouveautés (copies et compléments de gammes exclus), ainsi que les articles de la rubrique Vigilance, avant ce numéro 179.

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AGENCE DU MEDICAMENT
DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le 19 FEV. 1999

Note à l'attention de M. Le Pr ALEXANDRE

Objet : premier cas d'insuffisance aortique sous MEDIATOR (benfluorex)

Une observation d'insuffisance aortique survenue chez un homme de 43 ans, traité depuis 6 ans par MEDIATOR (benfluorex), a été rapportée le 10 février 1999 au CRPV de Marseille.

Il s'agit d'un patient ayant pour antécédents un tabagisme et une hypercholestérolémie. En janvier 1992, ce patient a présenté un infarctus du myocarde inférieur non compliqué. La coronarographie mettait en évidence une lésion interventriculaire antérieure et une insuffisance mitrale minime. Les examens pratiqués (échocardiographie, coronarographie et cathétérisme) ne montraient pas d'insuffisance aortique. Il n'y avait pas de souffle aux examens cliniques pratiqués en mars et juin 1993 et l'épreuve d'effort réalisée en juin 1993 ne montrait aucune anomalie.

Ce patient a été traité de juillet 1992 à octobre 1998 par MEDIATOR (benfluorex) à raison de 300 mg / jour pour surpoids, hypercholestérolémie et sensation hypoglycémique réactionnelle.
Il prenait par ailleurs du VASTEN (pravastatine) : 20 mg / jour depuis janvier 1993, de l'ASPEGIC (acétylsalicylate de DL lysine) : 250 mg / jour depuis 1992 et du TENORMINE (aténolol) : 100 mg / jour depuis janvier 1992.

En octobre 1998, lors d'un examen systématique, un souffle diastolique, facile à percevoir et évocateur d'une insuffisance aortique, est découvert à l'auscultation. Il existe également un souffle systolique d'accompagnement (l'insuffisance mitrale pouvant être rattachée à la cicatrice ischémique de l'infarctus du myocarde de 92).
Il n'existe aucun signe fonctionnel. L'échocardiographie met en évidence une insuffisance aortique nette ainsi qu'une insuffisance mitrale minime.
Il n'y a pas d'argument en faveur d'une endocardite chronique. Par ailleurs, le patient n'a jamais pris d'anorexigènes ou d'amphétamines.

En janvier 1999, l'insuffisance aortique demeure bien tolérée au plan clinique.

Nous avons averti les laboratoires SERVIER afin qu'ils prennent contact directement avec le CRPV de Marseille.
Par ailleurs, nous adressons ce jour à l'Agence Italienne, suite à leur demande, un line-listing accompagné des fiches CIOMS des effets indésirables cardio-vasculaires, pulmonaires et neurologiques graves rapportés en France avec le benfluorex. Nous joindrons à cet envoi l'observation d'insuffisance aortique.

SYSTEME NATIONAL DE PHARMACOVIGILANCE

1794

Annexe 3-54

Fiche N° : MA9900176 - Centre de : MARSEILLE Dossier : Complet

Type : Effet indésirable Date de notification : 10/02/1999 Date de mise à jour :

PATIENT

Age : 43 A Sexe : M Taille : 167 cm Poids : 72 kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Invalidité ou incapacité permanente Evolution : Sujet non encore rétabli

Date apparition : 17/10/1998 Durée :

	Date de survenue
aortique INSUFFISANCE MITRALE	

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2 DF	J	01/07/1992	17/10/1998	6 A	6 A	4	3	2	2	1	2	S

Indication

SALICYLIQUE (ACIDE)

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	250 MG	1 J					3	4					A

Indication

VASTEN

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J	02/01/1993			5 A	3	4					A

Indication

TENORMINE 100 mg , comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J	28/01/1992			6 A	3	4					A

Indication

COMMENTAIRES

MA 9900176

H, né le 28/10/55, 72 kg, présentant une insuffisance aortique découverte en octobre 1998 après traitement prolongé par MEDIATOR (2 cp/j) depuis 6 ans.

ANTECEDENTS : tabagisme, hypercholestérolémie. le 18/1/92 : infarctus du myocarde inférieur non compliqué. Coronarographie : lésion interventriculaire antérieure 50 %. Insuffisance mitrale minime. Pas d'insuffisance aortique décelée.

TRAITEMENT :
- MEDIATOR , po, 2 cp par jour pour surpoids, hypercholestérolémie et sensation hypoglycémique réactionnelle, depuis 92 jusqu'en octobre 98,

- VASTEN, TENORMINE, ASPEGIC depuis 92.

HISTOIRE DE LA MALADIE :
- Mi octobre 98 : découverte lors d'un examen systématique d'un souffle diastolique à l'auscultation, facile à percevoir, évocateur d'une insuffisance aortique.
- Souffle systolique d'accompagnement (l'insuffisance mitrale pouvant être rattachée à la cicatrice ischémique de l'infarctus du myocarde de 92 ?).
- Aucun signe fonctionnel.
- L'insuffisance aortique n'existait pas lors des examens pratiqués en 92 : cathétérisme et coronarographie, échocardiographie réalisées en milieu hospitalier puis en cabinet. Pas de souffle aux examens cliniques pratiqués en mars et juin 93. Epreuve d'effort : RAS en juin 93.

EXAMENS PARACLINIQUES :
- Pour l'effet indésirable :
  * échocardiographie le 17/10/98 : insuffisance aortique nette avec jet large, insuffisance mitrale minime.
- Pour le diagnostic différentiel :
  * pas d'argument en faveur d'une endocardite chronique,
  * jamais aucune prise d'anorexigène ou d'amphétamine.

DLUTION :
insuffisance aortique bien tolérée au plan clinique en janvier 99.

IMPUTABILITE :
Médicament suspect MEDIATOR (benfluorex).

2371

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

RÉPUBLIQUE FRANÇAISE

DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Saint-Denis, le 30 JUIL. 1999

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du Mardi 23 février 1999)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN H), M. ANDREJAK, Mme AUTRET-LECA, Mme BAVOUX, Mme DAVID-LAROCHE (suppléante de M. BECHTEL), M. BIOUR, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), M. CARON, Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme LAMAISON (suppléante de M. ESCHALIER), Mme SGRO (suppléante de M. ESCOUSSE), Mme HARAMBURU, Mme ALT (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme LILLO (suppléante de Mme KREFT-JAIS), Mme GINISTY (représentant le CRPV de Fernand Widal), Mme LAINE-CESSAC, M. LAROUSSE, M. MERLE, M. MONTASTRUC, M. MOULIN, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme JASSON (suppléante de Mme SOUBRIE), Mme TANASESCU (suppléante de M. THUILLEZ), M. TRENQUE, Mme FLEURANCEAU (suppléante de M. VANDEL), M. VIAL.
Madame LAGARDE (représentant Monsieur le Directeur des Hôpitaux),
Madame BARON (représentant Monsieur le Directeur Général de la Santé).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme CHAUVEAU-CHARTRIN
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
M. JACQUET
Melle JULLIAN
M. LANG
Mme PARIENTE-KHAYAT
Melle ROBINE
Melle VERSTUYFT

Assistaient à la réunion :

D.E.V. :
Mme PAVLOVIC
Mme ROSSI

C.R.P.V. :
Melle CASANOVA
Mme CHAUMERLIAC
Mme COUFFIN
Mme FERARD
M. ROUX
M. ROUX
Mme SARAZIN
Mme VEYRAC

Etaient excusés
M. BEGAUD, Vice-Président
M. MALLARET
Monsieur le Directeur Général de l'INSERM
Monsieur le Directeur Général de l'Agence du Médicament

II - TOUR DE TABLE DES CAS MARQUANTS

Seuls sont signalés les cas d'effets indésirables donnant suite à des mesures (mise en enquête, notes, ...) ou faisant l'objet d'une mise au point. La liste complète des cas est jointe en annexe 1.

- **CERVOXAN® (vinburnine), ZYLORIC® (allopurinol), ARICEPT® (donépezil) / CRPV de Nantes** : crise de porphyrie aiguë intermittente chez un homme de 86 ans.
Il n'existe aucune contre-indication pour les porphyries dans les RCP de ces spécialités.
Cette observation soulève le problème de l'absence d'une liste officielle et validée par l'Agence du Médicament, énumérant les médicaments contre-indiqués dans les porphyries.
Le problème est le même pour les médicaments contre-indiqués dans les déficits en G6PD.
→ Une note sera adressée à l'unité des Affaires Réglementaires de la Direction de l'Evaluation.

- **FRAXODI® (nadroparine calcique) / CRPV de Saint-Etienne** : hémorragie massive rétropéritonéale chez un homme de 73 ans après utilisation de FRAXODI® (0,8 ml x 2/j) au lieu de FRAXIPARINE® (0,8 ml x 2/j) initialement prescrite. Il n'existe pas d'équivalence d'activité anti-Xa entre les doses de ces deux spécialités de nadroparine calcique ce qui peut entraîner des confusions.
→ Un note sera adressée à l'attention de l'évaluateur de la classe des HBPM.

- **KETODERM crème 2% (kétoconazole) / CRPV de Caen** : eczéma aigü localisé chez une femme de 23 ans. Le libellé actuel de la rubrique "effets indésirables" du RCP est "1 cas d'eczéma de contact a été rapporté". Plusieurs cas sont rapportés dans la banque nationale ou décrits dans la littérature.
→ L'unité de pharmacovigilance adressera un courrier au laboratoire afin qu'il dépose une demande de modification de l'information.

- **LOPRIL® (captopril) / CRPV de Marseille** : augmentation de la lipase à 3,5 N (amylase normale) chez une femme de 71 ans. Cet effet est mentionné dans le RCP du captopril mais pas dans celui de l'énalapril alors que des cas sont décrits dans la littérature.
→ L'unité de pharmacovigilance adressera un courrier au laboratoire afin qu'il dépose une demande de modification de l'information.

- **MEDIATOR® (benfluorex), VASTEN® (pravastatine), ASPEGIC® (acétylsalicylate de DL lysine), TENORMINE® (aténolol) / CRPV de Marseille** : insuffisance aortique découverte chez un homme de 43 ans traité par benfluorex depuis 6 ans. Aucune prise d'anorexigènes ou d'amphétamines.
→ Le benfluorex qui se métabolise en norfenfluramine, fait l'objet d'une discussion au groupe de travail de pharmacovigilance européen. L'Italie qui envisage de saisir le CSP en vertu de l'article 12, rédige un rapport sur le métabolisme et les données de sécurité de ce produit en collaboration avec la France.

- **OESCLIM® (estradiol) / CRPV de Marseille** : eczéma chez une femme de 45 ans.
→ Cette spécialité est enregistrée selon une procédure de reconnaissance mutuelle (France Etat membre de référence). Dans le dernier RCP datant du mois d'octobre 1998, il est mentionné : "dermatite de contact allergique et démangeaisons". Cependant ce libellé n'apparaît pas au dictionnaire Vidal® 1999.

CENTRE DE PHARMACOVIGILANCE DE MARSEILLE

COMITE TECHNIQUE DU : 23 février 1999

N° des cas	Date de survenue	Sexe /Age	Médicaments suspects	Effets observés	Evol.	Imput	G	N	E	Commentaires *Interaction*
99-121	18 12 98	M,92	LOVENOX 0,6x2/j	J9 :Anémie, Hématome	D	I2	O	N	+/-	HBPM :cf Innohep
99-176	Oct. 98	M,43	MEDIATOR 2/j 6 ans	Insuffisance aortique	F	I2	O	O	O	Pb Europe _ 1° cas
99-113	Janv 99	F,71	LOPRIL	J4 :Augmentation lipase 3,5 N Amylase Normale	A	I1 C2S1	+/-	N	N	Vidal captopril : OK Vidal enalapril : RAS or cas et pub +++enalap.
99-180	Fev 99	F,36	LYSOCLINE	Fièvre à 39° paresthésies	A	I3	+/-	N	+/-	cf minocycline
99-77	Janv 99	F,45	OESCLIM	Eczéma	A	I3	N	O	N	A inscrire au RCP

Problème des modifications de l'annexe II et des notices destinées aux patients sans que les prescripteurs et les pharmaciens en soient avertis ainsi que les CRPV ?

Problème des mises en garde et précautions d'emploi qui ne sont pas reprises dans les effets secondaires ; cf CONTALAX et dépendance.

Réunion des Pharmaciens Sentinelles pour la Santé Publique du 22 février 1999 :

- Mésusage avec Diprosone crème : pour dépigmentation, mélangée à du lait Poupina ou Vichy.
- Boîtes identiques pour CORVASAL* 2mg et 4mg
  PROXALYOC* et SPASFON LYOC*
- Confusion de noms : TERNEURINE, TENORMINE,
  MOCLAMINE, MODAMIDE
  ZECLAR, ZEFRA
  BEVITINE, BELUSTINE
  LOGIRENE, LOGECINE
  COVERSYL, CORVASAL ....

Annexe 3-56

Lettre admission CHU Nord 01/92

. IDM

PHALEAIGUE : PAS de Caillle !

S.C.P. DE CARDIOLOGUES

Docteur Jean-Paul SARRADON
Ancien Interne Médaille d'Or des Hôpitaux
Attaché de Consultation des Hôpitaux
13 1 70059 3

Docteur Antoine ROMANI
Ancien Interne Médaille d'Or des Hôpitaux
Attaché de Consultation des Hôpitaux
13 1 70060 1

18192

DOC N°. 1

PHAse aigue
IDM
dom ich

Nom du Patient

Zabac
CHUSTeur

36

Cher ami

16H15. Madame vous fait rééducation match de TENNIS

- IDM INF. Postérieur. Pas d'IM - Pas de fièvre | pouls sec

2A 9

1 ASPIRINE cpr à 18H.

le SAM Thrombolyse - à domicile

Merci de vous en charger - Prévenir LAGANELLI de

Bien amicalement

1, Place du Vieux Platane - « La Maurelette » - 13015 MARSEILLE - Tél. : 91-60-33-09 - *Sur Rendez-vous*

Annexe 3-56

Assistance Publique
Hôpitaux de Marseille

F.P/MP.B
CENTRE HOSPITALIER REGIONAL ②
HOPITAL NORD
13326 MARSEILLE CEDEX 15
SERVICE DE CARDIOLOGIE
PROFESSEUR S. LEVY
Tél : 91.96.86.84
91.96.86.83

Marseille, le 31/01/1992.

Monsieur le Dr. CHICHE
La Maurelette
1, Place du Vieux Platane
13015 MARSEILLE

Cher Ami,

Tu trouveras ci-joint le compte-rendu de cathétérisme cardiaque effectué à Monsieur [redacted] hospitalisé dans notre Service pour nécrose inférieure thrombolysé à la deuxième heure. Il existe une sténose d'environ 50 à 60% sur l'I.V.A proximale à la limite de la significativité sur le plan angiographique La coronaire droite est strictement normale. Le réseau circonflexe est peu développé normal, La ventriculographie révèle une séquelle importante de nécrose inférieure. Je te le confie pour surveillance cardiovasculaire. Je reste à ta disposition pour toutes informations complémentaires.

Bien Amicalement.

Docteur F. PAGANELLI

Assistant - Chef de Clinique

Doc N°. 2
Cpte rendu
Cathetesme +
Coronaro

HOPITAL NORD
SERVICE DE CARDIOLOGIE
PR S. LEVY

DEPARTEMENT HE CA CO

Doc n° 2
27192 Bis
Pas d'IM Noté
Au ventriculo
Gauche

NOM :

DATE :27/01/92

MEDECIN :

CARDIOLOGUE :Dr CH

MOTIF CATHETERISME :

Infarctus du myocarde dans le territoire inféro latéral thrombolysé à la 1ère heure.

PRESSIONS : AO :109/78 VG :110/02 TDVG :06

OD : VD : AP : PC :

DC : INDEX CARDIAQUE :

CORONAROGRAPHIE SELECTIVE GAUCHE :

Tronc coronaire gauche court normal

Réseau IVA : Plaque d'environ 50% sur l'IVA proximale. Champs d'aval de bonne qualité angiographique

Réseau Cx Mg :moyennement développé indemne de lésions significatives

CORONAROGRAPHIE SELECTIVE DROITE :

Coronaire droite dominante remaniée,sans lésion significative.

VENTRICULOGRAPHIE GAUCHE (OAD ; OAG) : FE :50%

Akinésie inférieure
Altération modérée de la fonction ventriculaire gauche

CONCLUSION :

Lésion monotronculaire(IVA) à la limite de la significativité
Sequelle de nécrose inférieure
Altération modérée de la fonction ventriculaire gauche

DR F PAGANELLI
DR F PIERRON

Annexe 3-56

Doc 3

UNIVERSITE D'AIX-MARSEILLE
ASSISTANCE PUBLIQUE - HOPITAUX DE MARS
HOPITAL NORD - SERVICE DE CARDIOLOG
PROFESSEUR S. LEVY

TEL. SECRETARIAT 91.96.86.83
91.96.86.84
91.96.88.22
TELEFAX 91.96.21.62
URGENCES
SOINS INTENSIFS 91.96.88.58
MEDECIN DE GARDE 91.96.86.88

MARSEILLE, le 7

SL/MA

Monsieur le Docteur G
La Maurelette
1, Place du Vieux Platane

13015 MARSEILLE

Mon Cher Confrère,

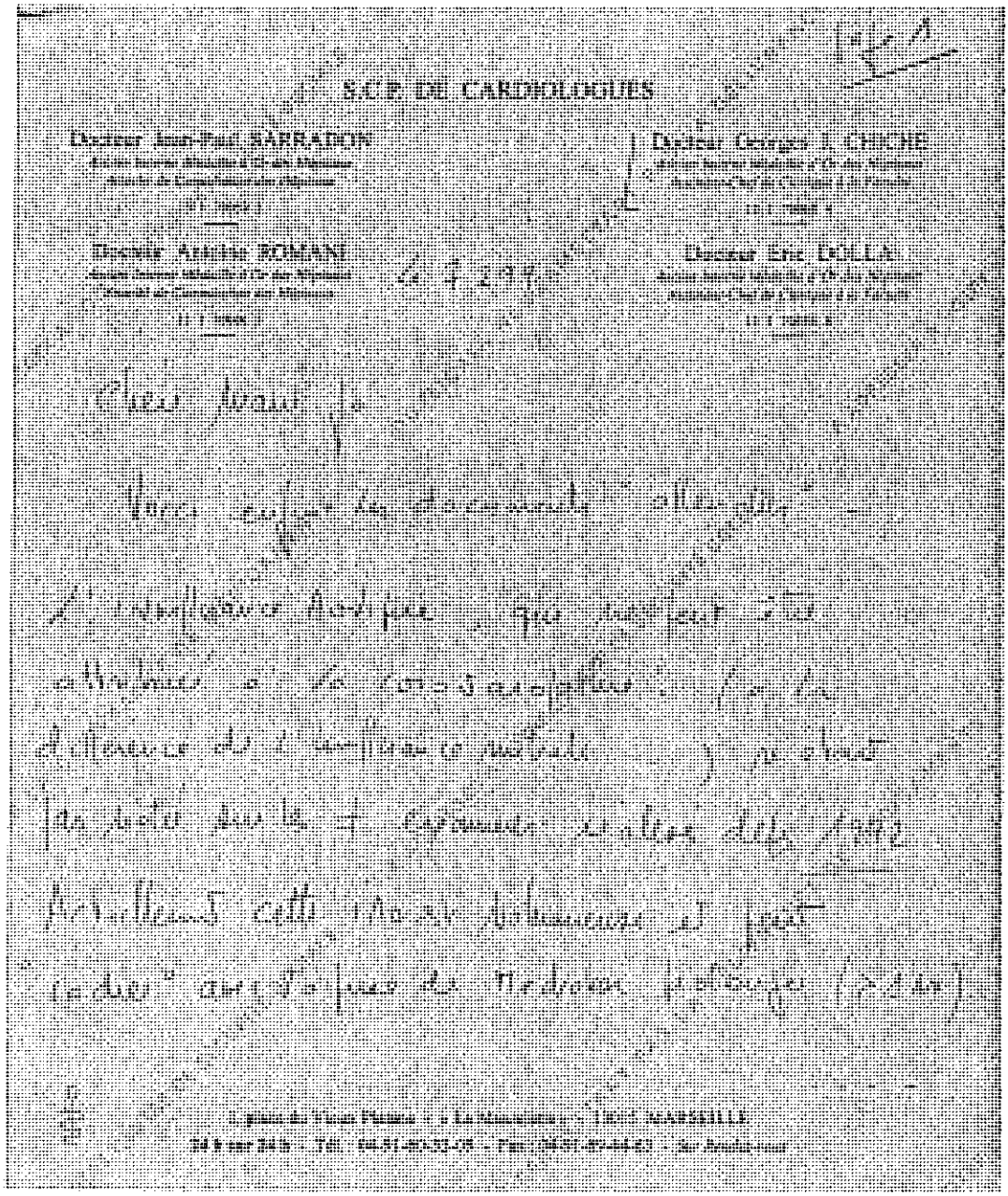
Je tiens à vous adresser personnellement le compte-rendu d'hospitalisation de votre patient [redacted] qui est rentré dans le Service le 18 Janvier 1992.

Je reste à votre disposition pour tous renseignements complémentaires.

Je vous remercie de votre confiance et vous prie d'accepter, Mon Cher Confrère, l'expression de mes sentiments dévoués.

Pr. Samuel LEVY

Annexe 3-56



S.C.P. DE CARDIOLOGUES

Docteur Jean-Paul SARRADON

Docteur Georges J. CHICHE

Docteur Annick ROMANI

Docteur Eric DOLLA

Annexe 3-56

1 page 2

S.C.P. DE CARDIOLOGUES

Docteur Jean-Paul SARRADON
Ancien Interne Médaille d'Or des Hôpitaux
Attaché de Consultation des Hôpitaux
13 1 70059 3

Docteur Georges J. CHICHE
Ancien Interne Médaille d'Or des Hôpitaux
Assistant-Chef de Clinique à la Faculté
13 1 70068 4

Docteur Antoine ROMANI
Ancien Interne Médaille d'Or des Hôpitaux
Attaché de Consultation des Hôpitaux
13 1 70060 1

Docteur Eric DOLLA
Ancien Interne Médaille d'Or des Hôpitaux
Assistant-Chef de Clinique à la Faculté
13 1 70354 8

- - - .

quoiqu'il en soit, il était connu
que le VIDAL mentionne l'allergie
du Benfluorex aux formes des amphétamines
(il note la possibilité de viol ou ⊕ à la recherche
de produits d'abus)
Le Benfluorex est SUR LA LISTE pour ma part
l'objet du médicament concernant les Anorexigènes
(cf Doc 10) Bien amicalement

1, place du Vieux Platane - « La Maurelette » - 13015 MARSEILLE
24 h sur 24 h - Tél. : 04-91-60-33-09 - Fax : 04-91-69-44-63 - *Sur Rendez-vous*

Annexe 3-56

Centre Hospitalier Régional Universitaire de Marseille

Docteur Marc VALLI
Maître de Conférences des Universités - Praticien Hospitalier
Tél. Direct : 04 91 74 49 77 - Mobile : 06 82 88 46 92
Fax : 04 91 74 24 18 - Mél : mvalli@mail.ap-hm.fr

CENTRE ANTI-POISONS

CENTRE REGIONAL DE PHARMACOVIGILANCE

- **Dr Marie-Josèphe JEAN-PASTOR**
  Praticien Hospitalier
  Mél : mjpastor@ap-hm.fr
- **Dr Marie-Claude GALLAND**
- **Dr Nhan NGUYEN**
- **Dr Nathalie PROST**
- **Dr Francis RODOR**
- **Dr Lucia TICHADOU**

Marseille, le 26 février 1999

M le Dr. **Georges CHICHE**
Cabinet de Cardiologie
1, place du Vieux Platane
« La Maurelette »

13015 MARSEILLE

N REF : MJJP/JS/141

OBJET : **MEDIATOR, insuffisance aortique.**
MA 99-176

Cher ami,

Merci pour les documents que tu m'as envoyés et merci pour l'excellente présentation que tu as faite de l'observation.

Tu trouveras, ci-joint, ce qui a été saisi dans la Banque de Pharmacovigilance à la suite de ta déclaration.

J'ai fait des photocopies et je te renvoie tous tes originaux. Je conserve, comme tu me l'as suggéré, les originaux que je n'ai pas pu photocopier.

Je t'envoie quelques feuilles vierges de déclaration d'effet indésirable... à moins que tu ne préfères écrire sur papier libre.

Bien amicalement,
A bientôt.

Dr. Marie-Josèphe JEAN-PASTOR
Praticien Hospitalier

Annexe 3-56

E HOSPITALIER UNIVERSITAIRE NORD
ice de Cardiologie Pr. S. LEVY
min des Bourrely
326 Marseille Cedex3
él 91 96 83 84

NS

MARSEILLE, LE 04 FEVRIER 1992

COMPTE RENDU D'HOSPITALISATION
****

[redacted]

Ref: 92 078
Dossier N° M 82
[redacted]/281055
Medecin tr.: [redacted]
Cardiologue tr.: Dr CHICHE
Responsable d'Unité : Dr LAURIBE

ENTREE LE: 18/01/92
SORTIE LE: 28/01/92

MOTIF D'HOSPITALISATION:
Infarctus du myocarde

HISTOIRE DE LA MALADIE:
Aprés un match de tennis, apparition de sig ... éructation)
plus barre précordiale peu intense.

ANTECEDENTS:
Asthmatique.Facteurs de risque : tabac, hyp
hérédité : père décédé d'un infarctus de myoc

TRAITEMENT EN COURS:

BILAN A L'ENTREE:
.Etat fonctionnel: Fond douloureux, éructa
.Examen clinique: . TA :90/70mmHg.
.ECG: sus-décalage ST englobant l'onde T
.Radio du thorax: normale.

Doc 3
IM MINIME
a l'écho
" NORMALE "
Pour 1
IDM INF
étendu
(Ao = 0 !)

RESULTATS DES EXAMENS COMPLEMENTAIRES:
.Echo :Séquelle d'infarctus du myocarde i
d'éjection 59 % ; insuffisance mitrale minim...
.Angio-coronarographie :Lésion monotroncülaire inter ventriculaire
antérieure à la limite de la significativité ; coronaire droite
remaniée sans lésion significative. Akinésie inférieure. Fraction
d'éjection 50 %.
.Examens Biologiques :Pic CPK : 6425 Cholestérol : 6.9
Triglycérides : 2.6

EVOLUTION DURANT L'HOSPITALISATION:
- Thrombolyse par Actilyse - Streptase à la 2ème heure avec signe
de reperméation électrocardiographique et clinique. Pas de signe
d'insuffisance cardiaque.

TRAITEMENT DE SORTIE:
TENORMINE : 1 comprimé par jour

CONCLUSIONS
Infarctus du Myocarde inférieur non compliqué thrombolysé à la 2ème
heure chez un patient de 36 ans. Coronarographie : lésion inter
ventriculaire antérieure 50 % ; coronaire droite remaniée.sans lésion Significative

Doc 4

écho du 6/02/92

- Hypoecmie INF

- PAS d'doppler

d'jet de fuite sur ce document

Mais ...

ouvre mot clé

VA de FLUTTERING DIASTOLIQUE des feuillets M. TRAVX

⇒ PAS IAO

Annexe 3-56

cerfa N°

ASSURANCE MALADIE
PROTOCOLE D'EXAMEN SPÉCIAL
ARTICLE L. 324-1 DU CODE DE LA SÉCURITÉ SOCIALE - ARTICLE 1038 DU CODE RURAL

VOLET 3
A RETOURNER AU MÉDECIN TRAITANT

ORIGINE ▶

C.N.A.M.T.S.
IDENTIFIANT MÉDICAL
DU CONTRÔLE MÉDICAL lyon
13914 MARSEILLE CEDEX 19

Dr Saindon

Doc 5
demande ACD
Pas de soufflés
mentionné
03/93

IDENTIFICATI
(Ne pas compléter si le cadre
NOM - Prénom :
NUMÉRO D'IDENTIFICATI

IDENTIFICA
(A compléter seulement par
NOM DE L'ÉTABLISSEMI
ADRESSE :
NUMÉRO F.I.N.E.S.S. :
CATÉGORIE DE L'ÉTABLISSEMENT :
DISCIPLINE D'ÉQUIPEMENT DU SERVICE :
NOM DU SERVICE :
NOM DU CHEF DE SERVICE :

Si le praticien exerce dans un établissement d'hospitalisation public, préciser si l'examen spécial a été effectué dans le cadre de son activité privée ☐ OUI ☐ NON

RÈGLEMENT D'HONORAIRES D'EXAMEN CONJOINT

L'organisme d'assurance maladie règle directement au médecin traitant le montant de l'acte pratiqué. Toute demande d'honoraires auprès du malade est proscrite.

MODE DE RÈGLEMENT :

☒ VIREMENT A UN COMPTE POSTAL, BANCAIRE OU DE CAISSE D'ÉPARGNE
Lors de la première demande de remboursement par virement à un compte postal, bancaire ou de caisse d'épargne ou en cas de changement de compte, JOINDRE LE RELEVÉ D'IDENTITÉ correspondant.

☐ Autre mode de paiement :

DATE DE L'EXAMEN : 19/02/93

SIGNATURE ET CACHET DU PRATICIEN OU DE L'ÉTABLISSEMENT

03 Cardiologie et Médecine des Affections Vasculaires
S.C.P. 1, Place du Vieux Platane
La Maurelette
13015 MARSEILLE "CONVENTIONNÉ"
13 1 70068 4 0 1 22 0

RENSEIGNEMENTS CONCERNANT L'ASSURÉ(E) (1)

Nom du Patient .....

RENSEIGNEMENTS CONCERNANT LE MALADE (1)

LE BÉNÉFICIAIRE DES SOINS :
☒ ASSURÉ(E)
☐ CONJOINT(E)
☐ ENFANT
☐ AUTRE AYANT DROIT

NOM - Prénom :
DATE DE NAISSANCE :
SEXE : ☐ M ☐ F

EN CAS D'HOSPITALISATION

DATE D'ENTRÉE DU MALADE :
NUMÉRO D'ENTRÉE :

CADRE RÉSERVÉ AU SERVICE MÉDICAL (1)

AVIS DU MÉDECIN CONSEIL :
☒ ACCORD
☐ Article L. 324-1 du Code de la Sécurité Sociale - Article 1038 du Code Rural
☒ Exonération du ticket modérateur
☒ A.L.D. 30 ☐ A.L.D.* (hors liste) ☐ A.L.D.** (pathologies multiples)
☐ DÉSACCORD
NATURE ET MOTIFS :

En cas de désaccord et avant d'émettre son avis, le médecin conseil est instamment appelé à entrer en contact avec le médecin traitant, dans la semaine qui suit, afin d'aboutir dans la concertation à un accord.

Je soussigné docteur : M. SOURDET

Médecin conseil, certifie que le médecin identifié ci-contre, a établi un protocole d'examen spécial (2)

☐ Pour soins ou arrêt de travail > 6 mois n'ouvrant pas droit à l'exonération du ticket modérateur :
☐ C 1.5 ☐ V 1.5 ☐ I K F

☒ Pour un examen spécial ouvrant droit à l'exonération du ticket modérateur
☒ C 2.5

DATE : 26/03/93

SIGNATURE DU MÉDECIN CONSEIL ET CACHET DU SERVICE MÉDICAL

★Docteur M. SOURDET★
Médecin Conseil

(1) Cocher la case de la réponse exacte
(2) Honoraires non cumulables : cocher une seule case.

Annexe 3-56

INFORMATIONS SUR LA MALADIE CONCERNÉE

EXAMEN CONJOINT POUR SOINS CONTINUS OU ARRÊT DE TRAVAIL > 6 MOIS N'OUVRANT PAS DROIT A L'EXONÉRATION DU TICKET MODÉRATEUR - ARTICLE L. 324-1 DU CODE DE LA SÉCURITÉ SOCIALE - ARTICLE 1038 DU CODE RURAL (1)

DIAGNOSTIC DE L'AFFECTION DE LONGUE DURÉE ET DESCRIPTION CLINIQUE (Joindre les résultats des examens complémentaires récents) — DATE DE DÉBUT : | | | | | | | | |

TRAITEMENT : Classes thérapeutiques - Hospitalisation - Périodicité et nature des examens complémentaires envisagés :

DURÉE PRÉVISIBLE DES SOINS : — DURÉE PRÉVISIBLE D'ARRÊT DE TRAVAIL :

RECLASSEMENT PROFESSIONNEL ENVISAGÉ : ☐ OUI ☐ NON

OBSERVATIONS COMPLÉMENTAIRES :

SI L'AFFECTION DÉCRITE ENTRE DANS LE CADRE DE L'EXONÉRATION DU TICKET MODÉRATEUR, REMPLIR L'ENCADRÉ CI-DESSOUS

PROTOCOLE INTER RÉGIMES D'EXAMEN SPÉCIAL OUVRANT DROIT A L'EXONÉRATION DU TICKET MODÉRATEUR ARTICLES L. 322-3.3 ET L. 322-3.4 DU CODE DE LA SÉCURITÉ SOCIALE (3)

DIAGNOSTIC DE(S) L'AFFECTION(S) EXONÉRANTE(S) - Cocher une seule case.

☒ AFFECTION(S) SUR LISTE - A.L.D. 30

☐ PROCÉDURE EXCEPTIONNELLE - A.L.D.* (hors liste).

☐ ASSOCIATION D'AFFECTIONS CARACTÉRISÉES A L'ORIGINE DE L'ÉTAT PATHOLOGIQUE INVALIDANT - A.L.D.** (pathologies multiples).

artério pathie chronique (Cnonante) avec manifestations clinique ischemique.

ARGUMENTS CLINIQUES ET RÉSULTATS DES EXAMENS COMPLÉMENTAIRES RÉCENTS SIGNIFICATIFS :

- IDM inf en 10/11 avec ↓ thrombose Cnonaire droite
- ZT par thrombolyse — Cnonaire = bonne modérée
- Lésions étendues d'1 ancienne VG — IVA en plus
- Infarctus avec ESV ++

PROJET THÉRAPEUTIQUE DE (OU DES) L'AFFECTION(S) EXONÉRANTE(S) : Classes thérapeutiques - Périodicité et nature des examens complémentaires envisagés - Soins paramédicaux - Hospitalisation etc.

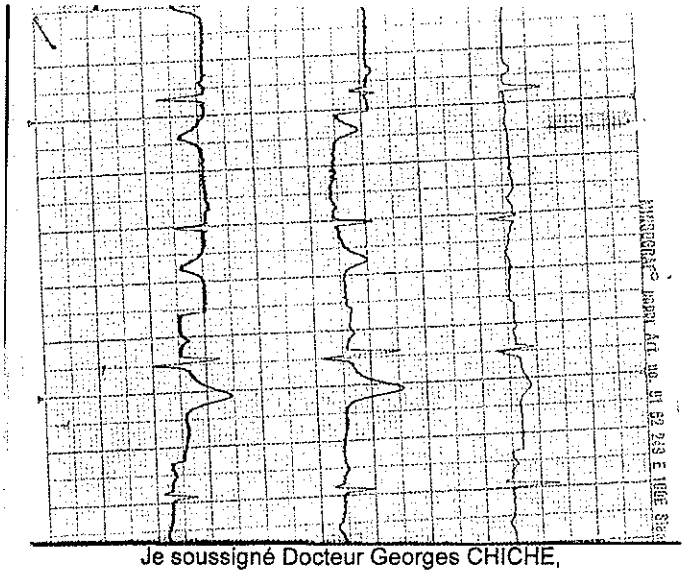
ZT par bétabloquants (Contre indiqué)
par ASPIRINE
par Lopril
par Hypolipémiants

OBSERVATIONS COMPLÉMENTAIRES :

SIGNATURE ET CACHET DU PRATICIEN OU DE L'ÉTABLISSEMENT

(3) Rappel des dispositions légales au verso du volet 3.

Annexe 3-56



"double" certificat médical

Doc 7

état clinique

06/93

Souffles = 0

Je soussigné Docteur Georges CHICHE,

Certifie donner mes soins à MR Nom patient ...

qui a présenté un infarctus du myocarde de siège inférieur en JANVIER 92

Cet infarctus a pu être thrombolisé avec succès en moins de 3h après le début du symptome.

L'évolution hospitalière a été favorable. La coronarographie de controle réalisée a montré une liberté totale de l'artère coronaire droite responsable de l'infarctus.

On ne retrouvera que quelques irrégularités sur le réseau gauche.

Il existait comme facteur de risque, une hyperlipidémie mixte, et un tabagisme modéré.

Ces deux facteurs ont été totalement supprimés tant pour le tabagisme que pour l'hyperlipidémie mixte grace à un traitement par VASTEN.

Actuellement Nom patient ... est totalement asymptomatique, il a repris ses activités professionnelles sans restriction.

Ses épreuves d'effort strandart, couplées à une scintigraphie du myocarde au thallium, et couplées à une échographie d'effort sont tout à fait satisfaisantes.

En effet, il n'y a ni angor ni modification du segment ST, ni trouble du rythme ventriculaire.

L'imagerie ne retrouvera qu'un défaut limité au niveau de la cicatrice inférieure, ou une simple hypocinésie au niveau de la paroi inférieure à l'échographie d'effort.

On ne retrouve pas de dyskinésie.

Son traitement comporte une association de béta bloquant (TENORMINE), d'I E C (LOPRIL) d'ASPEGIC et d'hypolipémiant (VASTEN)

Monsieur mène une vie normale, assume parfaitement ses activités professionnelles.

On peut considérer que le pronostique global de cette coronaropathie aigue est excellent.

Remis en mains propres pour servir et valoir ce que de droit.

MARSEILLE, le 23/06/93

Annexe 3-56

COMMENTAIRES ET CONCLUSIONS

TYPE DE L'EPREUVE :
- [ ] A charge constante
- [X] En paliers de charge croissante

TRAVAIL FOURNI :
- En watts en : 210 W
- En % de la capacité aérobie maximale : queu normale
- Double produit :

CAUSE D'ARRET :

[ ] Décision préalable	[ ] Céphalée, vertige, malaise	[ ] Altération ST.T
[X] Fréquence atteinte	[ ] Inadaptation tensionnelle	[ ] Troubles du rythme
[X] Epuisement musculaire	[ ] Douleur thoracique	[ ] Troubles de conduction

ADAPTATION A L'EFFORT : BONNE

REPONSE TENSIONNELLE : N

SYMPTOMES : RAS

DONNEES ELECTROCARDIOGRAPHIQUES :
- RAS

CONCLUSIONS :

(A) épreuve menée jusqu'à 210 W

SAN) aujourd'hui - SAN) modifications ST

(B) acte à ce jour : PAS d'altération de la conduite INF aux 210 W !

Dr Gomez

Annexe 3-56

NOM :

DATE :

MEDECIN TRAITANT :

PROFESSION :

AGE :

SEXE :

CARDIOLOGUE :

TRAITEM

Nom du patient ....

BUT DE

Rc 1

ELECTROCARDIOGRAMME DE REPOS :

2 Lobul 50 / Atrop 0,50 / Water
2 Medad. / 1,5 TD Nu /

W 18.693

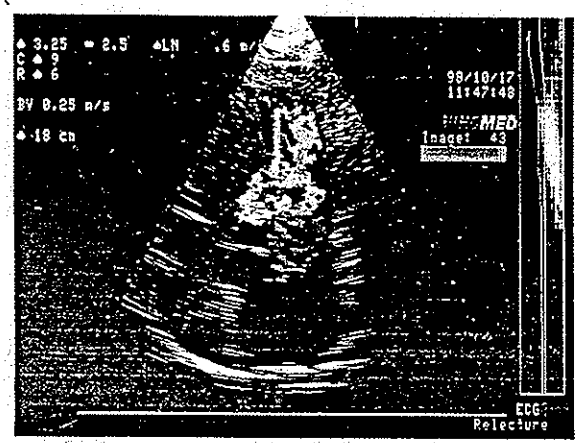
EPREUVE	CHARGES	F.C.	P.A.S.	P.A.D.
DECUBITUS		71	13	7
ASSIS				
EFFORT : ECHAUFF.				
1	30 W	88	13	8
2				
3	60 W	96	14	7
4				
5			14,5	7
6	90 W	110		
7				
8	120 W	123	16	8
9				
0	150 W	141	16,5	8
1		145	14	8
2	180 W			
3	210 W	150	Stop	
4				
5				

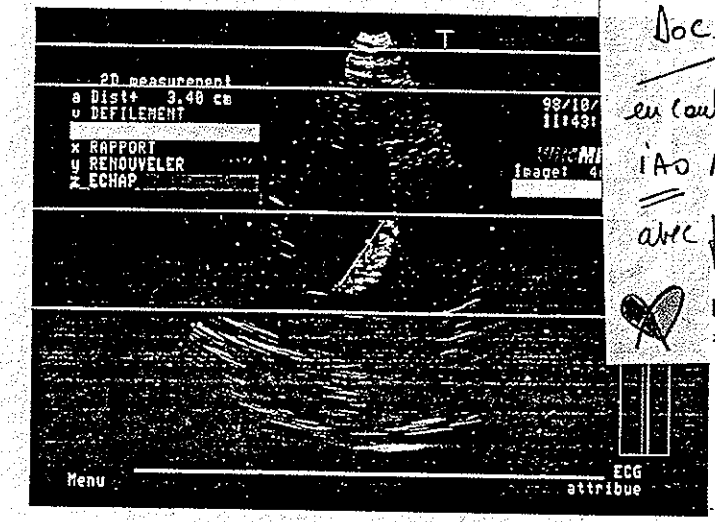
Doc 6
18/6/93
ellw ok

RECUPERATION :

1	R.	16	8
2			
3	12	14	8
4			
5			
6			

1107.





Doc 9
en couleur
IAo Nette
avec jet "Large"
IM minime

→ IAo grade II
→ Bon VG : FE 66%
→ IM (+) (I)

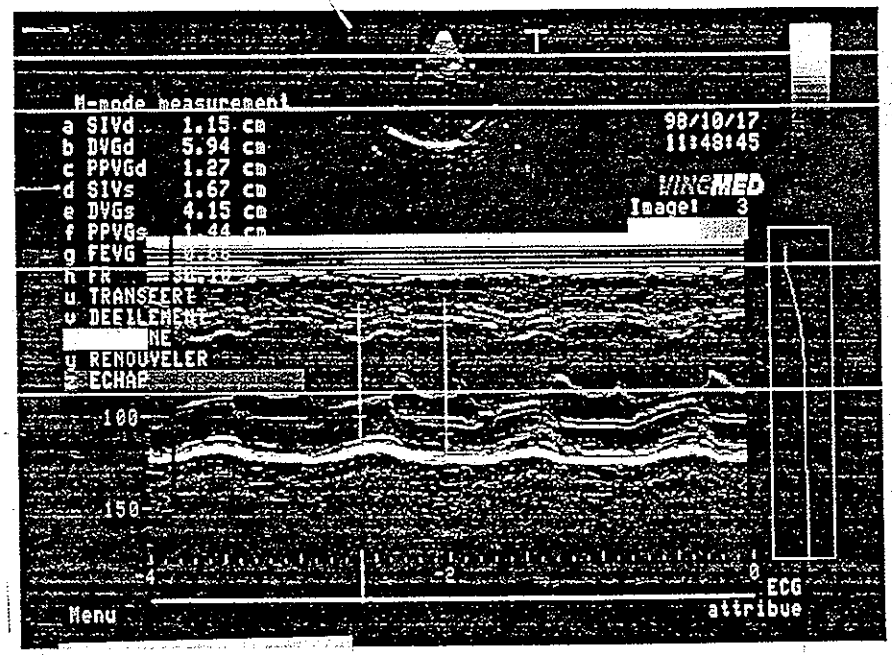
→ Cause Actuelle = Prod de Sanie

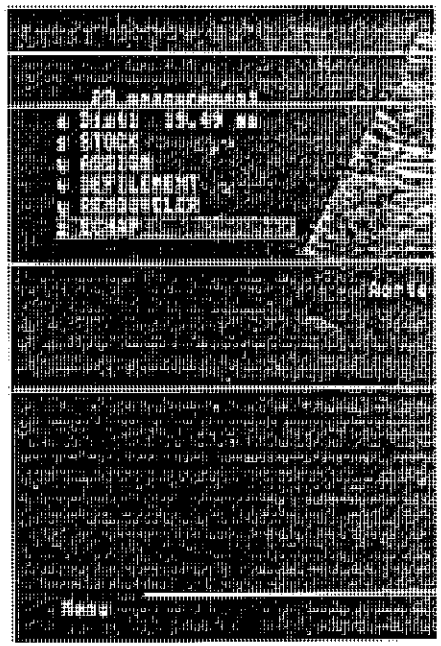
Cause : Médiator ?

doc 9 "Bis"
↓ L'AUSCULTATION et IMPREGNANTE
Prise de médiator depuis plusieurs Mois +++

1815

Annexe 3-56



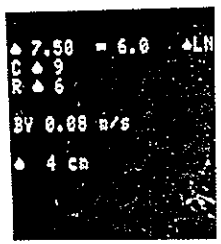


Doc 8

echo couleur du 17/10/98.

Noter le fluttering des feuillets mitraux

= IAO



Annexe 3-56

SYSTEME NATIONAL DE PHARMACOVIGILANCE

Fiche N° : MA9900176 Centre de : MARSEILLE Dossier Complet

Date de notification : 10/02/1999 Date de mise à jour :

PATIENT

Age : 43 A Sexe : M Taille : 167 cm Poids : 72 kg

Antécédents

Cause de décès

EFFET(S) INDESIRABLE(S)

Gravité : Invalidité ou incapacité permanente Evolution : Sujet non encore rétabli

Date apparition : 17/10/1998 Durée :

Date de survenue

INSUFFISANCE MITRALE) AORTIQUE

MEDICAMENT(S)

MEDIATOR 150 mg, comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	2 DF	J	01/07/1992	17/10/1998	6 A	6 A	4	3	2	2	1	2	S

Indication

TENORMINE 100 mg , comprimé enrobé

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J	28/01/1992			6 A	3	4					A

Indication

VASTEN

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	1 DF	1 J	02/01/1993			5 A	3	4					A

Indication

SALICYLIQUE (ACIDE)

Lot	Voie	Dose	Fréquence	Du	au	Durée	Délai surv.	Dech	Rech	C	S	B	I	OMS
	PO	250 MG	1 J					3	4					A

Indication

COMMENTAIRES

MA 9900176

H, né le 28/10/55, 72 kg, présentant une insuffisance aortique découverte en octobre 1998 après traitement prolongé par MEDIATOR (2 cp/j) depuis 6 ans.

ANTECEDENTS : tabagisme, hypercholestérolémie. le 18/1/92 : infarctus du myocarde inférieur non compliqué. Coronarographie : lésion interventriculaire antérieure 50 %. Insuffisance mitrale minime. Pas d'insuffisance aortique décelée.

TRAITEMENT :
- MEDIATOR , po, 2 cp par jour pour surpoids, hypercholestérolémie et sensation hypoglycémique réactionnelle, depuis 92 jusqu'en octobre 98,
- VASTEN, TENORMINE, ASPEGIC depuis 92.

Annexe 3-56

Fiche N° : **MA9900176** Centre de : **MARSEILLE** Dossier Complet

HISTOIRE DE LA MALADIE :
- Mi octobre 98 : découverte lors d'un examen systématique d'un souffle diastolique à l'auscultation, facile à percevoir, évocateur d'une insuffisance aortique.
- Souffle systolique d'accompagnement (l'insuffisance mitrale pouvant être rattachée à la cicatrice ischémique de l'infarctus du myocarde de 92 ?).
- Aucun signe fonctionnel.
- L'insuffisance aortique n'existait pas lors des examens pratiqués en 92 : cathétérisme et coronarographie, échocardiographie réalisées en milieu hospitalier puis en cabinet. Pas de souffle aux examens cliniques pratiqués en mars et juin 93. Epreuve d'effort : RAS en juin 93.

EXAMENS PARACLINIQUES :

- Pour l'effet indésirable :
  * échocardiographie le 17/10/98 : insuffisance aortique nette avec jet large, insuffisance mitrale minime.
- Pour le diagnostic différentiel :
  * pas d'argument en faveur d'une endocardite chronique,
  * jamais aucune prise d'anorexigène ou d'amphétamine.

EVOLUTION :
insuffisance aortique bien tolérée au plan clinique en janvier 99.

IMPUTABILITE :
Médicament suspect MEDIATOR (benfluorex).

AGENCE
PRODUITS SANTE
DIRECTION DE L'EVALUATION
Unité de Pharmacovigilance

Annexe 3-57

Saint-Denis, le 17 JUIN 1999

Note à l'attention de M. Le Pr ALEXANDRE

Objet : Hypertension artérielle pulmonaire (HTAP) sous MEDIATOR® (benfluorex)

L'unité de pharmacovigilance vient d'être contactée par le Pr SIMONEAU de l'Hôpital Antoine Béclère qui s'étonne de ne pas avoir été informé que le benfluorex se métabolisait en norfenfluramine (métabolite de la fenfluramine) et qu'il pouvait induire des HTAP.
Son appel fait suite à l'hospitalisation récente dans son service d'une patiente traitée par MEDIATOR® et présentant une HTAP.

Cette observation a été rapportée la semaine dernière au CRPV de Paris St-Antoine par le médecin qui suivait la patiente avant qu'elle soit ré-adressée pour exploration à l'hôpital A. Béclère.
A ce jour, nous disposons de peu d'information sur ce cas. Il s'agit d'une patiente de 50 ans traitée par benfluorex depuis 4 ans. Une dyspnée est apparue en décembre 1998. En mars 1999, il y a une exacerbation de la symptomatologie. Les examens réalisés mettent en évidence une HTAP d'allure primitive (PAPS à 91 mmHg) avec absence de shunt droit-gauche, EFR normales. La scintigraphie pulmonaire a permis d'éliminer une maladie thrombo-embolique chronique.
Le CRPV de Paris Saint-Antoine et le Pr Simoneau documentent l'observation.

En France, depuis 1995, le benfluorex a fait l'objet d'une enquête officieuse qui est devenue officielle en mai 1998. L'un des motifs de cette enquête était la métabolisation du benfluorex en 9 métabolites dont le principal est la norfenfluramine qui est également le métabolite de la fenfluramine.
11 observations d'HTAP ont été rapportées dans cette enquête. Dans 10 cas, le benfluorex était associé à de la dexfenfluramine et dans 1 cas à de l'amfépramone et du clobenzorex. Par ailleurs, 9 de ces 11 cas ont été expertisés dans le cadre de l'enquête officielle sur les anorexigènes.

Le nouveau cas rapporté au CRPV de Paris St-Antoine est le premier cas d'HTAP rapporté avec le benfluorex utilisé en monothérapie.

Il est à noter qu'à la demande de l'Agence italienne, le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen de pharmacovigilance (l'Italie et la France sont rapporteurs du dossier). Les données de notification spontanée et de pharmacocinétique disponibles ne permettent pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex. Le groupe de travail des 10 et 11 juin dernier a proposé que les deux pays rapporteurs adressent une liste de questions au laboratoire en demandant notamment la réalisation d'une étude de pharmacocinétique du benfluorex et de ses métabolites.

Au vu de ce nouveau cas d'HTAP qui vient s'ajouter au cas d'insuffisance aortique rapporté en février 1999 (cf. note ci-jointe), et compte-tenu de l'inquiétude des cliniciens, devons-nous accélérer la ré-évaluation de ce dossier ?

Annexe 3-58

Direction de l'Evaluation
Unité de pharmacovigilance

MEDIATOR® (benfluorex)

Résumé pour la Commission d'AMM du 8 juillet 1999

En France, le benfluorex a fait l'objet d'une enquête officieuse dès 1995 en raison de sa parentée structurale avec les anorexigènes amphétaminiques. Cette enquête est devenue officielle en mai 1998.

Depuis septembre 1998, à la demande de l'Agence italienne, le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen de pharmacovigilance (l'Italie et la France sont rapporteurs du dossier). L'un des motifs de cette enquête est la métabolisation du benfluorex en 9 métabolites dont l'un des 3 principaux est la norfenfluramine qui est également le métabolite des fenfluramines.

Les données de métabolisme, de pharmacocinétique et de notification spontanée disponibles ont été présentées au groupe de travail européen de pharmacovigilance de juin 1999.

Pharmacocinétique et métabolisme du benfluorex :

L'absorption gastro-intestinale du benfluorex est complète et rapide. Le Tmax est compris entre 1h et 2h.

Le benfluorex est rapidement métabolisé au niveau du foie en 9 métabolites au moins dont les trois principaux sont le S1475, le S422 et la (dl)-norfenfluramine (S585).
La concentration plasmatique de (dl)-norfenfluramine chez l'homme après administration de 3 x 150 mg / j de benfluorex pendant 14 jours est d'environ 40 ng / ml. Cette concentration est très proche de celle retrouvée chez l'homme après administration de 3 x 20 mg / j de fenfluramine qui est d'environ 50 ng / ml.
Il faut toutefois noter qu'après administration de fenfluramine, la quantité circulante de norfenfluramine vient s'additionner à celle de la fenfluramine ce qui n'est pas le cas après benfluorex.

Données de pharmacovigilance :

L'enquête de pharmacovigilance a été réalisée d'après les observations rapportées aux CRPV et au laboratoire jusqu'au 15 décembre 1998, soit 265 notifications.

Depuis la mise sur le marché du MEDIATOR®, les ventes correspondent à plus de 25 millions de mois de traitement.

Effets indésirables	enquête jusqu'au 15/12/98
cutanés et allergiques	64
neuro-psychiatriques	48
hépatiques	25
digestifs	21
métaboliques	21
respiratoires	20
vertiges	20
cardio-vasculaires	18
hématologiques	14
urologiques	13
divers	1
TOTAL	265

- **Atteintes respiratoires** : il s'agit principalement d'hypertension artérielle pulmonaire (HTAP) et de toux. Jusqu'au 15 décembre 1998, 11 observation d'HTAP ont été rapportées. Dans tous les cas, le benfluorex était associé à de l'ISOMERIDE® (dexfenfluramine) (10 cas) ou à de l'amfépramone et du clobenzorex (1 cas). 6 cas sur 11 ont été classés en HTAP d'allure primitive.

- **Atteintes cardio-vasculaires** : il s'agit principalement de cas d'HTA (3 cas), de tachycardie (2 cas), de syndromes de Raynaud (3 cas) et d'une fibrillation auriculaire pour laquelle le benfluorex était associé à de l'amfépramone.
En février 1999, une observation d'insuffisance aortique a été rapportée sans association avec un anorexigène. L'imputabilité reste douteuse.

- **Atteintes neuropsychiatriques** : il s'agit principalement d'asthénie, de somnolence, agressivité, agitation, nervosité, délire et paresthésies.

- **Atteintes cutanées et allergiques** : il s'agit principalement de chocs anaphylactiques (6 cas), d'oedèmes de Quincke (4 cas), d'urticaires, d'eczéma, de prurit et d'éruptions cutanées. Le RCP devra être modifié en conséquence.

- **Troubles de l'équilibre et vertiges** : cet effet est mentionné dans le RCP.

- **Atteintes hépatiques** : La plupart du temps, le benfluorex est associé à d'autres médicaments qui ont la même imputabilité. L'imputabilité a été jugée plausible dans 7 cas et vraisemblable dans 1 cas.

Annexe 3-58

- **Atteintes digestives** : il s'agit le plus souvent de diarrhées, effet mentionné dans le RCP.

- **Atteintes hématologiques** : l'imputabilité est douteuse dans tous les cas. Il existe très souvent un traitement associé pouvant être responsable de l'effet.

- **Atteintes rénales** : il s'agit le plus souvent de dysurie et pallakiurie.

- **Atteintes métaboliques** : il s'agit principalement d'hypoglycémies, d'hyperlipémies, d'hypertriglycéridémies, de goutte.

Ces données ne permettant pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex, le groupe de travail a souhaité que les pays rapporteurs (France et Italie) proposent des modifications de RCP et adressent une liste de questions au laboratoire en demandant une mise à jour des données de tolérance et la réalisation d'une étude de pharmacocinétique du benfluorex et de ses métabolites chez un petit nombre de volontaires sains après dose unique et dose répétée de benfluorex avec étude de la cinétique à l'état d'équilibre et en fin de course.

C'est alors que mi- juin 1999, un nouveau cas d'HTAP d'allure primitive a été rapporté chez une femme de 51 ans traitée par benfluorex depuis 4 à 5 ans (antécédents d'HTA et hypercholestérolémie). Pas d'autre étiologie retrouvée. Traitement par prostacycline envisagé. Il s'agit du premier cas d'HTAP rapporté avec le benfluorex utilisé sans association de médicament anorexigène.

Compte-tenu de ce cas, l'Agence a adressé un courrier aux laboratoires SERVIER leur demandant de verser une mise à jour des données de tolérance ainsi que les données de pharmacologie et pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines. Un infofax a par ailleurs été envoyé à tous les Etats-Membres.

Ces données ont été versées le 28 juin 1999. Globalement, il existe peu d'éléments nouveaux.

Pharmacocinétique et métabolisme du benfluorex :

Il est à noter que la l-norfenfluramine (représentant la moitié de la (dl)-norfenfluramine) n'aurait pas d'activité métabolique.
Dans le cas de la dexfenfluramine, l'exposition relative (AUC) à la d-norfenfluramine représente environ 50% de l'exposition à la dexfenfluramine. Cette valeur est de 37% pour la fenfluramine et de 4% pour les métabolites S1475 et S422 du benfluorex.

Pharmacologie comparée du benfluorex et des fenfluramines :

Les propriétés hypolipémiantes et antidiabétiques du benfluorex reposent sur l'activité de la molécule mère et de ses métabolites actifs. D'après des travaux menés in vitro dans différents systèmes cellulaires, le S422 et le S1475 sont les métabolites porteurs du plus grand nombre d'activités sur le métabolisme glucidique.

L'activité de la d-norfenfluramine sur le système sérotoninergique serait inférieure à celle de

la d-fenfluramine. L'affinité de la d-norfenfluramine pour le transporteur de la sérotonine serait 9 fois plus faible que celle de la d-fenfluramine. Sur des préparations de synaptosomes, l'inhibition de la capture de sérotonine par la d-norfenfluramine est 3 fois plus faible que celle exercée par la d-fenfluramine.

Données de pharmacovigilance :

Du 15 décembre 1998 au 1er juillet 1999, 22 observations ont été rapportées dans la banque nationale de pharmacovigilance.

Effets indésirables	du 15/12/98 au 01/07/99
cutanés et allergiques	6
neuro-psychiatriques	0
hépatiques	2
digestifs	1
métaboliques	1
respiratoires	1
vertiges	6
cardio-vasculaires	1
hématologiques	1
urologiques	0
divers	3
TOTAL	22

Conclusion

Au total, au vu de toutes ces données, il est difficile d'affirmer que le benfluorex a la même toxicité que les fenfluramines. Cependant, certains doutes persistent notamment en ce qui concerne le devenir de la norfenfluramine. La réalisation d'une étude cinétique des métabolites du benfluorex pourrait permettre de lever ces doutes.
De plus, le RCP devra être modifié afin d'y mentionner notamment les risques de réactions allergiques et cutanées.

Par ailleurs, le service de Pneumologie de l'hôpital A. Béclère entreprend une interrogation de tous les patients ayant une HTAP à la recherche d'une prise antérieure de MEDIATOR®.
Ce dossier devrait être discuté au prochain groupe de travail européen de pharmacovigilance (12-13 juillet 1999).

Annexe 3-59

WP du 12-14 juillet 99 :

→ les Italiens préparent une lettre pour la firme que nous co-signerons -

---

Le 19/07/99

Pour cas unmf aortiq / Marseille.

→ Mme Frich / Marseille / Médecin :

→ cas pour réflexion car on n'est jamais sûr.

Mme Frich a revu le médecin à son cabinet en mai 99.

Après le médecin a été contacté par cardiologue hospitalier qui travail avec le labo en essayant de démonter l'obs.

D'après M.T Jean Paston → pas d'éléments nouveau qui permette d'exclure l'obs.

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

Direction de l'Evaluation
des Médicaments et
des Produits Biologiques
Unité de pharmacovigilance
Dossier suivi par : C. FOSSET MARTINETTI

0 5 OCT. 1999

MEDIATOR® (benfluorex)

Point au 04/10/99

En France, le benfluorex a fait l'objet d'une enquête officieuse dès 1995 en raison de sa parentée structurale avec les anorexigènes amphétaminiques. Cette enquête est devenue officielle en mai 1998.

Depuis septembre 1998, à la demande de l'Agence italienne, le benfluorex fait également l'objet d'une évaluation au niveau du groupe de travail européen de pharmacovigilance (l'Italie et la France sont rapporteurs du dossier). L'un des motifs de cette enquête est la métabolisation du benfluorex en 9 métabolites dont l'un des 3 principaux est la norfenfluramine qui est également le métabolite des fenfluramines.

Les données de métabolisme, de pharmacocinétique[1] et de notification spontanée disponibles ont été présentées au groupe de travail européen de pharmacovigilance des 10 et 11 juin 1999.

Ces données ne permettant pas de conclure sur une possible neurotoxicité ou cardiotoxicité du benfluorex, le groupe de travail a souhaité que les pays rapporteurs (France et Italie) proposent des modifications de RCP et adressent une liste de questions au laboratoire en demandant une mise à jour des données de tolérance et la réalisation d'une étude de pharmacocinétique du benfluorex et de ses métabolites.

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1 **Résumé des données de pharmacocinétique et de métabolisme du benfluorex :**

L'absorption gastro-intestinale du benfluorex est complète et rapide. Le Tmax est compris entre 1h et 2h.

Le benfluorex est rapidement métabolisé au niveau du foie en 9 métabolites au moins dont les trois principaux sont le S1475, le S422 et la (dl)-norfenfluramine (S585).
La concentration plasmatique de (dl)-norfenfluramine chez l'homme après administration de 3 x 150 mg / j de benfluorex pendant 14 jours est d'environ 40 ng / ml. Cette concentration est très proche de celle retrouvée chez l'homme après administration de 3 x 20 mg / j de fenfluramine qui est d'environ 50 ng / ml.
Il faut toutefois noter qu'après administration de fenfluramine, la quantité circulante de norfenfluramine vient s'additionner à celle de la fenfluramine ce qui n'est pas le cas après benfluorex.

Annexe 3-60

En juin 1999, un cas d'HTAP d'allure primitive a été rapporté chez une femme de 51 ans traitée par benfluorex depuis 4 à 5 ans (antécédents d'HTA et hypercholestérolémie) : pas d'autre étiologie retrouvée ; traitement par prostacycline envisagé.
Il s'agit du premier cas d'HTAP rapporté avec le benfluorex utilisé sans association de médicament anorexigène. 11 cas avaient auparavant été rapportés lors d'un traitement associant le benfluorex à de la dexfenfluramine dans 10 cas et à de l'amfépramone et du clobenzorex dans 1 cas.
Le service de Pneumologie de l'hôpital A. Béclère entreprend une interrogation de tous les patients ayant une HTAP à la recherche d'une prise antérieure de MEDIATOR®.

Compte-tenu de ce nouveau cas, l'Agence a adressé le 18 juin 1999, un courrier aux laboratoires SERVIER leur demandant de verser une mise à jour des données de tolérance ainsi que les données de pharmacologie et pharmacocinétique du benfluorex et de ses métabolites et une étude comparative de ces données avec celles des fenfluramines. Un infofax a par ailleurs été envoyé à tous les Etats-Membres de l'Union Européenne.

Ces données ont été versées le 28 juin 1999 et n'apportent pas d'élément nouveau.

Conclusion

Au total, au vu de toutes ces données, il est difficile d'affirmer que le benfluorex a la même toxicité que les fenfluramines. Cependant, certains doutes persistent notamment en ce qui concerne le devenir de la norfenfluramine. La réalisation d'une étude cinétique des métabolites du benfluorex pourrait permettre de lever ces doutes.
Par ailleurs, le RCP devra être modifié afin d'y mentionner notamment les risques de réactions allergiques et cutanées.

L'Italie prépare un projet de courrier à l'attention des laboratoires SERVIER leur demandant :

- la réalisation d'une étude à long terme avec contrôle périodique de la glycémie et des lipides, échocardiographie et mesure des paramètres pharmacocinétiques,
- des modifications du RCP :
  - indications,
  - contre-indications,
  - mises en garde,
  - effets indésirables.

Ce courrier sera co-signé par l'Italie et la France. L'Italie devrait nous adresser son projet de lettre dans la semaine du 4 au 8 octobre 1999.

RÉPUBLIQUE FRANÇAISE

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 02 FEV. 2000

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 12 Octobre 1999)

Etaient présents

M. RICHE : Président
Mme ALBENGRES, Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), Mme CHICHMANIAN, M. COQUEREL, Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, M. IMBS, Mme JEAN-PASTOR, Mme JOLLIET, M. KANTELIP, Mme LE BELLER (représentant le CRPV de Paris-Broussais), Mme GINISTY (représentant le CRPV de Paris F. Widal), Mme LAINE-CESSAC, M. MALLARET, M. MERLE, M. MONTASTRUC, M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, Mme SGRO, Mme JASSON (suppléante de Mme SOUBRIE), Mme NOBLET (suppléant de M. THUILLEZ), M. TRENQUE, M. VIAL, Mme PERAULT (suppléante de M. VANDEL).
Mme CASTOT (représentant de M. le Directeur Général de l'AFSSAPS).

Conseiller Scientifique : M. LAGIER

Unité de pharmacovigilance :

Mme KREFT-JAIS
Mme BIDAULT
Melle DELEAU
M. DHANANI
Mme FOSSET-MARTINETTI
Mme JOLIMOY
Mme JOUSSELIN-PAUTROT
Mme LEREBOURS
Mme MESSAN-MURPHY
Mme PARIENTE-KHAYAT
Melle ROBINE

Modèle de tableau : à remplir par les CRPV (contenu dactylographié), avant chaque Comité Technique, pour le tour de table de la littérature.
Ce tableau sera joint en annexe du procès-verbal.

LITTÉRATURE

CRPV : St Etienne

COMITE TECHNIQUE DU 12/10/99.

Mots clefs (*en français*)	Titre de l'article, Auteurs, Revue, références	Commentaires (*facultatif*)
Anorexigènes, valvulopathie, Sérotonine Antiprotéases et troubles métaboliques, lipodystrophie,	~~Media~~ Williams (?). Médo Release 18 Août 1999 (USA) - KIMMEL SE : Am. J. cardiol., 1999, 84, 304-308 - ROTHMAN RB : Circulation, 1999, 100, 861-75 - RYAN DH : J. Obesity Res., 1999, 7, 313-22 ALDEEN T. AIDS, 1999, 13, 865-867 BEHRENS G. AIDS, 1999, 13, F63-F70 BLANCHE S - Lancet du 25 Sept 1999 BARKAUAM - Lancet du 25 Sept 1999 MERCIÉ P. - Lancet du 4 Sept 1999	- Dihydroergotamine - Surestimation des valvulopathies - mécanisme - fréquence des régurgitations

Annexe 3-61

LITTERATURE
REACTIONS N° PAIRES 960-968

Centre de Pharmacovigilance de :Saint-Etienne **COMITE TECHNIQUE DU** : 04/11/2003

Mots clefs (en Français)	Titre de l'article Auteurs Revue, références	Commentaires (facultatif)
Benfluorex et atteintes valvulaires cardiaques	RIBERA J.R. Revista Espanola de Cardiologia, 2003, 56, 215-216	1er cas rapporté
Infliximab infection à herpès simplex chez une enfant de 8 ans	SKRIPAK J.M. Ped. Research, 2003, 53, 340-341	Il fallait s'y attendre, après la tuberculose, l'herpès
SSRI et exposition in utero	LAINE K. : AADRAC : August 2003, Arch General Psychiatry, 2003, 60, 720-726	
ET TOUJOURS LA PHYTOTHERAPIE		
Hépatotoxicité après cure amaigrissante	KANDAT : J. Gastroenterol Hepatol, 2003, 18, 354-356	
Cardiotoxicité	ERNST E. Can. J. Cardiol., 2003, 19, 818-827	
Aspergillose sino-cérébrale invasive	BREMER C.T. Amer. J. Clin. Oncol., 2003, 26, 262-264	
Hépatite fulminante	ESTES J.D. Arch. Surg., 2003, 138, 852-858	
MAIS LA PHARMACOVIGILANCE MONDIALE VA BIEN		
- L'agence finnoise reçoit de 700 à 800 signalements d'EI par an (NURMINEN ML, Drug Inf. n. t. Agency for Med, 2003, 3, 50-52) - La Chine vient d'ouvrir sont 32ème centre régional. Le système national a reçu environ 17000 signalements d'EI en 2002 (uniquement avec des médicaments "étrangers" et rien avec la phytothérapie locale : sic !! - NDLR). Enfin, à ne pas manquer : Le Docteur KNOCK habite à Wall Street de P. CATHEBRAS. La Revue de Med. Interne, 2003, 24, 538-541		

ADOPTE

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE
Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du Mardi 16 avril 2002)

Etaient présents

M. CARON : Président
Mme POLARD (suppléante de M. ALLAIN), M. ANDREJAK, Mme JONVILLE-BE[illegible] (suppléante de Mme AUTRET-LECA), Mme MOACHON (suppléante de Mme BAVOUX), M. BIOUR, Mme PINZANI (suppléante de M. BLAYAC), Mme CHICHMANIAN, M. LE BOISSELIER (suppléant de M. COQUEREL), Mme ZENUT (suppléante de M. ESCHALIER), Mme HARAMBURU, Mme WELSCH (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), Mme MONASSON (suppléante de M. KANTELIP), M LAGIER, Mme LAINE-CESSAC, M. LE LOUET, Mme LE BELLER (suppléante de Mme LILLO-LE LOUET), M. MALLARET, M. MERLE, Mme OLIVIER (suppléante de M. MONTASTRUC), M. GILLET (suppléant de M. NETTER), M. OLLAGNIER, M. RICHE, Mme SGRO, Mme LEBRUN-VIGNES (suppléante de Mme SOUBRIE), Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, Mme PERRAULT, M. VIAL
Mme BAUCHOT (représentant Monsieur le Directeur Général de la Santé)
Mme KREFT-JAIS (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé)

Assistaient à la réunion

Unité de pharmacovigilance :
Mlle BACQUET
Mme BIDAULT
Mlle DELEAU
Mlle FERARD
Mlle HENRY
Mme LAHMAR
Mme LORENCE
Mme OUARET
Mme PARIENTE-KHAYAT
Mme POINSARD
Mlle ROBINE

Internes :
Mlle CARDONA
M. GALMICHE

Stagiaires :
Mlle MOUGIN
Mlle PAGE

CRPV :
M. BEN SALEM
M. CHENNOUGI
Mme EFTEKHARI
Mme GINISTY

DEMEB :
Mme JADEAU
Mme MORER
Mme MORGENSZTJEN

DG :
Mme GOULARD
Mme HERAIL

DEMEIS :
Mme MESSAN-MURPHY
Mme PIOTTO

CENTRE DE PHARMACOVIGILANCE DE TOULOUSE - MIDI-PYRENEES
(Professeur J.L. MONTASTRUC)

N° des cas	Date de survenue	Sexe /Age	Médicaments suspects	Effets observés	Evol.	Imput	G	N	E	Commentaires Interaction...
TO 020331	20/01/02	60 A	MEDIATOR	Valvulopathies	F	1,1,0	OUI	O		
TO 020372	14/12/01	63 A	VIOXX	Rectorragie , douleurs abdominales, colite Ischémique	A	2,2,3	OUI	N N O		
TO 020413	09/03/02	39 A	VIOXX VIAGRA	Colite Ischémique	A	2,2,0 1,1,0	OUI	O		

CAS MARQUANTS

CENTRE DE PHARMACOVIGILANCE DE :**LYON** COMITE TECHNIQUE DU : **16 avril 2002**

N° des cas	Date de survenue	Sexe Age	Médicaments suspects	Effets observés	Evol.	Imput	G	N	E	Commentaires Interaction ...
LY02000 94	13/02/20 02	F/86	DHEA 50 mg/j	Infarctus du myocarde	G	C2S 1	O	O	N	Patiente sans atcd angineux ou artéritique, arythmie sur IM jugée normale pour l'âge Survenue d'un infarctus massif 3 mois après mise sous DHEA
LY02003 44	10/12/20 01	M/78	DHEA 50 mg/j	Infarctus du myocarde	G	C2S 1	O	O	N	Facteur de risque limité à l'âge
LY02000 36 LY02000 37 LY02003 03	15/09/20 01 05/11/20 01 20/03/20 02	F/34 F/53 F/36	MEDIATOR	Manifestations psychiatriques survenues après l'arrêt du traitement sous la forme d'une psychose (cas 1), d'un état maniaque (cas 2) ou de troubles paniques (cas 3)	I I G	C1S 1 C1S 1 C1S 1	O O O	O O O		Dans le RCP, pas de mention de précautions particulières chez les patients ayant des antécédents psychiatriques

ADOPTE

Annexe 3-64

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du mardi 9 décembre 2003)

Etaient présents :
M. CARON : président
M. ANDREJAK : vice-président
Mme POLARD (suppléante de M. ALLAIN), Melle BENSOUDA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M BLAYAC, Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme MOSQUET (suppléante de M. COQUEREL), M. ESCHALIER, Mme HARAMBURU, Mme LATES (suppléante de M. IMBS), Mme JEAN-PASTOR, Mme JOLLIET, M. KANTELIP, M. LAGIER, Mme LAINE-CESSAC, Mme LILLO-LE LOUET, M. MALLARET, M. MERLE, Mme DURRIEU (suppléante de M. MONTASTRUC), M. GAMBIER (suppléant de M. GILLET), Mme GUY (suppléante de M. OLLAGNIER), Mme PERAULT, Mme CARLHENT (suppléante de M. RICHE), Mme SGRO, Mme SOUBRIE, M. TRENQUE, M. VIAL.
Mme DAHAN (représentant Monsieur le Directeur Général de la Santé)
Mme CASTOT (représentant Monsieur le Directeur Général de l'Agence Française de Sécurité Sanitaire des Produits de Santé)

Unité de Pharmacovigilance :
Mme KREFT-JAIS
Melle BOUTRON
Melle CARDONA-GIORDANO
Mme CHOULIKA
Melle DELEAU
M. DHANANI
Mme DUGUE
Mme GOEBEL
Mme GRENE
Melle HENRY
M. JACQUET
Mme OUARET
Melle PAGE
Mme POINSARD
Mme SCHLOSSER
M. VESQUE

Internes :
Melle BARD
Melle VAZ

DEMEB :
Melle CACHIN
Mme DEGUINES
M. HO
M. NOUYRIGAT
Mme PONS
Mme SAINT-SALVI

Stagiaire :
Melle FRAUGER

CRPV :
Mme BENABDALLAH
Mme EFTEKHARI
Mme LAGARCE
Mme LOUBNA
Mme MOACHON
M. RODOR
Mme VEYRAC

Etaient excusés :
M. LELOUET
M. THUILLEZ
Monsieur le Directeur Général de l'INSERM
Monsieur le Directeur de l'Hospitalisation et de l'Organisation des Soins

TABLES DES MATIERES

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I - ADOPTION DU PROCES-VERBAL DE LA SEANCE DU MARDI 4 NOVEMBRE 2003

Le procès-verbal de la séance du 4 novembre 2003 a été adopté avec les corrections suivantes :

Page 4 : II – Tour de table des cas marquants et de la littérature

- Ligne 14 : remplacer « FURADANTINE (nitrofurantoïne) et mésusage » par « Nitrofurantoïne (FURADANTINE, FURADOINE, MICRODOINE) et mésusage »
- Ligne 16 : remplacer « FURADANTINE (nitrofurantoïne) » par « Nitrofurantoïne (FURADANTINE, FURADOINE, MICRODOINE) »

Page 5 : II – Tour de table des cas marquants et de la littérature

- Ligne 31 : remplacer « Le CRPV de Marseille a signalé 3 ou 4 appels de patientes qui ont reçu MIFEGYNE » par « Le CRPV de Marseille a signalé 3 ou 4 appels récents pour des patientes qui ont reçu MIFEGYNE »

Page 9 : IV – Enquête officielle : sclérosants veineux et réactions anaphylactiques, sclérosants veineux et céphalées »

- Ligne 26 : ajouter « Les RCP d'AETOXISCLEROL® et de SCLEREMO® doivent être harmonisés ».

Page 10 : V – Enquête officielle sur les pneumopathies interstitielles diffuses et Lipiocis® / Lipiodol®

- Ligne 40 : remplacer « Le service de radiologie du Centre Hospitalier E. Marquis de Rennes (CRLCC) considéré comme centre français de référence dans l'utilisation de Lipiocis® dans le CHC, a décidé de faire une étude rétrospective visant à répertorier tous les cas de pneumopathies » par « Le Centre Régional de Lutte Contre le Cancer (CRLCC) de Rennes, étant considéré comme centre français de référence dans l'utilisation de Lipiocis® dans le CHC, une étude rétrospective y a été menée dans le cadre d'un travail de thèse de doctorat en médecine. L'objectif était de répertorier tous les cas de pneumopathies ».

Page 12 : V – Enquête officielle sur les pneumopathies interstitielles diffuses et Lipiocis® / Lipiodol®

- Ligne 4 : remplacer « Enfin ces pneumopathies peuvent être dues à des embols » par « Enfin ces pneumopathies pourraient être dues à des embols ».

Page 17 : VIII – Questions diverses

- Ligne 27 : ajouter

« Dictionnaire Vidal® et pharmacovigilance

Afin d'améliorer la lisibilité en matière d'information sur la sécurité d'emploi des médicaments dans le dictionnaire Vidal®, l'Afssaps a souhaité recueillir les propositions et les remarques des différents CRPV.

Ainsi, les CRPV ont suggéré de :

1- permettre une identification claire et rapide des modifications récentes apportées aux RCP des médicaments ;
2- indiquer systématiquement la quantité exacte de principe actif par unité de conditionnement ;
3- Indiquer la quantité de principe actif sous forme de sel mais également la quantité de principe actif base par unité de prise ;
4- indiquer l'ASMR (amélioration du service médical rendu) ou le SMR (service médical rendu) en fonction de l'indication pour chaque médicament ;

5- clarifier les données de pharmacocinétique ;
6- indiquer si la rubrique « grossesse » a fait l'objet d'une réévaluation récente (avec la date de réévaluation) ;
7- créer une rubrique « femme en âge de procréer et contraception » ;
8- lister tous les génériques dans le Vidal® ;
9- indiquer les excipients à effet notoire pour chaque médicament ;
10- ajouter dans les premières pages du Vidal® un espace d'information concernant la pharmacovigilance et l'antibiothérapie en général ainsi que la liste des médicaments dont la commercialisation a été arrêtée (avec les dates d'arrêt) et les raisons de ces arrêts de commercialisation ;
11- indiquer pour chaque médicament la date d'AMM et la nature de la procédure d'enregistrement d'AMM ;
12- harmoniser les informations entre les versions papier et informatique (Vidal Pro®) du dictionnaire Vidal® ;
13- faire figurer dans le Vidal® tous les médicaments commercialisés (et pas uniquement les médicaments dont les laboratoires veulent faire la promotion).

Il est à noter que le livret « Interactions médicamenteuses » ne devrait plus être intégré au Vidal® 2004. Une nouvelle version sera élaborée par l'Afssaps et mis à disposition sur le site internet de l'Afssaps.

Conclusion : l'Afssaps doit rencontrer le PDG ainsi que le directeur scientifique du Vidal® fin novembre 2003 afin d'intégrer certaines des propositions des CRPV dans l'édition 2004 du Vidal®. »

II - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Sont signalés les cas d'effets indésirables, de mésusages, d'erreurs et de manque de cohérence de l'information ainsi que les risques potentiels d'effets indésirables pouvant donner lieu à des mesures (mises en enquête, notes…) ou pouvant faire l'objet d'une mise au point dans le cadre de la prévention du risque médicamenteux. La liste complète des cas est jointe en annexe 1.

Effets indésirables avérés :

AGREAL (véralipride) et syndrome parkinsonien / CRPV d'Amiens

Le CRPV d'Amiens a signalé un syndrome parkinsonien avec galactorrhée chez une patiente de 69 ans traitée sans interruption depuis 25 ans par AGREAL (véralipride) à la suite d'une hystérectomie. La fenêtre thérapeutique recommandée dans le RCP n'a pas été respectée. Onze autres cas de syndrome parkinsonien sont rapportés dans la base nationale de pharmacovigilance avec ce médicament.

→ L'unité de pharmacovigilance demandera à l'unité pharmaco-toxico-clinique 2 si l'indication de ce médicament dans le « traitement des bouffées vasomotrices invalidantes associées aux manifestations psycho-fonctionnelles de la ménopause confirmée », est justifiée.

REMINYL (galantamine) et crise d'épilepsie / CRPV d'Amiens

Le CRPV d'Amiens a signalé un cas de crise d'épilepsie chez une patiente de 72 ans sans antécédent épileptique avec bilan négatif. Trois autres cas de crise d'épilepsie sont signalés dans la base nationale de pharmacovigilance.

→ L'unité de pharmacovigilance demandera à la firme de déposer une demande de modification d'information afin d'introduire cette mention dans la rubrique « Effets indésirables » du Résumé des Caractéristiques du Produit.

DIAMICRON 80mg (gliclazide) et interaction avec les anticoagulants / CRPV de Clermont-Ferrand

Le CRPV de Clermont-Ferrand a signalé que l'interaction des sulfamides hypoglycémiants avec les anticoagulants n'est pas mentionnée dans les RCP de DIAMICRON 80mg (gliclazide) et des anticoagulants, alors qu'elle est mentionnée pour DIAMICRON LP30mg®. Cette intéraction n'est pas mentionnée dans le livret interaction.

→ L'unité de pharmacovigilance transmettra cette information aux unités pharmaco-toxico-clinique concernées pour suite à donner avec copie à l'unité coordination des actions transversales et interaction médicamenteuse.

PROPOFOL FRESENIUS (propofol) et inefficacité / CRPV de Dijon

Le CRPV de Dijon a signalé 3 cas nécessitant une augmentation très importante des doses de PROPOFOL FRESENIUS (propofol), forme ampoule de 20 ml, pour obtenir une efficacité lors d'anesthésies courtes et rapides. PROPOFOL FRESENIUS (propofol) est le générique de DIPRIVAN®. Il a été supposé que la baisse d'efficacité du médicament pourrait être lié à un problème de conservation des ampoules dans le service pendant la canicule des mois de juillet et août 2003.

→ Le CRPV de Dijon transmet à la Direction des Laboratoires et des Contrôles les échantillons d'ampoules qui ont été utilisées ainsi que les ampoules du même lot restant dans le service pour analyse physico-chimique (dosage du principe actif).

CALMOSINE (extrait d'aneth) et état de mal épileptique / CRPV de Lyon

Le CRPV de Lyon a signalé un cas de convulsion chez un nouveau-né de 3 mois traité pour des troubles digestifs par CALMOSINE (extrait d'aneth).

→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification d'information sur ce produit afin de mettre à jour les rubriques concernant la sécurité d'emploi.

GEMZAR (gemcitabine) et atteintes hépatiques / CRPV de Grenoble et CRPV de Lyon

Le CRPV de Grenoble a signalé un cas d'hépatite veino-occlusive et le CRPV de Lyon un cas d'hépatite fulminante sous GEMZAR (gemcitabine). D'autres cas d'hépatites fulminantes ont été rapportés dans la base nationale de pharmacovigilance et deux cas d'hépatites cholestatiques fatales ont été récemment publiés.

→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification de l'information médicale, laquelle sera évaluée par le CRPV de Poitiers.

5 Fluoro-uracile et leucoencéphalopathie / CRPV de Paris - Saint-Vincent de Paul

Le CRPV de Paris-Saint-Vincent de Paul a signalé le cas d'une patiente de 48 ans, ayant un déficit en enzyme dihydropyrimidine déhydrogénase (DPD), traitée par FLUORO-URACILE (5 fluorouracile) et CISPLATYL (cisplatine) pour un cancer utérin qui a manifesté des convulsions suivi d'un coma puis du décès de la patiente. Il a été observé une leucoencéphalopathie à l'IRM sans manifestation d'aplasie médullaire ni de troubles digestifs. 35 autres cas d'encéphalopathie ou de coma sous 5 fluoro-uracile, associé ou non au cisplatine, ont été signalés dans la base nationale de pharmacovigilance.

A la suite du point présenté par le CRPV d'Angers, la conclusion qui était d'effectuer un test permettant de dépister les patients ayant un déficit en DPD, n'a pas été retenue par le Groupe de travail onco-hématologie (GTOH) faute de méthode de dosage validée.

→ Le CRPV d'Angers proposera néanmoins au GTOH un nouveau libellé pour les rubriques 4.4 et 5.2.

Méconnaissance des effets indésirables centraux du MEDIATOR (benfluorex) par les professionnels de santé / CRPV de Reims

Le CRPV de Reims a signalé les cas de deux patientes de 79 et 66 ans traitées par MEDIATOR (benfluorex) et qui ont présenté des effets indésirables centraux (asthénie, somnolence, malaise, désorientation, stupeur) qui ont disparu en quelques jours à l'arrêt du traitement. Il semblerait qu'il y ait une méconnaissance des effets indésirables centraux par les prescripteurs de MEDIATOR®.

→ L'unité de pharmacovigilance demandera à la firme l'évolution des chiffres de vente de ce médicament.

PROPRANOLOL RATIOPHARM (propanolol) et inefficacité / CRPV de Saint-Etienne

Le CRPV de Saint-Etienne a signalé les cas de deux patients traités efficacement depuis 3 ans par AVLOCARDYL (propranolol) pour des troubles du rythme. Lors de la substitution du princeps par le générique, PROPANOLOL RATIOPHARM®, les patients se plaignent de palpitations et de malaise. La reprise du traitement par AVLOCARDYL® a permis le retour à un traitement efficace des troubles du rythme.

→ L'unité de pharmacovigilance demandera à la Direction des laboratoires et des contrôles d'analyser si possible le(s) lot(s)concerné(s) de PROPRANOLOL RATIOPHARM® (dosage du principe actif).

MEGACE (mégestrol) et insuffisance surrénalienne / CRPV d'Amiens

Le CRPV d'Amiens a signalé un cas d'insuffisance surrénalienne chez une patiente de 39 ans traitée par MEGACE pour un cancer du sein. Aucun autre cas n'est retrouvé dans la base nationale de pharmacovigilance. Toutefois, ce type d'observation est bien documenté au niveau de la littérature.

→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification de l'information médicale afin de compléter les rubriques « effets indésirables » et « pharmacodynamie ».

Documents distribués :

- Rapport annuel 2002 de l'Afssaps,
- Les déclarations d'intérêts des membres des conseils, des commissions et groupes de travail 2002.

III - POINT SUR LES EFFETS INDESIRABLES VISUELS RAPPORTES SOUS OMEPRAZOLE (MOPRAL®) PROCEDURE NATIONALE

A la suite de la notification de plusieurs cas de vision trouble rapportés avec l'oméprazole, l'Afssaps a demandé aux laboratoires AstraZeneca et aux laboratoires Aventis, commercialisant respectivement les spécialités Mopral® (oméprazole) et Zoltum® (oméprazole), de fournir une revue des effets indésirables visuels, et en particulier des cas de cécité et de vision trouble, rapportés avec leur spécialité. Tous les cas de troubles visuels enregistrés dans la base de données d'AstraZeneca au 30 novembre 2002 et dans la base de données d'Aventis au 22 octobre 2002 ont été transmis.
L'analyse de cette revue a été confiée au CRPV de Marseille qui a présenté son rapport au Comité technique de Pharmacovigilance le 9 décembre 2003.

En 1994, les autorités sanitaires allemandes ont soulevé le problème de la survenue d'atteintes visuelles irréversibles lors de l'utilisation d'oméprazole en bolus à de fortes doses. Ce point a fait l'objet d'une analyse la même année par le Comité des Spécialités Pharmaceutiques. Il a été conclu, au vu des données disponibles, qu'un lien de causalité entre l'oméprazole et les atteintes observées n'était pas établi. Les résultats de deux études de cohortes (Garcia Rodriguez L.A. et al[1], 1996 et Mannino S. et al, 1998[2]), portant sur 140 128 patients traités par anti-ulcéreux concluent à la bonne tolérance oculaire de l'oméprazole.

Concernant la notification spontanée, 944 cas d'effets indésirables visuels correspondant à 1085 effets, dont 141 graves, ont été rapportés aux laboratoires AstraZeneca.
Parmi ces cas, 251 sont des observations de « vision trouble », dont 18 présentent un rechallenge positif et 104 un déchallenge positif. Dans 17 cas, dont certains avec rechallenge positif, on retrouve un médicament concomitant susceptible de modifier la vision. La moyenne d'âge des patients ayant présenté cet effet est de 55 ans et dans la plupart de cas, ces patients présentent une pathologie associée (pathologie oculaire dans 22 cas, cardiaque dans 21 cas, allergique dans 17 cas,…). D'autre part, 216 observations de troubles visuels susceptibles d'entraîner une vision trouble mais non rapportés comme tel ont été analysées. Parmi ces cas, 9 présentent un rechallenge positif et 61 un déchallenge positif. Comme pour les observations précédentes, ces cas concernent des patients d'âge moyen de 55 ans, présentant souvent des pathologies associées.
Les données transmises par les laboratoires Aventis se limitent à 3 observations, toutes d'imputabilité douteuse.
Enfin, 30 cas relatifs à une atteinte de l'appareil visuel ont été enregistrés dans la Base Nationale de Pharmacovigilance. L'imputabilité est douteuse dans 25 cas, plausible dans 4 cas et vraisemblable dans 1 cas.
Au total, compte-tenu de la large utilisation de l'oméprazole, la fréquence de survenue de « vision trouble » lors de traitement par Mopral® ou Zoltum® est faible. Dans la majorité des cas, l'imputabilité est douteuse. Toutefois, le rôle du médicament ne peut être exclu dans certains cas.

Le terme « vision trouble » est mentionné dans le document interne à la firme (Company Core Data Sheet) pour la spécialité Mopral®. Les troubles de la vision sont un effet mentionné dans le Résumé des Caractéristiques de tous les autres inhibiteurs de la pompe à protons. Il est à noter que dans le Résumé des Caractéristiques d'Inexium® (ésoméprazole), la possibilité de survenue de vision trouble est mentionnée à la rubrique 4.8 comme un effet ayant été observé avec le racémique oméprazole et qui pourrait survenir avec l'ésoméprazole.

Au vu de ces données et afin d'harmoniser les Résumés des Caractéristiques du Produit des différents inhibiteurs de la pompe à protons, le Comité technique de Pharmacovigilance s'est montré favorable à l'ajout de la mention « vision trouble » à la rubrique 4.8 « Effets indésirables » des spécialités Mopral® et Zoltum®. Le dépôt d'une demande de modification de l'information sera demandé aux laboratoires AstraZeneca et Aventis.

[1] Garcia Rodriguez LA, Mannino S, Wallander MA, Lindblom B.
A cohort study of the ocular safety of anti-ulcer drugs.
Br J Clin Pharmacol. 1996 Aug ; 42(2) : 213-6.

[2] Mannino S, Troncon MG, Wallander MA, Cattaruzzi C, Romano F, Agostinis L, Marighi PE, et al.
Ocular disorders in users of H2-antagonists and of omeprazole.
Pharmacoepidemiol Drug Saf. 1998 ; 7(4) : 233-241.

IV - ENQUETE OFFICIELLE SUR LE SYNDROME DE SEVRAGE LIE A ZOLPIDEM (STILNOX®) ET ZOPICLONE (IMOVANE®)
PROCEDURE NATIONALE

Le CRPV de Nantes a présenté les résultats de l'enquête officielle concernant les syndromes de sevrage au zolpidem et à la zopiclone rapportés entre le 1er janvier 1996 et le 31 décembre 2002.
Cette enquête regroupe les cas de syndrome de sevrage et les cas d'effets thérapeutiques inattendus ou ETI (effets psychiques positifs, effets antalgiques, améliorations cognitives) responsables de mésusage, pouvant également être à l'origine de syndromes de sevrage.

1/ Zolpidem et syndrome de sevrage

Le zolpidem (STILNOX®) est un hypnotique d'action rapide commercialisé par les laboratoires SANOFI SYNTHELABO depuis février 1988 ; il est indiqué dans le traitement des insomnies occasionnelle, transitoire, et chronique.

a/ Données des CRPV et des laboratoires
112 observations correspondant à 132 effets indésirables ont été retenues (39 cas provenant des CRPV et 73 cas du laboratoire). Ces observations concernent une population jeune, 49% des patients étant âgés de moins de 40 ans.

- 61 dossiers (54%) font état de syndromes de sevrage, dont les principaux symptômes sont anxiété (33%), convulsions (30%), tremblements (10%) et plus rarement, insomnie, cauchemars, céphalées, douleurs musculaires, crampes, irritabilité. Ces syndromes ont entraîné une hospitalisation dans 32 cas (52%). 44 % des patients présentant un syndrome de sevrage n'avaient pas de facteur de risque connu. 25% des symptômes de sevrage sont survenus après arrêt du zolpidem pris à doses thérapeutiques.
20 dossiers associent un syndrome de sevrage à un ETI et font état d'un dépassement de posologie, la posologie minimale observée étant de 30 mg/j. Dans 65% des cas le zolpidem était associé à d'autres psychotropes et dans 60% des cas, les patients avaient des troubles psychiatriques. Le taux de réussite de sevrage dans ce groupe a été de 54%.
Dans 41 dossiers, le syndrome de sevrage n'est pas associé à un ETI, et dans 41% de ces dossiers, le syndrome de sevrage est survenu après arrêt du zolpidem pris à doses thérapeutiques. 19% des patients avaient des troubles psychiatriques associés et 46% recevaient d'autres psychotropes que le zolpidem. Le taux de réussite de sevrage dans ce groupe était de 56%.
- 51 dossiers font état d'ETI. Il s'agit notamment d'effets anxiolytiques (15 cas), euphoriques (12 cas) et antalgiques (5 cas). Dans 2 cas, l'ETI est survenu à dose recommandée (10 mg/j). 10 patients (20%) ne présentaient pas de facteurs de risque et 26 patients (50%) ont été hospitalisés. 12 patients (24%) ne présentaient pas de somnolence malgré des posologies s'échelonnant de 30 à 400 mg.

b/ Données de la littérature
Les données de la littérature suggèrent, d'après des études expérimentales menées chez le primate non humain et des résultats d'essais cliniques, que :

- la tolérance, le rebond d'insomnie et les symptômes de sevrage sont moins fréquents et moins significatifs cliniquement avec le zolpidem qu'avec les benzodiazépines ;
- l'incidence du syndrome de sevrage est faible après un traitement à dose et à durée recommandées (10 mg/j pendant 4 semaines).

36 cas de syndrome de sevrage ont été publiés dans la littérature (dont 13 avec ETI). Ces cas possèdent les mêmes caractéristiques que les observations des CRPV et du laboratoire.

2/ Zopiclone et syndrome de sevrage

Le zopiclone (IMOVANE®) est un hypnotique commercialisée par le laboratoire AVENTIS, qui bénéficie d'une AMM depuis le 10 décembre 1984. Une douzaine de génériques sont également commercialisés mais cette enquête ne repose que sur les cas rapportés avec le médicament princeps, les laboratoires génériqueurs ayant peu ou pas répondu aux requêtes du rapporteur.

a/ Données des CRPV et des laboratoires
22 observations, correspondant à 23 effets indésirables, ont été retenues (17 cas provenant des CRPV et 5 cas

du laboratoire). Ces observations concernent une population jeune, 55% des patients sont en effet âgés de moins de 40 ans.

• 21 dossiers rapportent un syndrome de sevrage, principalement caractérisé par des convulsions (7 cas soit 33%) et plus rarement par des effets indésirables tels qu'insomnie, cauchemars, céphalées, douleurs musculaires, crampes, irritabilité. Ces effets ont nécessité une hospitalisation dans 48% des cas. Dans 7 cas (37%), la zopiclone avait été administrée à doses thérapeutiques. Dans 9 cas (41%), les patients ne présentaient pas de facteur de risque et 74 % des patients utilisaient une dose inférieure ou égale à 15 mg soit 2 comprimés. A noter que 29 % des notifications correspondent à des sevrages néonataux (d'évolution favorable) de mères toxicomanes ou alcooliques.
Dans un dossier, le syndrome de sevrage a été associé à un ETI.
• 1 dossier rapporte un ETI.

b/ Données de la littérature
L'analyse de la littérature suggère les mêmes constatations que pour le zolpidem, à savoir que l'incidence du syndrome de sevrage est faible lors d'un traitement à dose et à durée recommandées (7,5 mg/j pendant 4 semaines)
15 cas de syndrome de sevrage au zopiclone ont été publiés et sont similaires aux cas rapportés aux CRPV et au laboratoire.

3/ Conclusions du rapporteur
Etant donné la gravité potentielle de ces effets indésirables, même si leur incidence est faible (avec un effet pour 61 millions de jours de traitement pour le zopiclone et un effet pour près de 15 millions de jours de traitement pour le zolpidem), le rapporteur a insisté sur :
- le fait qu'en aucun cas, la zopiclone ne devrait être utilisée dans un but d'anxiolyse,
- la nécessité d'être vigilant chez les patients à risque, toxicomanes, alcooliques ou dépendants aux benzodiazépines, et chez les patients sans risque apparent qui augmentent rapidement leur dose initiale,
- la nécessité de prévenir les patients du risque de symptômes de sevrage et de rebond d'insomnie à l'arrêt brutal de la zopiclone ou du zolpidem, à dose thérapeutique ou supra thérapeutique.

Le rapporteur a suggéré d'intégrer dans la rubrique 4.4 du RCP de zopiclone et de zolpidem les informations suivantes :
- A l'arrêt du traitement, les symptômes d'un syndrome de sevrage peuvent apparaître pour des doses thérapeutiques et/ou chez des patients ne présentant pas de facteur de co-morbidité psychiatrique.
- À dose thérapeutique, les syndromes de sevrage ou les rebonds d'insomnie sont exceptionnels.

Le Comité technique n'émet pas de remarque particulière.
Le dossier sera présenté lors de la Commission nationale de mars 2004.

V - POINT CONCERNANT L'ENQUETE D'OPINION AUPRES DES MEDECINS LIBERAUX DU MAINE ET LOIRE SUR LES MEDICAMENTS GENERIQUES

Le Centre Régional de Pharmacovigilance d'Angers a présenté les résultats de l'enquête d'opinion sur les spécialités génériques menée au mois de mars 2002 auprès des médecins libéraux du Maine et Loire.
Cette enquête, présentée sous forme de questionnaire, avait pour objectif de connaître l'opinion des médecins libéraux sur les médicaments génériques mais également de recueillir les propositions des cliniciens pour une prescription plus sécuritaire des spécialités génériques.

Taux de participation des médecins libéraux

Le CRPV d'Angers a envoyé le questionnaire à 1235 médecins libéraux du Maine et Loire et a obtenu un taux de réponse de 35%, émanant majoritairement des généralistes (67%).

Opinion des médecins sur les spécialités génériques

Pour les médecins libéraux ayant répondu au questionnaire, les spécialités génériques :

- présentent un intérêt économique (64% des répondants)
- sont de même qualité, efficacité et sécurité que les médicaments de référence (56% des répondants)
- sont trop nombreux (62% des répondants)
- sont préjudiciables à la recherche (53% des répondants)
- sont inutiles (20% des répondants)

Facteurs influençant la fréquence de prescription des spécialités génériques

L'enquête montre que 59% des médecins libéraux prescrivent peu ou pas de génériques. Les différents facteurs susceptibles d'influencer la prescription de génériques sont :

- Liés au médecin :

- les médecins généralistes et les médecins référents prescrivent plus de génériques que les spécialistes

Les médecins référents sont des médecins particulièrement sensibilisés aux médicaments génériques. Les médecins adhérant à l'option « médecin référents » s'engagent, entre autre, à prescrire des médicaments moins chers à hauteur de 15% de leurs prescriptions dont 5% de médicaments génériques.

- la taille de la ville d'exercice du prescripteur influence également la fréquence de prescription : les médecins prescrivant peu ou pas de génériques exercent leur activité dans les villes de plus de 10 000 habitants.

- Liés au patient :
  - 80% des médecins déclarent ne tenir compte ni de l'âge, ni du caractère aigu ou chronique de la pathologie, lors de la prescription de génériques.
  - les facteurs susceptibles d'influencer cette prescription :
  *les commentaires, la personnalité du patient
  *l'absence de mutuelle complémentaire
  *l'inscription à la CMU (Couverture Maladie Universelle)
  - 30% des médecins prescrivent les génériques à l'instauration du traitement.
- Liés aux médicaments :
  - la présence d'excipients à effet notoire n'est pas prise en compte par 60% des médecins
  - 41% des médecins ne connaissent pas le prix des médicaments
  - la forme galénique, la facilité d'utilisation et la connaissance de l'existence du générique influencent sa prescription.

De nombreuses informations (prix, forme galénique, présence d'excipients à effet notoire, emballage extérieur et conditionnement…) relatives aux médicaments génériques ne sont pas toujours facilement accessibles aux médecins dans leur pratique quotidienne.

Risques liés à l'utilisation des génériques :

- Liés à la différence de biodisponibilité :

Au plan réglementaire, le médicament générique est bioéquivalent à la spécialité de référence. En revanche, la bioéquivalence des médicaments génériques entre eux n'est pas exigée. De ce fait, un risque de survenue d'effet indésirable ou de moindre efficacité d'un générique est possible, notamment pour les principes actifs à marge thérapeutique étroite.

- Liés à la différence de présentation :
  Le médicament générique étant différent du princeps par sa présentation, des risques de mauvaise observance, de confusion voire de surdosage (par prise simultanée du princeps et du générique) sont susceptibles de survenir. De nombreux médecins ont observé ce type d'effets et 69% d'entre eux ont été confrontés à des plaintes de leurs patients rapportant un effet indésirable ou une moindre efficacité d'un médicament générique.

Droit de substitution :

- Attitude des médecins face au droit de substitution :
  Environ 45% des médecins exercent un contrôle de la substitution, 52% laissent faire le pharmacien et 3% la refusent. Ces chiffres varient en fonction de l'âge du médecin et de sa qualité de généraliste ou de spécialiste. Les médecins ne semblent pas opposés à l'utilisation des génériques, mais soulignent qu'il est important, pour les patients de toujours recevoir le même générique.
- Craintes des médecins :
  - problème médico-légal
  - risque pour le patient (mauvaise observance)
  - dérive commerciale
  - atteinte à la liberté de prescription (méconnaissance de la substitution)

Diverses actions permettant une meilleure utilisation du générique

- Prescription en DCI :
  Plus de la moitié des praticiens ayant répondu estiment qu'ils prescriraient plus en DCI si un cadre légal était instauré, ce qui est le cas aujourd'hui. Les médecins soulignent néanmoins la difficulté de cette pratique (formation inadaptée, complexité des dénominations, similitude des noms des produits d'une même classe avec risque de confusion).
- Concertation entre médecins et pharmaciens sur le choix des génériques : 57% des médecins y sont favorables
- Incitation ou pénalités financières :
  20% des médecins pourraient être influencés par ces mesures.
- Amélioration de la formation et de l'information : diverses voies sont à explorer.
  - Intégration au cursus universitaire
  - Formation médicale continue spécifique à la prescription des génériques (non souhaitée par 64% des médecins)
  - Visite médicale spécifique (70% y sont opposés)
  - Elaboration de documents de travail aisément consultables
  - Sensibilisation aux risques des excipients à effet notoire
  - Information des patients par les professionnels de santé et les médias.
- Proposition des prescripteurs :
  - Diminution du nombre de génériques
  - Instauration d'un prix unique ou prix de référence
  - Eviter les noms de fantaisie
  - Repenser le conditionnement extérieur

Utiliser la carte Vitale comme support d'information sur la spécialité générique délivrée.

VI - PHARMACOVIGILANCE EUROPEENNE

Vaccins hexavalents : Hexavac® et InfanrixHexa®

Les vaccins hexavalents InfanrixHexa® (GSK) et Hexavac® (Aventis Pasteur MSD) sont des vaccins combinés, utilisés pour protéger contre six maladies infectieuses graves (diphtérie, tétanos, poliomyélite, coqueluche, hépatite B, infections invasives à Haemophilus influenzae).
La sécurité d'emploi de ces vaccins, autorisés depuis 2000 selon une procédure européenne centralisée et commercialisés dans la majorité des pays européens, a été réévaluée par le Comité des Spécialités Pharmaceutiques (CSP) de l'Agence européenne pour l'évaluation des médicaments (EMEA) en avril 2003. Cette réévaluation a été conduite suite à 5 cas de décès inexpliqués, en Allemagne et en Autriche, survenant chez des enfants dans les 24 heures suivant l'administration de ces vaccins. Le CSP a conclu que le rapport bénéfice/risque de ces vaccins demeurait inchangé, mais a continué l'évaluation.
Une analyse exhaustive de l'ensemble des cas rapportés de mort subite a plus particulièrement identifié la survenue de 4 cas de décès dans les 48 heures suivant la vaccination (Hexavac®) chez des enfants âgés de plus de 1 an. Ce signal a été confirmé par une étude cas attendus-cas observés, réalisée en Allemagne, qui a montré que le nombre de décès inexpliqués au décours de la 2ème année de vie et dans les 24 heures suivant l'administration du vaccin hexavalent (Hexavac®) était supérieur au nombre de cas attendus. Cependant, en raison du très faible nombre de cas recensés et de certaines limites méthodologiques, cette analyse ne permettait pas d'établir une quelconque relation de cause à effet.
En novembre 2003, le CSP et l'ensemble des Etats membres ont estimé cependant nécessaire de mettre en place d'autres études pour examiner l'existence ou non d'un risque de mort subite liée à la vaccination hexavalente. Ils ont conclu qu'en l'état actuel des connaissances, aucune modification des conditions actuelles d'utilisation de ces vaccins n'était justifiée et que la balance bénéfice/risque de ces vaccins demeurait favorable.
Il est à noter qu'en France, aucun cas de décès n'a été recensé depuis la mise à disposition de ce vaccin (depuis leur mise sur le marché jusqu'à fin septembre 2003, environ 150 000 doses ont été délivrées en France). Les vaccins hexavalents ne sont actuellement distribués que dans certaines collectivités et ne sont pas remboursés par la sécurité sociale.

COXIBS : conclusion de la procédure d'arbitrage (Art.31) déclenchée par la France

Le 8 juillet 2002, la France a saisi l'EMEA en vue d'une réévaluation du rapport bénéfice/risque des inhibiteurs de la cyclooxygénase-2 (coxibs ou COX-2), notamment en raison des risque digestif et cardiovasculaire.
La procédure d'arbitrage a débuté le 25 juillet 2002 et les firmes concernées (Pfizer et MSD) ont été entendues par le CSP de septembre 2003. Le 20 novembre, le CSP a conclu à un rapport bénéfice/risque positif pour l'ensemble des coxibs (célécoxib, étoricoxib, parécoxib, rofécoxib et valdécoxib).
Le 21 novembre, l'EMEA a publié les conclusions de cet arbitrage en expliquant que les mises en gardes concernant les risques cardiaque, digestif et cutané avaient été ajoutées ou renforcées. Par ailleurs, l'EMEA a rappelé qu'aucune communication nationale ne devrait être réalisée avant la publication de la décision de la Commission européenne, comme l'impose la procédure.

Le Comité technique de pharmacovigilance s'est interrogé sur les conclusions de cet arbitrage au vu des modifications apportées au RCP qui lui ont été présentées. Il a été souligné que ces conclusions sont le reflet d'une position européenne et non nationale.
De plus, le Comité technique a regretté l'absence de lien du site de l'Afssaps à celui de l'EMEA, ce qui aurait permis, en France, aux praticiens d'avoir un accès direct à l'information européenne.

Erythroblastopénies rapportées avec les érythropoïétines

Un point sur le nombre de cas d'érythroblastopénies avec présence d'anticorps anti-érythropoïétine rapportés avec les érythropoïétines a été présenté.
En novembre 2001, la notification de 40 cas mondiaux d'érythoblastopénie chez des insuffisants rénaux chroniques traités avec Eprex® (époétine alfa) a conduit l'Afssaps à déclencher une mesure de restriction urgente

(USR) qui a permis de modifier l'information du Résumé des Caractéristiques du Produit (mention de l'effet indésirable et conduite à tenir en cas de suspicion). Devant l'augmentation du nombre de cas, une deuxième mesure de restriction urgente a été déclenchée par la France en juillet 2002 recommandant l'utilisation préférentielle de la voie intraveineuse dès lors de celle-ci était possible. En décembre 2002, une troisième USR visant à contre-indiquer l'administration d'Eprex® par voie sous-cutanée chez les patients insuffisants rénaux chroniques a été déclenchée par la France.

L'analyse des dernières données (jusqu'au 31 août 2003) révèle qu'une très nette diminution du nombre de cas a été rapportée depuis le début de l'année 2003.

Il est à noter que les causes de ce problème sont vraisemblablement multifactorielles et qu'aucune étiologie précise n'est à ce jour identifiée. Néanmoins, le Comité technique se réjouit que les différentes mesures prises précitées ont permis de juguler le problème.

VII - QUESTIONS DIVERSES

Dossier suivi par E. POINSARD

Dictionnaire Vidal®2004

Afin d'améliorer la lisibilité en matière d'information sur la sécurité d'emploi des médicaments dans le dictionnaire Vidal®, l'Afssaps a rencontré fin novembre 2003 le PDG ainsi que le directeur scientifique du Vidal®. Un espace d'information sur la pharmacovigilance dans les pages figurant au début du dictionnaire devrait être ajouté dans l'édition 2004, une demi-page environ serait réservée aux informations importantes de pharmacovigilance et trois quart de page aux nouveautés en antibiothérapie. La rubrique intitulée « informations importantes de pharmacovigilance » expliquerait l'intérêt des lettres d'informations destinées aux professionnels de santé et répertorie leurs thèmes de l'année 2002 jusqu'en juin 2003.
Un point relatif à la réalisation du dictionnaire Vidal® devrait être présenté lors d'un prochain Comité technique de pharmacovigilance.

Protection de l'identité du notificateur

Le CRPV de Limoges a signalé que l'identité du pharmacien a été révélée par le département alerte de la Direction de l'inspection et des établissements (DIE). En effet, la notification du pharmacien révélant un cas de brûlure sous SEREVENT® a été faxée, intempestivement, par le département alerte à la firme commercialisant ce médicament.

Analyse d'échantillons par la Direction des laboratoires et des contrôles / CRPV de Paris-Saint-Vincent de Paul

Le CRPV de Paris-Saint-Vincent de Paul a signalé que l'échantillon d'ELOXATINE (oxaliplatine) transmise à la Direction des laboratoires et des contrôles pour analyse a fait l'objet d'une recherche d'endotoxine, alors que le CRPV aurait préféré que soit réalisé l'essai de stérilité.
L'unité pharmacovigilance précisera désormais à la direction des laboratoires et des contrôles le type d'analyse sollicité en particulier lors de la transmission des échantillons.

Transmission des convocations et dossiers de la Commission d'AMM

Le Président de la Commission Nationale de Pharmacovigilance a signalé qu'il ne recevait pas les convocations et les dossiers de la Commission d'AMM. Ceci a été signalé aux personnes en charge de transmettre les convocations et les dossiers.

Versement du solde de la subvention 2003 de fonctionnement des CRPV

Le solde de la subvention 2003 de fonctionnement des centres a été versé par mandat administratif sur le compte de vos établissement de santé le 12 décembre 2003.

Convention triennale de fonctionnement des centres

Il a été rappelé que les centres doivent adresser à l'unité pharmacovigilance au plus tard le 16 décembre les conventions signées ainsi que les demandes de subvention 2004. Les problèmes relatifs à l'établissement des bilans financiers et aux conventions sont à adresser par écrit à l'unité pharmacovigilance pour qu'ils soient transmis au contrôleur financier.

ANNEXES

ADOPTE

Annexe 3-65

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du mardi 7 Décembre 2004)

Etaient présents :
M. CARON : président
M. ANDREJAK : vice-président
Mme POLARD (suppléante de M. ALLAIN), Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, Mme HILLAIRE-BUYS (suppléante de M. BLAYAC), Mme CHICHMANIAN, Mme DE LA GASTINE (suppléante de M. COQUEREL), Mme ZENUT (suppléante de M. ESCHALIER), M. GILLET, Mme HARAMBURU, Mme JEAN-PASTOR, Mme VEYRAC (suppléante de Mme JOLLIET), Mme LAROCHE-DAVID (suppléante de M. KANTELIP), Mme EFTEKHARI (suppléante de M. CALVO), Mme LAINE-CESSAC, Mme LEBRUN-VIGNES, M. LE LOUET, Mme LE BELLER (suppléant de Mme LILLO-LE LOUET), M. MALLARET, M. MERLE, M. MONTASTRUC, M. OLLAGNIER, Mme PERAULT, Mme CARLHANT-KOWALSKI (suppléante de M. RICHE), Mme SGRO, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VIAL.
Mme DAHAN (représentant Monsieur le Directeur Général de la Santé)

Unité de Pharmacovigilance :
Mme KREFT-JAIS
Mme BIDAULT
Mlle BOUTRON
Mme CARDONA-GIORDANO
Mme CHOULIKA
Mlle DELEAU
M. DHANANI
Mlle FERARD
Mme GOEBEL
Mme GRENE
Mlle HENRY
M. JACQUET

Mme LAHMAR
Mme OUARET
Mlle PAGE
Mme POINSARD.
Mme POROKHOV
Mlle ROBINE
Mme SCHLOSSER
M. VESQUE

Internes :
Melle ANDRIANTAFIKA
Melle FAYE

Stagiaire :
Melle DAUDET

DEMEB :
M. FERNANDEZ
Mme LABOURET
Mme COURNE
Mme DIARTE

CRPV :
Melle SOUYRI

DEMEIS :
Mme DIARTE

Etaient excusés :
Mme WELSCH
M. le Directeur Général de l'INSERM
M. le Directeur de l'Hospitalisation et de l'Organisation des Soins
M. le Président de la Commission Nationale de Pharmacovigilance vétérinaire

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I - ADOPTION DU PROCES-VERBAL DU 12/10/2004

Le procès-verbal de la séance du 12 octobre 2004 a été adopté avec les corrections suivantes :

Page 4 : II – Tour de table des cas marquants et de la littérature

- Ajouter après « 450 mg deux fois par jour de NEORAL » soit « 4 à 9 fois la dose usuelle ».

Page 7 : III – Bilan des données de pharmacovigilance des vaccins contre l'hépatite B au 31/12/2003

- Ligne 29 : supprimer « Enfin, le CRPV de Strasbourg suggère que l'incidence nationale des formes graves d'hépatopathies virales aiguës ou chroniques liées au virus de l'hépatite B fasse l'objet d'un suivi rigoureux durant les 10 années à venir. »

Page 9 : IV – Effets neuro-excitateurs de la morphine par voie générale

- Ligne 60 : remplacer « 3 par voie sous-cutanée, dont 2 représentaient une IR sévère» par « 3 par voie sous-cutanée (dans deux cas avec une dose de 10 mg/jour, dans un autre cas avec une dose non calculable) ».

Page 10 : IV – Effets neuro-excitateurs de la morphine par voie générale

- Ligne 1 : remplacer « 3 par voie intra-veineuse » par « 3 par voie intra-veineuse (dans un cas avec une dose de 500 mg/ jour, dans un cas avec une dose de 16 mg en 30 heures, et dans un dernier cas avec une dose inconnue mais probablement élevée chez un toxicomane) ».
- Ligne 6 : remplacer « Le remplacement, ou la diminution de la posologie de la morphine doivent être envisagés » par « La diminution de la posologie de la morphine ou sa substitution par un autre opiacé doivent être envisagés ».

Page 14 : V –Point sur les hyperkaliémies induites par l'association inhibiteurs de l'enzyme de conversion et spironolactone

- Ligne 13 : ajouter après « les notifications ne sont pas toutes spontanées » la phrase « comme en témoigne la répartition des observations en fonction du CRPV. En effet deux CRPV, Amiens et Angers, totalisent 46% des observations de la période post-RALES. Début 2003, le CRPV d'Angers a recueilli dans le cadre d'une enquête prospective une quarantaine de cas d'hyperkaliémie médicamenteuse. »
- Ligne 23 : remplacer « le taux de prescription de la SPIRO est passée de 34/1000 patients à 149/1000 » par « le taux de prescription de la SPIRO chez des patients hospitalisés sous IEC pour insuffisance cardiaque est passé de 34/1000 patients à 149/1000 ».
- Ligne 24 : remplacer « le taux d'hospitalisation pour hyperkaliémie est passé de 2,4/1000 patients à 11/1000 patients » par « le taux d'hospitalisation pour hyperkaliémie est passé de 2,4/1000 à 11/1000 chez ces mêmes patients ».

Page 15 : V –Point sur les hyperkaliémies induites par l'association inhibiteurs de l'enzyme de conversion et spironolactone

- Ligne 4 : rajouter « et la dose de spironolactone » après « essai ».

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Page 21 : VII – Questions diverses

- Ligne 19 : supprimer « significative ».

Page 22 : VII – Questions diverses

- Ligne 18 : remplacer « aucune valvulopathie chez les témoins » par « l'absence de signe de valvulopathie chez les témoins ».

Annexe 3-65

II - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Sont signalés les cas d'effets indésirables, de mésusages, d'erreurs et de manque de cohérence de l'information ainsi que les risques potentiels d'effets indésirables, pouvant donner lieu à des mesures (mises en enquête, notes...) ou pouvant faire l'objet d'une mise au point, dans le cadre de la prévention du risque médicamenteux.
La liste complète des cas est jointe en annexe 1.

Effets indésirables avérés :

Agénésie de la coupole diaphragmatique et hypoplasie pulmonaire bilatérale chez un nouveau-né de mère traitée par KEPPRA (lévétiracétam) pendant la grossesse/ CRPV de Clermont-Ferrand

Le CRPV de Clermont-Ferrand a signalé un cas d'hypoplasie pulmonaire bilatérale fatale chez un nourrisson né à 35 semaines d'aménorrhée d'une mère traitée par KEPPRA (lévétiracétam) et EPITOMAX (topiramate) pendant la grossesse.
→ Une note sera transmise à la cellule grossesse afin de signaler ce nouveau cas.

Oedèmes des membres inférieurs bilatéraux en présence de différents vaccins / CRPV de Clermont-Ferrand

Le CRPV de Clermont-Ferrand a signalé, à la suite de l'administration de différents vaccins, plusieurs observations d'oedèmes des membres inférieurs bilatéraux, nécessitant pour deux d'entre elles une hospitalisation (9 cas sous PENTACOQ®, 2 cas sous PENTAVAC®, 2 cas sous PREVENAR® associé à PENTAVAC® ou HBVaxPRO®). Le CRPV de Paris-HEGP a également signalé 4 cas sous PENTAVAC®.
→ Une enquête prospective des cas d'oedèmes survenant en présence de vaccins sera effectuée par les CRPV de Clermont-Ferrand, Dijon, Tours avec la collaboration des Centres de Protection Maternelle et Infantile.

TROXERUTINE MAZAL et choc anaphylactique / CRPV de Dijon

Le CRPV de Dijon a signalé un cas de choc anaphylactique sous TROXERUTINE MAZAL® sachet, qui est un générique de VEINAMITOL®.
→ Une note sera transmise au département pharmaceutique afin de connaître les excipients contenus dans la spécialité TROXERUTINE MAZAL® susceptibles d'être à l'origine d'un choc anaphylactique.

DEROXAT (paroxétine) et colite lymphocytaire / CRPV de Lyon

Le CRPV de Lyon a signalé un 10ème cas de colite lymphocytaire sous inhibiteurs sélectifs de la recapture de la sérotonine (DEROXAT®) avec normalisation après arrêt du traitement. Des cas de colites lymphocytaire sous paroxétine ont été rapportés dans une étude clinique rétrospective de 199 patients atteints de colites lymphocytaires publiés récemment dans Gut 2004 ; 53:536-541.
→ Une revue des données sur les colites lymphocytaires et les diarrhées chroniques sera demandée aux firmes commercialisant les inhibiteurs sélectifs de la recapture de la sérotonine (citalopram, escitalopram, fluoxétine, fluvoxamine, paroxétine, sertraline).

MIRENA (lévonorgestrel) et alopécie / CRPV Marseille

Le CRPV de Marseille a signalé un cas d'alopécie majeure 5 semaines après la pose de MIRENA (lévonorgestrel) chez une femme de 35 ans. 6 cas de chutes de cheveux ou d' alopécie sont signalés dans la base nationale de pharmacovigilance. Cet effet n'est pas mentionné dans le RCP de ce médicament. Dans la littérature, ce médicament semble entraîner plus d'alopécie que d'autres produits contraceptifs.
→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification d'information pour cette spécialité afin d'ajouter cet effet indésirable.

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Intoxication au méthotrexate / CRPV de Marseille

Le CRPV de Marseille a signalé un cas d'intoxication au méthotrexate (20 fois le taux attendu) avec insuffisance rénale aiguë d'apparition retardée à la suite de l'administration de doses recommandées de DANTRIUM (dantrolène) et de méthotrexate à forte posologie. Le CRPV de Montpellier a fait état des nombreux surdosages en méthotrexate associé au développement d'une insuffisance rénale. Le seul antidote efficace est le carboxypeptidase G2, a priori seulement disponible en Allemagne

→ Un point sera effectué par le CRPV de Montpellier sur le sujet et en particulier les modalités du suivi thérapeutique des traitements par méthotrexate.

CHLORAMINOPHENE (chlorambucil) et neuropathie périphérique / CRPV de Marseille

Le CRPV de Marseille a signalé un cas de neuropathie sensitivo-motrice sous CHLORAMINOPHENE (chlorambucil) chez un homme de 48 ans. Cinq autres cas sont signalés dans la base nationale de pharmacovigilance et cet effet n'est pas mentionné dans le RCP de cette spécialité.

→ L'unité de pharmacovigilance demandera à la firme le dépôt d'une demande de modification d'information pour cette spécialité afin d'ajouter ce type d'effet indésirable.

BRONCHODERMINE et troubles du comportement / CRPV de Marseille

Le CRPV de Marseille a signalé le cas d'un enfant de 20 mois traité par ADVIL, OCTOFENE, BRONCHODERMINE suppositoires, BRONCHOKOD, CELESTENE, hospitalisé pour troubles du comportement pendant 12 heures avec somnolence, aréactivité et regard fixe. La spécialité BRONCHODERMINE (cinéole ou eucalyptol, gaïacol, huile essentielle de pin) contient un dérivé terpénique pouvant être à l'origine de ces effets indésirables. La forme suppositoire n'est pas contre-indiquée chez l'enfant de moins de 30 mois. Seules les formes en application cutanée ou nasale sont contre-indiquées chez l'enfant de moins de 30 mois suite à une décision de la Commission d'AMM en 1996. Le 3 décembre 2004, le baume Vicks BABYBALM, contenant deux dérivés terpéniques avait été retiré du marché et il était envisagé une révision des spécialités contenant des dérivés terpéniques.

→ Ce cas sera signalé au groupe de travail concerné pour suite à donner.

UVESTEROL vitaminé A, D, E, C (vitamines A, D2, E, C) et volume de délivrance inadapté aux nouveaux-nés / CRPV de Montpellier

Le CRPV de Montpellier a signalé trois cas de cyanose dont un avec hospitalisation, chez des nouveaux-nés à la suite de fausses routes lors de la prise d'UVESTEROL (vitamines A, D2, E, C). L'injection trop rapide du volume nécessaire de la pipette (1 ml) aurait entraîné ces fausses routes.

→ Un point sur l'utilisation de l'UVESTEROL vitaminé A, D, E, C (vitamines A, D2, E, C) chez les nouveaux-nés sera effectué par les CRPV de Nantes et de Paris – Saint-Vincent de Paul.

FUZEON (enfuvirtide) et pneumopathies bactériennes / CRPV de Paris – Henri-Mondor

Le CRPV de Paris – Henri-Mondor a signalé deux cas de pneumopathies bactériennes survenues deux à quatre semaines après le début d'un traitement par FUZEON (enfuvirtide) chez une femme de 38 ans et un homme de 41 ans, sans qu'il y ait de mise en garde dans le RCP sur ce risque.

→ L'unité pharmacovigilance vérifiera les données d'essais cliniques sur le risque de survenue d'infections bactériennes précoces.

Mode d'administration des collyres et information dans les notices / CRPV de Paris – Saint-Vincent de Paul

Le CRPV de Paris – Saint-Vincent de Paul a fait état d'un cas étranger de surdosage massif lié à l'utilisation du collyre SKIAKOL (cyclopentolate), avec état de mal et décès survenu chez un enfant de 4 ans. Les notices des collyres précisent mal leurs modalités pratiques d'administration de ces produits.

→ Un point sur l'informativité des notices quant aux modes d'administration des collyres sera réalisée par le CRPV de Paris - Saint-Vincent de Paul.

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MEDIATOR (benfluorex) et bouffées délirantes / CRPV Toulouse
Le CRPV de Toulouse a signalé un cas de vision floue et malaise et un cas de bouffée délirante sous MEDIATOR (benfluorex), produit amphétaminique. Cette spécialité fait l'objet d'un large mésusage comme anorexigène.
→ Une mise à jour de l'enquête MEDIATOR sera effectuée par le CRPV de Besançon. Une relance sera effectué auprès de l'Italie sur ce sujet.

Effets indésirables potentiels

PROTOPIC (tacrolimus) et intolérance à l'alcool / CRPV Tours
Le CRPV de Tours a signalé deux cas d'érythèmes de la face sous PROTOPIC (tacrolimus) pommade, après la prise d'une boisson alcoolisée. Cet effet est mentionné en rubriques 4.4 et 4.8 du RCP de PROTOPIC pommade, alors qu'il n'est pas mentionné dans le RCP de PROGRAF gélule (tacrolimus).
→ L'unité de pharmacovigilance demandera l'avis du groupe de travail concerné.

Association MEXITIL® et CORDARONE® / CRPV Tours
A la suite d'une question posée au CRPV de Tours sur le RCP de MEXITIL (méxilétine), il a été observé une anomalie dans la rubrique « interaction médicamenteuse » puisque l'association avec l'amiodarone (CORDARONE®) est citée à deux niveaux : « contre-indiquée » et « nécessitant des précautions d'emploi » ce qui peut induire un risque de confusion.
→ Une note sera adressée à l'unité interaction médicamenteuse afin de signaler ce risque de confusion.

ZOMETA (acide zolédronique) et ostéonécrose de la mâchoire / CRPV Lille
Le CRPV de Lille a signalé un cas d'osctéonécrose de la mâchoire chez un patient atteint de myélome et traité par ZOMETA. Ce problème, soulevé au niveau européen, a conduit à la modification de la rubrique « effets indésirables » du RCP de ZOMETA et à l'ajout de cet effet indésirable. Par ailleurs, une DMI d'AREDIA (acide pamidronique) devant intégrer cet effet indésirable est en cours de finalisation par le CRPV de Reims.
→ Une information relative aux ostéonécroses des mâchoires pouvant survenir lors de traitement par acide zolédronique ou acide pamidronique sera effectuée auprès des prescripteurs.

Trimétazidine et syndrome extrapyramidal / CRPV Toulouse
Le CRPV de Toulouse a évoqué la publication de 8 cas de syndromes parkinsoniens observés avec la trimétazidine. Une vingtaine d'observations de ce type sont par ailleurs retrouvées dans la base nationale de pharmacovigilance.
→ Un point sur les syndromes parkinsoniens observés sous trimétazidine sera effectué par la CRPV de Toulouse.

MICROPAKINE (acide valproïque) et hyponatrémie / CRPV Reims
Le CRPV de Reims a signalé un cas d'hyponatrémie ayant entraîné une hospitalisation chez une patiente de 77 ans traitée avec MICROPAKINE. Plusieurs observations de ce type avec ce médicament sont retrouvées dans la base nationale de pharmacovigilance et dans la littérature.
→ Une analyse de l'ensemble des cas d'hyponatrémie rapportés avec l'acide valproïque sera demandée à la firme par l'unité de pharmacovigilance.

Documents distribués :

- Lettres aux pharmaciens hospitaliers et neurologues relatives au rappel des conditions de prescriptions d'ELSEP® et de suivi des patients atteints de sclérose en plaque selon l'autorisation de mise sur le marché.

Nouvelles enquêtes officieuses et officielles de pharmacovigilance :
- Une enquête prospective des cas d'oedèmes survenant en présence de vaccins sera effectuée par les CRPV de Clermont-Ferrand, Dijon, Tours avec la collaboration des Centres de Protection Maternelle et Infantile.

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- Un point sera effectué par le CRPV de Montpellier sur le sujet et en particulier les modalités du suivi thérapeutique des traitements par méthotrexate.
- Un point sur l'utilisation de l'UVESTEROL vitaminé A, D, E, C (vitamines A, D2, E, C) chez les nouveaux-nés sera effectué par les CRPV de Rennes et de Paris – Saint-Vincent de Paul.
- Une mise à jour de l'enquête MEDIATOR sera effectuée par le CRPV de Besançon.
- Un point sur l'informativité des notices quant aux modes d'administration des collyres sera réalisée par le CRPV de Paris - Saint-Vincent de Paul.

Annexe 3-65

III - ENQUETE OFFICIELLE RELATIVE AUX EFFETS INDESIRABLES GRAVES OBSERVES AVEC LA DESMOPRESSINE

Le Centre Régional de Pharmacovigilance (CRPV) de Caen a présenté l'enquête officielle relative aux effets indésirables graves observés avec la desmopressine.

Introduction

La desmopressine est un principe actif analogue de la vasopressine naturelle, aussi appelée hormone anti-diurétique (ADH). Cette dernière possède deux actions principales : une action anti-diurétique et un effet vasopresseur puissant. La structure chimique de la desmopressine diffère de celle de l'ADH, ce qui lui confère une demi-vie beaucoup plus longue et une forte diminution de l'effet vasopresseur au profit de l'effet anti-diurétique.

Statut

La desmopressine a obtenu une autorisation de mise sur le marché (AMM) en France le 22 janvier 1980. La spécialité Minirin®, commercialisée depuis 1982, existe sous 3 formes : Minirin® solution injectable 4µg/ml Intraveineuse (IV), Intramusculaire (IM) ou sous-cutanée (SC), Minirin® comprimé 0,1mg et 0,2mg (la forme sublinguale n'est pas encore disponible), Minirin® intranasal soit sous forme de Minirin® 0,1 mg/ml avec tube gradué (Rhinyle®) pour les posologies inférieures à 10 µg, soit Minirin® spray 10 µg/dose pour les posologies supérieures à 10 µg/dose.

Trois voies d'administration sont donc possibles, avec des indications distinctes :

Voie INTRA-NASALE :

- diabète insipide central pitresso-sensible ;
- traitement symptomatique de courte durée (3 mois) de l'énurésie nocturne de l'enfant de plus de 5 ans après élimination d'une pathologie organique sous-jacente ;
- étude du pouvoir de concentration du rein.

Voie ORALE :

- diabète insipide central pitresso-sensible ;
- traitement symptomatique de l'énurésie nocturne de l'enfant de plus de 6 ans après élimination d'une pathologie organique sous-jacente, la durée d'utilisation étant limitée à 6 mois ;
- depuis août 2003, extension des indications au traitement symptomatique de la nycturie chez l'adulte âgé de moins de 65 ans, lorsqu'elle est associée à une polyurie nocturne.

Voie INJECTABLE :

- traitement correcteur et préventif des accidents hémorragiques observés dans l'hémophilie A modérée et atténuée, maladie de Willebrand en dehors des formes sévères ou de type IIB, allongement inexpliqué du temps de saignement en particulier au cours de l'insuffisance rénale chronique ;
- traitement du diabète insipide central pitresso-sensible en particulier quand l'administration intra-nasale est malaisée ou impossible ;
- étude de pouvoir de concentration du rein.

Il existe une autre spécialité Octim® commercialisée en France depuis 1998, présente sous une seule forme à 150 µg/dose pour une administration intra-nasale, indiquée pour la prévention et la correction des accidents hémorragiques (tels que déjà définis ci-dessus).

Objectifs de l'enquête

- caractériser les effets indésirables (Ei) les plus fréquents de la desmopressine et déterminer l'imputabilité du médicament ;
- comparer l'incidence des Ei graves avec l'indication, l'âge des patients et la posologie ;
- évaluer les mesures préventives susceptibles de minimiser le risque.

Données de vente, données d'exposition

Le laboratoire Ferring titulaire de l'AMM de Minirin® et d'Octim® a transmis les données de vente pour la France et au niveau mondial.

Entre 1995 et 2003, **11,6 millions de patients** ont été traités par desmopressine dans le monde (11 millions par Minirin® et 600 000 par Octim®), ce qui représente 1,29 millions de patients traités par an.

En France, la voie intra-nasale est toujours la plus utilisée, même s'il apparaît que la voie orale prenne de plus en plus d'importance. Ainsi, en 1997, 10,4 fois plus de patients étaient traités par voie nasale que par voie orale, alors qu'en 2002 ce rapport n'est plus que de 1,9.
Au niveau mondial, depuis 2001 (et contrairement aux années 1996-2000), la desmopressine est plus souvent utilisée par voie orale que par voie intra-nasale, avec un rapport de 2,25 pour l'année 2003.

Analyse des cas notifiés en France
Les cas rapportés sont issus de la base nationale de pharmacovigilance et des cas enregistrés par le laboratoire Ferring.

La base nationale de pharmacovigilance contient 118 fiches d'effets indésirables (87 graves) en rapport avec la desmopressine dont 61 en relation avec une intoxication par l'eau. Il existe par ailleurs 29 autres observations en rapport avec une intoxication par l'eau dans la base du laboratoire. Au total 90 observations d'intoxication par l'eau ont été notifiées en France depuis la commercialisation.

- *Observations non liées à une intoxication par l'eau.*

Sur les 118 observations d'effets indésirables, 57 n'avaient pas de rapport avec une intoxication par l'eau. Sur les 57 observations, 29 concernent des effets indésirables graves. Dans 7 cas, l'imputabilité est vraisemblable. Il faut souligner la notification d'un décès par hépatite fulminante sur cirrhose (la desmopressine a une imputabilité douteuse).

- *Observations en rapport avec une intoxication par l'eau.*

Sur les 118 observations, 61 (dont 59 concernent des effets indésirables graves) concernent une intoxication par l'eau. Ces observations sont marquées par la survenue d'une hyponatrémie aiguë, associée ou non, en fonction de la gravité, aux signes cliniques suivants : asthénie, céphalées, nausées, vomissements, rétention hydrique, hypertension artérielle, œdème cérébral, troubles de l'humeur, confusion, coma, convulsions, détresse respiratoire.
L'imputabilité est vraisemblable dans 83,6% des cas.

Par ailleurs, le laboratoire Ferring a enregistré 29 observations françaises d'effets indésirables graves en rapport avec une intoxication par l'eau avec une imputabilité vraisemblable de la desmopressine.

La voie d'administration (connue dans 86/90 cas) se répartit en: **intra-nasale dans 77,9%** (67 cas), intra-veineuse dans 15,1% (13 cas) et orale dans 7% des cas (6 cas).

Les indications se répartissent en : **énurésie 53,3% (48 cas),** diabète insipide 13 cas, anomalies de la coagulation 12 cas, troubles mictionnels 11 cas, hypotension orthostatique 3 cas, test au Minirin® 1 cas, indication inconnue 1 cas.

L'âge des patients se répartit en : 58 cas concernent des enfants entre **0 et 15 ans, soit 64,4%.** Une majorité d'enfants est concernée par la voie d'administration intra-nasale qui représente les trois quarts des notifications, avec 86% de prescriptions dans l'indication énurésie. Pour la voie orale, la majorité des cas d'intoxication par l'eau concerne des adultes de plus de 65 ans (dans 2/3 des cas). En ce qui concerne la voie intra-veineuse, dans 12 cas sur 13, l'indication est en rapport avec un trouble hémorragique et les patients concernés sont des adultes de moins de 65 ans dans 62% des cas et des enfants de 0 à 16 ans dans 38% des cas.

La posologie par kilogramme de poids et par jour a été estimée dans 63 cas. Par voie intra-nasale la posologie moyenne est de **1,33 µg/kg/jour**, par voie intra-veineuse de **0,63 µg/kg/jour** et par voie orale, de **5,33 µg/kg/jour**. Une très grande disparité entre les valeurs extrêmes des posologies pour les formes intra-nasale et intra-veineuse, avec un rapport de 1 à 40 est mise en évidence. Pour la forme orale, il existe un rapport de 7,7 seulement entre les posologies les plus extrêmes.

Analyse des cas cliniques internationaux
Le laboratoire Ferring a reçu 1830 observations d'effets indésirables survenus sous desmopressine, dont 36,8% sont des cas graves (674). Sur ces 674 cas graves, 632 sont associés au Minirin® (dont 371 par voie intra-nasale) et 42 à Octim/Octostim®. Parmi les 1156 effets non graves, 1106 sont associés au Minirin® dont 766 lors d'une administration intra-nasale.

L'analyse des cas a porté sur les observations d'effets indésirables graves en rapport avec une intoxication par l'eau, ce qui représente **315 observations** issues de 25 pays. On observe que :

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- dans plus de 2/3 des cas, il s'agit de formes intra-nasales (67,9%) ;
- l'indication la plus souvent retrouvée est l'énurésie (43,2%) ;
- l'âge est inférieur ou égal à 16 ans dans 52,7% des cas (dont 1 sur 3 inférieur à 5 ans), entre 17 et 64 ans dans 23,5%, supérieur à 65 ans dans 15,6%.

Indications	Voies d'administration				
	Intranasale	Intraveineuse	Orale	Inconnue	TOTAL
Enurésie	**127**	0	10	1	**138**
Diabète insipide	49	6	9	2	66
Troubles mictionnels	8	0	20	1	29
Troubles de la coagulation	13	38	0	2	53
Test au Minirin®	11	5	0	1	17
Inconnue	6	0	3	3	12
TOTAL	**214**	41	42	10	**315**

Répartition des observations internationales d'effets indésirables graves relatives à une intoxication par l'eau sous desmopressine, en fonction de l'indication et de la voie d'administration.

Indications	Age					
	< 5 ans	5 – 16 ans	17 – 64 ans	> 65 ans	Inconnu	TOTAL
Enurésie	6	**103**	17	4	8	**138**
Diabète insipide	18	6	25	5	12	66
Troubles mictionnels	0	0	2	27	0	29
Troubles de la coagulation	16	2	21	9	5	53
Test au Minirin®	13	0	3	1	0	17
Inconnue						12
TOTAL	53	**111**	68	46	25	**315**

Répartition des observations internationales d'effets indésirables graves relatives à une intoxication par l'eau sous desmopressine, en fonction de l'indication et de l'âge.

Il est à souligner que l'indication de la desmopressine dans l'**énurésie** est réservée aux enfants de plus de 5 ans, or 4,3% des observations rapportées dans cette indication concernent des enfants de **moins de 5 ans**. Par ailleurs, la restriction d'âge à moins de 65 ans dans l'indication de **nycturie** n'est pas présente dans tous les pays, ce qui peut expliquer que 27/29 cas d'intoxication par l'eau dans cette indication soient décrits chez des patients de **plus de 65 ans.**

Dans l'indication de **diabète insipide**, la répartition en fonction de l'âge des cas d'intoxication par l'eau est de 24 enfants (dont 18 concernent des enfants de moins de 5 ans) et 25 adultes de moins de 65 ans. Cette répartition entre enfants et adultes est beaucoup plus homogène que celle observée dans l'indication énurésie où 109 observations d'effets indésirables graves sur 138 concernent des enfants.

Les cas concernant les **troubles de coagulation** sont assez équilibrés quant à la répartition par âge avec une forte représentation des très jeunes enfants de moins de 5 ans (30% de l'ensemble des cas).

Synthèse et discussion

L'incidence globale des effets indésirables notifiés sous desmopressine est estimée à **1,63 pour 10000 patients traités**. La proportion de notifications d'effets indésirables en rapport avec une **intoxication par l'eau** est importante puisqu'elle représente **51,7% des cas de la base nationale** de pharmacovigilance (**67,8% des effets graves**) et **51% des effets graves rapportés à la firme**.

La forme intra-nasale est le plus souvent en cause et représente 77,9% des cas français et 67,9% des cas internationaux d'intoxication par l'eau. Entre 1997 et 2002 en France, 4 fois plus de patients ont été traités par voie intra-nasale que par voie orale.

L'indication la plus souvent retrouvée dans les cas d'intoxication par l'eau sous desmopressine est **l'énurésie** (53,3% des cas français et 43,2% des cas internationaux).

Les observations d'intoxication par l'eau concernent en majorité des **enfants** de 0 à 16 ans (64,4% des cas français et 52% des cas internationaux).
L'analyse des **posologies** par indication, âge et voie d'administration montre une grande disparité avec des fourchettes de dose extrêmement importantes, ce qui illustre que la posologie n'est pas le seul facteur en cause dans ces observations.

Propositions :

- définir, si cela s'avère possible, des posologies initiales particulières (en µg/kg) :
  - chez le nourrisson pour le traitement du diabète insipide,
  - chez l'enfant de moins de 25 kg pour le traitement de l'énurésie
- insister sur la nécessité en cas d'énurésie de ne pas instaurer de traitements en dessous de 5 ans ;
- insister sur l'information donnée aux patients et à leur famille telle que la restriction hydrique, avec un ordre de grandeur du volume de boissons autorisé, identifier les situations à risque de déséquilibre, savoir reconnaître les éventuels symptômes d'une intoxication à l'eau, et insister sur les associations médicamenteuses à risque ;
- favoriser l'usage de la voie orale par rapport à la voie intra-nasale. Une forme sublinguale (Minirin® melt) permettrait de remplacer la voie intra-nasale.
- insister sur les risques lors d'une utilisation hors AMM ;
- harmoniser les différents RCP. L'ajout d'un tableau d'équivalences posologiques entre les différentes présentations et en particulier entre les formes orales et les formes intra-nasales pourrait être utile.

Le Comité technique estime par ailleurs que la ré-évaluation du rapport bénéfice/risque pourrait se justifier dans l'indication « énurésie ». Une présentation de cette enquête par domaines d'indication est prévue en Commission nationale de pharmacovigilance.

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IV - ENQUETE OFFICIELLE : MIRTAZAPINE ET ARTHRALGIES ET MYALGIES, MIANSERINE ET MYALGIES

Le CRPV de Nantes a présenté les résultats de l'enquête officielle concernant d'une part la mirtazapine et les myalgies – arthralgies et d'autre part la miansérine et les myalgies. Cette enquête recense les observations notifiées du 1er septembre 1999 au 31 décembre 2003.

1/ mirtazapine (NORSET®) et myalgies – arthralgies

NORSET® est autorisé en France depuis 1997 et commercialisé depuis le 1er septembre 1999 par les laboratoires Organon. Il est indiqué dans les épisodes dépressifs majeurs.

Données des Centres Régionaux de Pharmacovigilance (CRPV)

221 observations ont été recensées avec la mirtazapine dont 7 cas d'arthralgie, 9 cas de myalgie et 3 cas possédant les deux items, soit 13 notifications correspondant à 16 effets indésirables. Ces observations, le plus souvent non graves, concernent une population à légère prédominance féminine, âgée de 30 à 60 ans. Le délai de survenue est variable (de une heure à un an) et dans 4 cas, la mirtazapine était administrée en monothérapie. Ces effets indésirables sont tous survenus à la posologie recommandée. Aucune utilisation hors autorisation de mise sur le marché (AMM) n'a été relevée.

Il s'agit dans ces observations de polyarthralgies concernant essentiellement les petites articulations (mains, poignets, coudes) et pouvant être associées à des oedèmes (face, membres inférieurs, mains), une prise de poids, une asthénie. Ces effets indésirables ne semblent pas dose-dépendants. L'évolution a été favorable dans la grande majorité des cas à l'arrêt de la mirtazapine. Un cas de réadministration positive a été observé.

A noter que les arthralgies sont déjà signalées dans le Résumé des Caractéristiques du Produit (RCP) de la miansérine qui appartient, comme la mirtazapine, à la classe des pipérazinoazépines.

Données des laboratoires Organon

330 dossiers d'arthralgie - myalgie ont été colligés par le laboratoire sur un total de 6492 cas au niveau mondial. 16 cas, correspondant à 18 effets indésirables ont été rapportés en France. Ces observations sont superposables à celles notifiées aux CRPV.

Données des essais cliniques

Sur une population de 2521 patients, 46 cas d'arthralgie (soit 1,8%) et 51 cas de myalgie (soit 2%) ont été rapportés. Ces cas présentent les mêmes caractéristiques que ceux décrits après la mise sur le marché.

Au total, 29 cas d'arthralgie – myalgie ont été notifiés en France (330 dans le monde) avec la mirtazapine, d'où une fréquence de cas notifiés de l'ordre de $0{,}23.10^{-6}$ (le nombre de traitements vendus en France du 1er septembre 1999 au 31 décembre 2003 étant de 743306). Il est probable que ces effets indésirables fassent l'objet d'une sous-notification, en raison de l'absence de gravité de ces cas, de la chronologie variable et de la sémiologie banale. Cependant, l'information mérite d'apparaître dans le RCP afin d'éviter un traitement symptomatique par AINS.

Le rapporteur a suggéré d'intégrer dans la rubrique 4.8 du RCP de la mirtazapine :
« Dans de rares cas, les effets indésirables suivants ont également été rapportés : arthralgies, myalgies ».

2/ Miansérine (ATHYMIL® et molécules génériques) et myalgies

ATHYMIL® est un antidépresseur commercialisé depuis 1979 par les laboratoires Organon et indiqué dans les épisodes dépressifs majeurs. 14 médicaments génériques ont à ce jour une Autorisation de Mise sur le Marché (AMM) et 11 sont commercialisés.

Données des CRPV

1879 observations ont été recensées avec la miansérine dont 13 cas de myalgie. Ces observations, le plus souvent non graves, concernent une population à prédominance féminine, âgée de 34 à 80 ans. Le délai de survenue est variable (de 3 jours à 2 ans) et dans 2 cas, la miansérine était administrée en monothérapie.

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Il s'agit dans ces observations de myalgies associées à d'autres effets indésirables tels que asthénie, anorexie, élévations des transaminases, diarrhées, nausées, vertiges, ou augmentation des CPK. L'évolution a été favorable dans la grande majorité des cas à l'arrêt de la miansérine. Un cas de réadministration positive a été observé.

Données des laboratoires

13 observations de myalgie rapportés avec ATHYMIL®, présentant les mêmes caractéristiques que celles décrites plus haut, ont été transmis par le laboratoire Organon (sur 649 notifications françaises). 60 cas de myalgie ont été signalés dans le monde.

Un cas supplémentaire australien a été transmis par le laboratoire Merck générique et concerne la spécialité MIANSERINE MERCK®.

Données de la littérature

L'analyse de la littérature a permis de retrouver un article issu du bulletin de pharmacovigilance des autorités de santé australiennes, l'ADRAC (Australian Adverse Drug Reactions Bulletin) de février 1984, recensant 14 cas de douleurs musculaires et articulaires sous miansérine.

Le rapporteur a suggéré d'intégrer dans la rubrique « Effets indésirables » 4.8 du RCP de la miansérine :
« Ont été signalés : de rares cas de myalgies ».

Le Comité technique a suivi l'avis du rapporteur, mais a proposé le terme « arthromyalgies » en remplacement de « arthralgie, myalgie ».
Le dossier sera présenté lors de la Commission nationale de janvier 2005.

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V - POINT SUR LES EFFETS CORONAIRES DES TRIPTANS

Le Centre Régional de Pharmacovigilance de Toulouse a présenté un point sur les effets indésirables coronaires des triptans. Ce point a été demandé par le Comité technique suite à la notification de 2 cas d'infarctus du myocarde chez des sujets jeunes (35 et 36 ans).
Les triptans sont des agonistes des récepteurs sérotoninergiques 5HT1B et 5HT1D, présents sur les artères intracrâniennes mais également sur les artères périphériques, comme les artères coronaires. Ces récepteurs déterminent, quand ils sont activés par un agoniste, un effet vasoconstricteur. Par ailleurs, les triptans inhibent l'extravasation des protéines plasmatiques.

A ce jour, 5 triptans sont commercialisés en France :

- *sumatriptan* (IMIGRANE® : comprimés pelliculés, solution injectable, solution pour pulvérisation nasale et IMIJECT® : solution injectable)
- *zolmitriptan* ZOMIG® (comprimés pelliculés) et sous forme de comprimés orodispersibles sous le nom de ZOMIGORO®
- *naratriptan* NARAMIG® (comprimés pelliculés)
- *almotriptan* ALMOGRAN® (comprimés pelliculés)
- *élétriptan* RELPAX® (comprimés pelliculés)

Ils sont indiqués dans deux indications :

- *« Traitement de la phase céphalalgique de la crise avec ou sans aura »*. La forme injectable est réservée *« au traitement de la crise de migraine sévère lorsque les autres traitements de la crise de migraine n'ont pas été efficaces au cours des crises précédentes »*.
- *« Traitement de la crise d'algie vasculaire de la face »* pour IMIGRANE® solution injectable et IMIJECT® solution injectable.

Analyse de la Base nationale de Pharmacovigilance :

Une interrogation de la Base Nationale de Pharmacovigilance en juin 2004, avec les mots clés « triptans » et « collapsus cardiovasculaire, troubles cardiaques, angine de poitrine, angine de poitrine compliquée, coronaropathie » a révélé 11 observations. Ces observations concernent 7 hommes et 4 femmes (le ratio homme/femme dans la migraine est de 1/3).

Dans 3 cas sur 11, le tableau a été qualifié de « non grave ». il s'agit de :

- 2 cas de précordialgie,
- un trouble visuel conduisant à la découverte de troubles de la repolarisation avec susdécalage du segment ST,

Dans les 8 autres cas, le tableau été qualifié de grave. Il s'agit de :

- un arrêt circulatoire avec fibrillation ventriculaire,
- quatre infarctus
- un angor spastique,
- deux spasmes coronariens.

Des facteurs de risque cardiovasculaire ont été noté dans 8 cas sur les 11 rapportés.
L'évolution a été favorable dans tous les cas sauf un. Il s'agit d'un cas concernant un homme de 36 ans ayant présenté un arrêt circulatoire avec fibrillation ventriculaire. L'évolution s'est faite vers un coma et une encéphalopathie post-anoxique avec décès ultérieur.

Concernant les triptans imputés, il s'agissait :

- dans 5 cas, du *zolmitriptan* comprimés,
- dans 3 cas, du *naratriptan*,
- dans 2 cas, du *sumatriptan* injectable (IMIJECT®)
- dans 1 cas de la prise successive à 1 heure d'intervalle de zolmitriptan puis de spray de *sumatriptan*.

L'imputabilité a été jugée :

- douteuse (I1) dans 7 cas,
- plausible (I2) dans 1 cas,
- vraisemblable (I3) dans 2 cas,
- très vraisemblable (I4) dans 1 cas.

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Dans un cas, a été notée l'association a de l'oxymétazoline (ATURGYL®) aux propriétés alpha stimulantes pouvant potentialiser les effets coronaroconstricteurs des triptans.
Dans 5 cas (45,5 %), une notion de mésusage a été retrouvée. Il s'agit dans 2 cas, d'interaction médicamenteuse et dans 3 cas, de non respect des posologies recommandées.

Analyse de la littérature :
Les symptômes thoraciques représentés par une impression d'oppression thoracique avec parfois une symptomatologie algique et observés très classiquement sous triptans, ont été exclus de ce travail.
La revue de la littérature réalisée au 3 septembre 2004 a permis de retrouvé 41 articles.
Concernant les cas rapportés dans ces articles, on note :

- Une dizaine d'accidents ischémiques myocardiques, coliques et cérébraux
- Des cas d'infarctus du myocarde, essentiellement rapportés avec le sumatriptan injectable
- De façon très anecdotique, la survenue d'infarctus du myocarde chez des patients sans pathologie cardiovasculaire préexistante
- Deux observations d'effets indésirables coronaires après utilisation de sumatriptan par voie orale.

Le « Groupe d'Experts de Sécurité Cardiovasculaire des Triptans » a publié ses résultats en 2004 (Doddick et al, Headache 2004, 44, 414-425). Ce groupe, travaillant au nom de l'American Headache Society, a conduit une revue générale de l'ensemble des données scientifiques et cliniques sur le risque cardiovasculaire associé aux triptans. Le groupe d'experts conclut que : « le risque d'effets indésirables cardiovasculaires sous triptans apparaît très faible chez les patients respectant les critères d'inclusion ou d'exclusion des essais cliniques ou recevant les triptans selon les recommandations officielles ». Ainsi, « les triptans peuvent être prescrits en confiance sans bilan cardiovasculaire préalable ».

Conclusion :
Les accidents coronaires graves sous triptans surviennent dans presque 50 % des cas en dehors de tout mésusage et peuvent apparaître en l'absence de tout antécédent cardiovasculaire connu. Ces accidents graves concernent non seulement le sumatriptan (injectable ou administré par voie orale) mais également les autres triptans disponibles par voie orale. Ces données conduisent à rappeler qu'il faut, avant la prescription de tout triptan, évaluer le terrain coronaire par un interrogatoire sur les facteurs de risque cardiovasculaires et l'existence ou non d'un comportement addictif (ou d'une tendance addictive). L'évaluation du risque cardiovasculaire doit être dynamique dans le temps : il convient donc de la renouveler régulièrement car l'âge est un facteur de risque en soi et le risque augmente donc au cours du temps.
L'information présente dans les résumés des caractéristiques des produits (RCP) des différents triptans mériterait d'être mieux présentée et surtout d'être mieux connue des prescripteurs. Des propositions pourront être faites dans ce sens au niveau européen, pour les produits enregistrées selon des procédures européennes. Les RCP des produits enregistrés en procédure nationale (ZOMIG® et IMIGRAN® solution pour pulvérisation nasale, solution injectable et comprimés) pourront être modifiés.
Par ailleurs, l'ajout, dans les RCP, de l'interaction avec les alpha-stimulants qui ne sont pas des dérivés de l'ergot de seigle (comme l'oxymétazoline) devra être discutée.

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VI – POINT SUR LES CEPHALEES PAR ABUS MEDICAMENTEUX

1 - POINT SUR L'ABUS DES TRIPTANS ET MIGRAINES AGGRAVEES

Le Centre régional de Pharmacovigilance (CRPV) de Dijon a présenté un point sur les migraines aggravées induites par abus de triptans. Ce point a été réalisé conjointement par le CRPV de Dijon et le Centre d'Evaluation et d'Information sur les Pharmacodépendances (CEIP) de Toulouse.
Ce point ne concerne que la classe des triptans même si l'abus dans la migraine est le plus souvent plurimédicamenteux. Les triptans sont des agonistes sélectifs des récepteurs $5HT_{1B}$ et $5HT_{1D}$ vasculaires. Il sont indiqués dans le traitement de la crise de migraine, avec ou sans aura et ne doivent pas être utilisés en traitement prophylactique.
Cinq spécialités sont commercialisées en France, sous des formes orales, injectables ou inhalées.

Définitions :

En 2004, l'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) a publié des recommandations concernant le diagnostic, et a précisé le rôle de l'abus médicamenteux dans ces circonstances et la prise en charge **des céphalées chroniques quotidiennes (CCQ)**. Les CCQ y sont définies comme : « un ensemble hétérogène défini par la présence de céphalées plus de 15 jours par mois et plus de 4 heures par jour en l'absence de traitement, depuis plus de 3 mois, sans *substratum* lésionnel ou symptomatique. Il s'agit le plus souvent d'une céphalée initialement épisodique (migraine ou céphalée de tension) qui évolue vers une céphalée chronique, sous l'influence notamment d'un abus médicamenteux et de facteurs psychopathologiques.»
Selon l'International Headache Society (IHS), **l'abus médicamenteux** se définit comme un usage excessif intentionnel, persistant ou sporadique, de médicaments, accompagné de réactions physiques ou psychologiques nocives et caractérisé par une prise médicamenteuse régulière et qui dure depuis plus de 3 mois et qui est présente plus de 15 jours par mois pour les antalgiques non opioïdes (AINS, aspirine, paracétamol) et plus de 10 jours par mois pour les autres traitements de la crise (opioïdes ergotés, triptans, spécialités antalgiques associant plusieurs principes actifs). L'abus médicamenteux serait à l'origine d'un tiers des CCQ dans la population générale.

Les céphalées par abus médicamenteux (CAM) sont définies par les 3 critères suivants :
- la céphalée est présente plus de 15 jours par mois
- la céphalée se développe ou s'aggrave lors de la surconsommation médicamenteuse
- la céphalée disparaît ou revient à son état initial dans les deux mois après l'arrêt de la surconsommation médicamenteuse.

La CAM répond à des caractéristiques cliniques dépendant du type de substance consommée. En cas de CAM liée à une prise excessive de triptans, la céphalée secondaire doit être à prédominance unilatérale, et /ou de nature pulsatile, et/ou d'intensité modérée à sévère, et/ou aggravée par les activités physiques usuelles, et/ou associées soit à des nausées, des vomissements, soit à une phono- et photophobie. L'aggravation clinique se traduit souvent par une augmentation de la fréquence des crises.
Les **céphalées de sevrage** surviennent après l'utilisation d'une dose importante de substance pendant plus de 3 mois, apparaissent dans les heures suivant son arrêt, sont soulagées par une réadministration et disparaissent dans les 14 jours après l'arrêt total.

Analyse de la Base Nationale de Pharmacovigilance :
La recherche des observations enregistrées dans la Base Nationale de Pharmacovigilance a été réalisée, pour chaque molécule de triptan en recherchant les effets indésirables suivants : céphalée, migraine, céphalée par abus médicamenteux, céphalalgie, aggravation des céphalées, abus médicamenteux. Chaque observation a ensuite été revue et ont été sélectionnées comme abus toutes celles pour lesquelles les critères de l'IHS étaient retrouvés :
- céphalée par abus médicamenteux : céphalées durant plus de 15 jours par mois, s'aggravant avec la consommation de triptans, cédant à l'arrêt de la surconsommation,
- surconsommation : prise de triptans pendant plus de 15 jours par mois et pendant au moins 3 mois,
- nécessité d'un ou plusieurs sevrages,
- indication d'abus (terme préférentiel), ou présence d'éléments tels que la falsification d'ordonnance.

La recherche, menée en juillet 2004, a permis d'identifier 49 observations, enregistrées depuis 1992, année de mise sur le marché du premier triptan. Ces observations concernent 43 femmes et 6 hommes, d'âge moyen 48 ans.

Pour ces 49 observations, le diagnostic de céphalées par abus médicamenteux a été objectivé par :
- une amélioration des céphalées après sevrage en triptans : 35 observations,
- une fréquence de prise trop importante d'après les critères de l'IHS : 8 observations,
- une falsification d'ordonnance dans 1 observation,
- une prise chronique dans 2 observations,
- un abus probable mais difficile à objectiver par manque de renseignements dans 2 observations.

Dans 20 % des observations, un syndrome dépressif associé est indiqué.
Les triptans imputés sont :
- Zolmitriptan dans 30 cas (58%),
- Naratriptan dans 15 cas (30,6%),
- Sumatriptan dans 10 cas (20,4%) voie orale 6 fois, voie SC 2 fois, voie inhalée 2 fois,
- Almotriptan dans 1 cas (2%).

Dans 7 observations, une association de plusieurs triptans a été constatée. Une association aux autres traitements de la crise a été notée dans 61,2% des cas et aux antalgiques simples dans 12% des cas.
Dans les cas avec abus objectivé selon les critères de l'IHS, les consommations vont de 10 jours par mois (limite inférieure pour parler d'abus) à 6 comprimés par jour tous les jours au maximum.
Un sevrage médical a été nécessaire dans 37 cas, dont 24 en milieu hospitalier.

Données des CEIP :
Ces données ont été obtenues en utilisant les outils des CEIP à savoir OSIAP (Ordonnances Suspectes, Indicateur d'Abus et de Pharmacodépendance), NOTS (Notifications Spontanées) et OPPIDUM (Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse). Vingt-sept cas d'abus ont été recensés grâce à ces outils.
Dans 22 cas sur 27, le triptan était associé à d'autres médicaments. Il s'agissait notamment d'antalgiques, dans 15 cas, de caféine dans 9 cas. Dans 1 cas, il y avait également consommation de substances illicites (héroïne, ectasy).
Treize des 27 cas ont été identifiés comme étant des doublons des observations de la base nationale de Pharmacovigilance.

Analyse de la littérature
Les céphalées chroniques induites par abus médicamenteux ne semblent survenir que chez des patients qui sont déjà céphalalgiques, le plus souvent migraineux.
Une étude portant sur la consommation de sumatriptan par la population danoise en 1994 et 1995 a montré une prévalence d'utilisation en 1994 à 7,8/1000, avec un sexe ratio F/H à 3,8.
L'analyse des délivrances de médicaments par les pharmacies au Danemark en 1995, représentant 46 500 patients, a montré le caractère inapproprié de la consommation de sumatriptan dans la population : 5% des patients consomment 40% des triptans. Trois grands groupes de consommateurs ont été définis : importants (plus de 60 unités par mois), intermédiaires (entre 30 et 59), et modérés (moins de 30 unités /mois). Dans chaque groupe la proportion de céphalées induites a été estimée respectivement à 86 %, 47% et 14%.
Une étude israélienne visant à documenter la relation entre consommation de sumatriptan et changement de la nature des migraines, a montré chez tous les patients une recrudescence des crises 3-4 semaines après introduction, des modifications des caractéristiques des céphalées et une augmentation de leur durée.
Concernant la prise en charge, le sevrage médicamenteux est indispensable, mais les protocoles thérapeutiques sont actuellement très hétérogènes et mal évalués. Les moyens non médicamenteux sont parfois déterminants. L'éducation du patient céphalalgique et le suivi régulier sont primordiaux pour éviter les rechutes. Des facteurs pronostiques ont été mis en évidence mais ne seraient pas déterminants à long terme. Le taux de réussite, actuellement évalué à 60% à 5 ans, et les bénéfices d'une prise en charge adaptée encouragent à détecter précocement ces céphalées induites encore largement sous-diagnostiquées

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Information contenue dans les Résumés de Caractéristiques du Produit (RCP)

Il a été signalé qu'une information concernant le risque de céphalées chroniques induites par abus est mentionnée en section Mises en garde et précautions d'emploi pour tous les triptans commercialisés excepté pour Naramig, pour lequel une procédure de variation européenne est en cours à ce sujet, et Zomig, enregistré selon une procédure nationale. Une information est présente dans la section concernant les effets indésirables que pour Zomig.

2 - POINT SUR LES CEPHALEES PAR ABUS D'ANTALGIQUES

A la suite d'une alerte rapportée par deux médecins du centre de la douleur et de traitement des céphalées du CHU de Saint-Etienne en juin 2004, le CRPV de Saint-Etienne a souhaité présenter un point sur les céphalées par abus médicamenteux (CAM). Ce point a été réalisé en collaboration avec la Société Française d'Etudes des Migraines (SFEMC).

Après avoir rappelé les définitions de la CAM et de la surconsommation médicamenteuse, les données de la SFEMC ainsi que les cas de la base nationale de pharmacovigilance ont été présentés.

Données de la SFECM

Depuis le 1er juin 2002, cette société a créé un registre multicentrique de patients céphalgiques reçus dans 13 centres hospitalo-universitaires spécialisés dans la prise en charge des douleurs chroniques et/ou des céphalées.

Au 31 mars 2004, 20 628 patients étaient dénombrés, les conclusions suivantes pouvaient être dégagées :

- 1544 (7,5%) patients ont été identifiés comme souffrant de CAM
- les médicaments responsables se répartissent comme suit :
  - antalgiques non opiacés : 38,2%
  - triptans : 29,3%
  - antalgiques opiacés : 22,3%
  - ergotamine : 3,2%
  - associations : 4,3%
  - autres (sans précision) : 2,7%.

Par ailleurs, à la suite de ces premiers résultats, la SFEMC a instauré une étude épidémiologique observationnelle, transversale, multicentrique, réalisée auprès des centres hospitalo-universitaires spécialisés dans la prise en charge de patients céphalalgiques. L'objectif de cette étude est de décrire les caractéristiques sémiologiques des patients souffrant de CAM. Elle a débuté en juillet 2004 et doit inclure 500 patients au total.

Données de la base nationale de pharmacovigilance

Le recueil des données de la base nationale a été effectué sur une période identique (du 1er juin 2002 au 31 mars 2004) à celle de la SFEMC, afin de permettre une comparaison des résultats.

La recherche croisée de céphalalgie / migraine / abus de médicament / pharmacodépendance avec tous les principes actifs antalgiques ou antimigraineux appartenant aux listes « antalgiques » et « neurologie, antimigraineux, traitement de la crise » extraits du classement des médicaments par famille pharmacothérapeutique (section jaune du Dictionnaire Vidal 2004), a permis de colliger 44 observations, contre 1544 pour la SFECM.

Les données comparatives peuvent être résumées de la façon suivante :

	REGISTRE SFECM	BNPV
Nombre de patients	1544	44
Abus d'antalgiques non opiacés	38,2%	32,1%
Abus de triptan	29,3%	18,3%
Abus d'antalgiques opiacés	22,3%	24,8%
Abus d'ergotamine	3,2%	9,1%
Autres	7%	15,7%

Information contenue dans les Résumés de Caractéristiques du Produit (RCP)

Après avoir revu l'ensemble des RCP concernés, il apparaît que le risque de CAM est de façon générale peu mentionné dans les RCP. En effet, seules les spécialités contenant de l'aspirine, du zolmitriptan ou de la dihydroergotamine comportent un libellé relatif au risque de CAM.

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Le CRPV de Saint-Etienne a l'issue de sa présentation a tiré les conclusions suivantes :

- La faible notification des cas de CAM, peut s'expliquer par la méconnaissance du problème des professionnels de santé et des patients eux-mêmes
- Le CRPV a rappelé la récente publication, par l'Agence Nationale d'Accréditation en Santé (ANAES)[1], de recommandations de prise en charge des céphalées chroniques quotidiennes.
- A la lumière de ces différentes données, le CRPV a souligné la nécessité de modification des RCP et des notices des produits concernés .

Par ailleurs, le CRPV de Saint-Etienne a fait part, lors de l'adoption du procès-verbal, de nouvelles informations : une étude concernant la surconsommation des triptans a été coordonnée par l'URCAM de la région Rhône-Alpes et certains neurologues. Le CRPV de Saint-Etienne est en attente des résultats.

CONCLUSION GENERALE

A la lumière de ces différentes données, le Comité technique a souligné la nécessité de modification des RCP et des notices des produits concernés.

Concernant les RCP, il a été rapporté qu'une NUI (Non Urgent Information) avait été demandée par le Danemark auprès de l'Europe en septembre 2004, concernant les CAM. 9 Etats Membres ont répondu (Irlande, Suède, Royaume-Uni, Lettonie, Portugal, Malte, Italie, Islande et France). Au total, les résultas français correspondent à la tendance européenne qui se dégage des réponses reçues.

Par ailleurs, une identification plus précise de la consommation des triptans dans la population française et le nombre d'abuseurs est nécessaire.

En accord avec le CRPV de Dijon, il a été conclu de centrer en premier lieu les actions sur les triptans. De plus, le CRPV de Dijon s'est engagé à finaliser le protocole d'une étude de suivi de consommations des triptans dans le région Bourgogne, en partenariat avec la Caisse d'Assurance Maladie.

[1] . Recommandations pour la pratique clinique. CCQ (Céphalées Chroniques Quotidiennes) : Diagnostic, rôle de l'abus médicamenteux, prise en charge. Septembre 2004. disponibles sur le site www.anaes.fr;

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VIII - QUESTIONS DIVERSES

Rappel des conditions de prescription d'ELSEP® (mitoxantrone) et de suivi des patients :

La spécialité ELSEP® (mitoxantrone) 2mg/ml a obtenu une autorisation de mise sur le marché en Octobre 2003 dans le traitement des formes agressives de sclérose en plaques de type récurrente/rémittente ou de type secondairement progressive. ELSEP®est agréé aux collectivités depuis le 4 Mai 2004. Ce médicament est en réserve hospitalière et sa prescription est limitée exclusivement aux neurologues des services spécialisés en neurologie.

En raison, notamment, des risques hématologiques (8 cas de leucémie rapportés) et cardiaques, liés à l'utilisation du produit, l'autorisation de mise sur le marché octroyée pour ELSEP prévoit :

- le recueil d'un accord de soins du patient avant l'initiation du traitement,
- une surveillance particulière et obligatoire de la pharmacovigilance, chez tous les patients traités, tout au long du traitement et pendant 5 ans après la fin de celui-ci.

Le 15 décembre 2004, une lettre d'information a été adressée par l'Afssaps aux neurologues hospitaliers exerçant en service de neurologie et aux pharmaciens hospitaliers concernés, afin de rappeler les conditions de prescription d'ELSEP® et de suivi des patients traités. Un communiqué de presse a également été diffusé sur le site internet de l'Afssaps. Il est rappelé dans ces documents que les patients traités par mitoxantrone dans le cadre d'une sclérose en plaques doivent impérativement recevoir la spécialité ELSEP et non NOVANTRONE, et ce afin de bénéficier du suivi de pharmacovigilance prévu. Les prix de ces deux spécialités sont aujourd'hui identiques.

Les Centres Régionaux de Pharmacovigilance ont demandé à disposer d'un exemplaire du classeur de suivi des patients traités par ELSEP, transmis aux prescripteurs pour toute initiation de traitement. Une demande en ce sens sera faite aux laboratoires Wyeth.

Exposition in utero à des hormones sexuelles, naturelles ou synthétiques et troubles psychiatriques ; cas recueillis par l'Association HHORAGES / CRPV de Bordeaux

Dans le cadre de l'étude des effets de l'exposition in utero au DiéthylStilbestrol et aux autres hormones stéroïdes naturelles ou de synthèse, un recueil de témoignages spontanés portés à la connaissance des associations de patients est effectué. L'association HHORAGES (Halte aux Hormones Artificielles pendant la Grossesse) s'intéresse tout particulièrement aux troubles psychiatriques induits. Cette association a collecté environ 525 témoignages, soit faits directement par les sujets exposés soit le plus souvent par l'intermédiaire des familles. Le Dr. F. Haramburu du CRPV de Bordeaux, membre du groupe de travail de l'Afssaps sur les conséquences de l'exposition au diéthylstilbestrol, a pris connaissance des cas transmis. Dans la majorité des cas, l'exposition est imprécise (nature, date d'exposition par rapport à la grossesse, durée de l'exposition, posologie) et la pathologie psychiatrique est vague, non médicalement confirmée. Soixante témoignages correspondant à 60 familles avec 74 enfants présentant des troubles psychiatriques (sur 89 exposés, pour un total de 144 enfants dans ces familles) ont été retenus. Si la nature de l'exposition est connue dans la plupart de ces cas, les autres caractéristiques de l'exposition sont le plus souvent imprécises ; il n'y a pas dans la majorité des cas de confirmation médicale des diagnostics psychiatriques retenus. Les tableaux cliniques présentés semblent très variés ; en revanche un certain nombre de cas correspondent indubitablement à des cas graves (hospitalisations, suicides, invalidité). Aussi, si ces témoignages représentent une source d'information intéressante et sans aucun doute un signal fort, ils ne peuvent pas constituer une base d'analyse pour l'évaluation d'une relation causale.

Suite à une étude pharmaco-épidémio-génétique « REGISCAR » des syndromes de Steven's Johnson et de Lyell, une copie des dossiers remplis par les investigateurs sera adressée par le centre de Paris–Henri-Mondor aux différents CRPV selon leur territoire d'intervention.

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ADOPTE

RÉPUBLIQUE FRANÇAISE

afssaps

Agence française de sécurité sanitaire des produits de santé

Saint-Denis, le 08 FEV. 2005

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

COMITE TECHNIQUE DE PHARMACOVIGILANCE

(Procès-verbal de la réunion du mardi 11 Janvier 2005)

Etaient présents :

M. CARON : président
M. ANDREJAK : vice-président
Mme POLARD (suppléante de M. ALLAIN), Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA), Mme BAVOUX, M. BIOUR, M. BLAYAC, Mme GINISTY (suppléante de M. CALVO), Mme SPREUX (suppléante de Mme CHICHMANIAN), Mme MOSQUET (suppléante de M. COQUEREL), Mme ZENUT (suppléante de M. ESCHALIER), M. GAMBIER (suppléant de M. GILLET), Mme HARAMBURU, Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), M. KANTELIP, Mme LAINE-CESSAC, Mme LEBRUN-VIGNES, M. LE LOUET, Mme LILLO-LE LOUET, M. MALLARET, M. MERLE, M. MONTASTRUC, Mme GUY (suppléante de M. OLLAGNIER), Mme PERAULT, M. RICHE, Mme SGRO, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VIAL.
Mme BURNEL (représentant Monsieur le Directeur des Hôpitaux)
Mme DAHAN (représentant Monsieur le Directeur Général de la Santé)
Mme KREFT-JAIS (représentant M. le Directeur Général de l'Afssaps)

Unité de Pharmacovigilance :
Mme KREFT-JAIS
Mlle BOUTRON
Mme CARDONA-GIORDANO
Mme CHOULIKA
Mlle FERARD
Mme GOEBEL
Mme GRENE
Mlle HENRY
M. JACQUET
Mme LAHMAR
Mme OUARET
Mlle PAGE
Mme POINSARD
Mme POROKHOV
Mlle ROBINE
Mme SCHLOSSER
VESQUE

Unité Pharmaco-Toxico-Clinique :
M. GUEHO
Mme ROCHE
Mme YOLDJIAN

CRPV :
Mme CARLHANT
Mme HESSAINE
M. IMBS
Mme OLIVIER

Etaient excusés :

M. le Directeur Général de l'INSERM
M. le Président de la Commission nationale de Pharmacovigilance Vétérinaire

Internes :
Melle ANDRIANTAFIKA
Melle FAYE

Stagiaire :
Melle DAUDET

143/147, bd Anatole France - F-93285 Saint-Denis cedex - tél. 33 (0)1 55 87 30 00 - www.afssaps.sante.fr

COMITE TECHNIQUE DU : 11 janvier 2005

CENTRE DE PHARMACOVIGILANCE de MONTPELLIER

N° des cas	Date de survenue	Sexe /Age	Médicaments suspects	Effets observés	Evol.	Imput.	G	N	E	Commentaires *Interaction...*
MP0500076	1995	F/42	Isoméride® 30 mg/ pdt 20 mois	Triple valvulopathie	F	C1S2B3	Oui	Non	Non	Responsabilité dans l'aggravation de sa cardiopathie du Médiator ??

- Evolution : selon le code OMS, A, F, B, U, D, C, N
- Pour Gravité, Nouveauté, Enquête : répondre par Oui ou Non

Traitement à base d'Isoméride® 30 mg / J du 05-07-1985 à mars 1986, puis de juillet 1988 à mai 1989
Poids de Juillet 1985 70 kg, 1,58 m, IMC 28; poids de mars 1986 58 kg
Poids de juillet 1988 71 kg ; poids de mai 1989 59 kg

1ers signes apparus en 1990 à type de dyspnée,
en 1995 apparition œdèmes des membres inférieurs, malaises, dyspnée d'effort majeure,
en 1996 prise de 17 kg en quelques mois et diagnostic d'une hypothyroïdie traitée par Levothyrox®.
1ère hospitalisation le 18-03-1997 et évocation d'une HTAP avec décompensation cardiaque globale, PAPsytolique estimée à 42 mmHg, fuite mitrale grade 2 et aortique grade 1-2. Prescription de Lasilix®. En décembre 1997 ajout de Lipanthyl® et Médiator®.
Bilan du 29-08-04, PAPsystolique estimée à 50 mmHg, fuite mitrale grade 3, aortique grade 2 et tricuspide grade 3.

Rafel Ribera J, Casanas Munoz R, Anguera Ferrando N, Batalla Sabun N, Castro Cels A, Pujadas Capmany R. Valvular heart disease associated with benfluorex. Rev Esp Cardiol. 2003 Feb;56(2):215-6.

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Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du mardi 8 Mars 2005)

Etaient présents :
M. CARON : président
M. ANDREJAK : vice-président
Mme POLARD (suppléante de M. ALLAIN), Mme AUTRET-LECA, Mme MOACHON (suppléante de Mme BAVOUX), M. BIOUR, Mme PINZANI (suppléante de M. BLAYAC), Mme EFTEKHARI (suppléante de M. CALVO), Mme CHICHMANIAN, M. COQUEREL, Mme ZENUT (suppléante de M. ESCHALIER), M. GILLET, Mme MIREMONT-SALAME (suppléante de Mme HARAMBURU), Mme JEAN-PASTOR, Mme CHIFFOLEAU (suppléante de Mme JOLLIET), M. KANTELIP, Mme LAINE-CESSAC, Mme LEBRUN-VIGNES, Mme BROCUIELLE (suppléante de M. LE LOUET), M. BOUSQUET (suppléant de Mme LILLO-LE LOUET), Mme BARJHOUX (suppléante de M. MALLARET), M. MERLE, Mme OLIVIER (suppléante de M. MONTASTRUC), Mme GUY (suppléante de M. OLLAGNIER), Mme LAFAY-CHEBASSIER (suppléante de Mme PERAULT), M. RICHE, Mme SGRO, Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VIAL, Mme ALT (suppléante de Mme WELSCH).
Mme KREFT-JAIS (représentant M. le Directeur Général de l'Afssaps)

Unité de Pharmacovigilance :
Mlle BOUTRON
Mme CARDONA-GIORDANO
Mme CHOULIKA
Mlle DELEAU
M. DHANANI
Mlle FERARD
Mme GRENE
Melle HENRY
M. JACQUET
Mme LAHMAR
Mme OUARET
Mme POINSARD
Mme POROKHOV
Mlle ROBINE
Mme SCHLOSSER
M. VESQUE

CRPV :
Mlle LAPEYRADE
Mme PEYRIERE

Experts :
M. BAUD
M. DONADIEU
M. PUGLIESE

Interne :
Mlle FAYE

Stagiaire :
Mlle DAUDET

Etaient excusés :
M. le Directeur Général de la DHOS
M. le Directeur Général de l'INSERM
M. le Directeur Général de la Santé
M. le Président de la Commission Nationale de Pharmacovigilance Vétérinaire

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I – ADOPTION DU PV DU 8 FEVRIER 2005

Le procès-verbal de la séance du 8 février 2005 a été adopté avec les corrections suivantes :

Page 4 : II – Tour de table des cas marquants et de la littérature

- Ligne 44 : supprimer la cas marquant intitulé « TISANE MEDIFLOR à visée amaigrissante... »
- Ligne 57 : remplacer le terme « sublinguale » par « orale »

Page 21 : IX – Questions diverses

- Ligne 28 : ajouter « le CRPV de Nantes a indiqué qu'il avait réussi à limiter ce type de problème. Toutefois, certaines prescriptions sont réalisées en dehors du cadre strict prévu par l'AMM (posologie ou durée d'exposition supérieure etc...). Dans ce contexte, une lettre très informative destinée aux patients, leur expliquant que ce médicament leur est prescrit en dehors du cadre prévu par l'AMM, a été élaborée. De plus, dans ces situations, le patient devra signer un consentement éclairé. Ces documents seront présentés au Comité d'éthique du CHU mi-mars, pour avis. »

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II - POINT SUR LE BENEFICE/RISQUE DES CORTICOÏDES EN PERIODE PERINATALE

Compte tenu de plusieurs publications faisant état d'effets délétères possibles des glucocorticoïdes à long terme chez des nouveau-nés exposés, un point sur le rapport bénéfice-risque des corticoïdes en période périnatale a été présenté par le Pr Autret-Leca du CRPV de Tours. Cette analyse a été complétée par l'avis d'un expert, le Dr Baud, néonatologiste.

1- L'effet bénéfique des glucocorticoïdes anténataux en cas de menace d'accouchement prématuré avant 32-34 semaines (réduction de la mortalité et de la survenue de détresses respiratoires et d'hémorragies intra-ventriculaires) a été clairement établi dans une récente méta-analyse portant sur 18 essais. Toutefois, l'intérêt de répéter les cures de corticoïdes jusqu'à l'accouchement reste controversé.
Une étude de cohorte a montré que l'administration anté-natale de béthaméthasone (BMT) est associée à une réduction du risque de leucomalacie périventriculaire (LPV) par rapport à l'absence de traitement par corticoïdes et par rapport à la dexaméthasone (DMT). Le rôle neurotoxique des sulfites contenus dans le Soludécadron® a été proposé comme hypothèse pouvant expliquer les mauvais résultats observés avec la DMT *(Baud et al. N Engl J Med 1999)*.
Le suivi d'une seconde cohorte a montré que l'exposition répétée à la DMT est associée à une augmentation du risque de LPV et de troubles du neurodéveloppement par rapport à une exposition répétée à la BMT *(Spinillo et al. Am J Obstet Gynecol 2004)*.
Un essai randomisé évaluant l'administration de BMT soit en cure unique soit en cures répétées a montré qu'il n'existait pas de différence entre ces deux procédures sur le critère principal composite (détresse respiratoire, dysplasie bronchopulmonaire, hémorragie intra-ventriculaire, entérocolite, sepsis ou décès) bien que les cures répétées permettent de réduire l'incidence des détresses respiratoires sévères *(Guinn et al. JAMA 2001)*. Le suivi à long terme de ces enfants, annoncé par les auteurs, est d'une importance majeure (essai randomisé) puisque des études non randomisées ont suggéré un retard du développement neurocomportemental associé à la DMT.

Ainsi, le bénéfice des corticoïdes administrés <u>en pré-natal</u> dans la MAP est acquis si la naissance a lieu entre 32 et 34 semaines de gestation. Toutefois, l'intérêt de les renouveler si l'accouchement n'a pas eu lieu dans la semaine suivante n'est pas résolu. Les Sociétés américaines et canadiennes de gynécologie et obstétrique ont émis des recommandations en faveur d'un traitement par cure unique (DMT ou BMT) en cas de menace d'accouchement prématuré dans les 7 jours entre 24 et 34 semaines. En France, il n'existe pas de recommandations mais il semblerait que la pratique d'utilisation des corticoïdes en période anténatale se soit homogénéisée avec une utilisation majoritaire de la BMT, et un recul du recours à des cures répétées. Une étude européenne conduite en 1999 *(Truffert et al. Acta Paediatr 2003)* a montré qu'en pré-natal, le corticoïde le plus utilisé est la BMT (2/3 des cas) alors que la DMT est prescrite dans 1/3 des cas. Le recours à des cures répétées est par contre, quasi constante (99% en France). Enfin, la corticothérapie est prescrite dans 37% des cas en France chez des enfants nés dans un contexte de chorio-amniotite, alors que cette situation est une contre-indication à la corticothérapie.

2- En néonatologie, les propriétés anti-inflammatoires des glucocorticoïdes ont amené les médecins à tester ces produits dans la prévention et le traitement de la bronchodysplasie pulmonaire (BDP), pathologie chronique fréquemment rencontrée chez les prématurés. Les essais sont nombreux et ont d'abord étudié la réponse à des doses élevées pendant des durées prolongées (jusqu'à 42 jours) alors que les études plus récentes ont évalué des doses et des durées de traitement plus faibles.
Une large méta-analyse *(Halliday et al. Cochrane Database Syst Rev. 2003)*, portant sur 39 essais, permet de faire le point des données sur la corticothérapie en post-natale. Trois périodes de traitement sont à distinguer :
- <u>la corticothérapie précoce, avant les 96 premières heures de vie (J4)</u> et qui a pour but de prévenir la maladie, a fait l'objet de 20 essais randomisés portant sur 3072 prématurés. Le traitement précoce par DMT permet de diminuer l'incidence des BDP et facilite l'extubation. Toutefois, les effets indésirables précoces (effets digestifs, hyperglycémie, hypertension) et les effets à long terme (retard de croissance, anomalies neurologiques dont retard psychomoteur) suggèrent que le rapport bénéfice-risque est insuffisant. En effet, les données les plus inquiétantes sont celles correspondant au suivi sur le long terme des enfants. Il est ainsi rapporté à deux et six ans des retards psychomoteurs sévères (diminution du quotient intellectuel et des performances motrices) et des retards de

croissance chez les enfants ayant reçu de la DMT (résultats portant cependant sur seulement 56% des inclusions dans les études).
- la corticothérapie entre J4 et J14, dans un but préventif ou curatif, a fait l'objet de 7 essais portant sur 670 prématurés. Une diminution de la mortalité et de l'incidence des BDP a été observée. Les effets indésirables à court terme sont les mêmes que ceux observés en cas d'administration précoce et il n'y a pas de données sur les effets à long terme.
- la corticothérapie au-delà des 3 premières semaines de vie à visée curative a été évalué dans 9 essais portant sur 562 enfants. Les corticoïdes confirment leur effet positif sur la mortalité précoce et la ventilation mais aussi une tendance à un moins bon développement neurologique à plus long terme.

Ainsi, les données de l'utilisation post-natale des corticoïdes, en prévention ou traitement de la BDP, indiquent clairement un effet délétère majeur à 18 mois et à 8 ans.
Ces données ont amené les Académies de pédiatrie canadienne et américaine à publier des recommandations en 2002 qui rappellent que la DMT n'est pas recommandée en routine pour prévenir ou traiter la maladie pulmonaire chronique des enfants de petits poids de naissance. Toutefois, deux études nord américaines récentes montrent qu'en dépit de ces recommandations, 19 à 23% des prématurés recevaient en 2002 des corticoïdes en post natal. Une étude européenne conduite en 1999 *(Truffert et al. Acta Paediatr 2003)* a montré que 80% des centres de néonatologie utilisaient des corticoïdes en post natal. La DMT est prescrite dans 84% des cas y compris chez 31% des enfants non ventilés avec une FiO2 <50%.
Le Pr Autret-Leca afait également remarquer qu'une série de cardiomyopathie hypertrophique est enregistrée dans la base nationale de pharmacovigilance avec le Soludécadron®.

En conclusion, selon le Pr Autret-Leca et le Dr Baud il existe en France une utilisation non standardisée des corticoïdes en période périnatale avec un recours à une large utilisation de produits non évalués ou insuffisamment évalués. Il apparaît donc urgent de faire un état des lieux actualisé de la pratique en néonatologie afin de pouvoir émettre rapidement des recommandations appropriées sur l'utilisation des corticoïdes en période périnatale. Comme suggéré par certains auteurs, si des essais sont encore envisagés avec des corticoïdes, ils ne devraient cibler que les enfants chez lesquels un bénéfice est attendu (persistance de la ventilation assistée à 3 semaines de vie, atteinte pulmonaire progressive), en utilisant les doses les plus faibles possibles, pendant une durée la plus courte possible et avec un suivi systématique du développement neurologique et staturo-pondéral. Dans ce cadre, la place de la BMT devrait, plus particulièrement, être précisée car elle est utilisée par de nombreux centres depuis que les effets délétères de la DMT sur le long terme ont été mis en avant. Toutefois, si la BMT a fait preuve d'effets bénéfiques à court terme, elle n'a pas fait l'objet d'études d'utilisation et on ne connaît pas ses effets éventuels sur le long terme. L'hydrocortisone, potentiel corticoïde de substitution de la DMT, devrait également faire l'objet d'essais thérapeutiques. La place de la corticothérapie inhalée, un peu moins efficace mais offrant l'avantage d'un moindre passage systémique, pourrait aussi faire l'objet d'essais thérapeutiques. Enfin, il semble primordial que les parents soient informés des effets possibles de la corticothérapie à court terme et à long terme et que leur consentement soit recueilli avant l'administration d'une corticothérapie périnatale.

Le Comité technique de pharmacovigilance est favorable à la mise en place d'une enquête permettant de faire un état des lieux de la pratique actuelle sur l'utilisation de la corticothérapie en néonatologie et souhaite qu'un groupe de travail se mette en place rapidement afin d'émettre des recommandations sur cette problématique.

Annexe 3-67

III - DOSSIER MEDICAL INFORMATISE RELATIF AUX ANTIRETROVIRAUX (PROJET NADIS)

Le Docteur P. Puglièse du Service du Pr Dellamonica (Maladies Infectieuses, Hôpital Larchet, Nice) a présenté le Dossier Médical Informatisé NADIS et son application à un suivi de pharmacovigilance de l'atazanavir.

Introduction

Le dossier médical informatisé NADIS a été déployé en 2000 dans 6 sites pilotes[1]. Son but est l'exploitation de données scientifiques, l'évaluation des pratiques médicales et la mise en place d'études de phase IV. Plus récemment, a été développé un module de pharmacovigilance.

Les Enjeux

L'intérêt de ce dossier réside en une amélioration de la prise en charge individuelle du patient, grâce à la saisie en temps réel des données et au partage de l'information entre les différents intervenants.

L'exploitation scientifique collective des données peut être réalisée soit en mono-site soit en multi-site sur plusieurs établissements. Enfin, ce dossier permet d'évaluer non seulement les pratiques médicales de la prise en charge des patients VIH positifs, mais également de screener des patients susceptibles d'être inclus dans des essais cliniques de phase IV.

Le dossier

NADIS comporte divers types d'informations à renseigner successivement :

- Données administratives et sociales,
- Informations clés relatives à l'infection par le VIH ou/et par les VHB et VHC,
- Histoire clinique et thérapeutique du patient
- Examen clinique,
- Eléments biologiques spécifiques et généraux,
- Prescriptions médicamenteuses et examens paracliniques,
- Diagnostics et conclusions avec possibilité de texte libre.

Toutes ces données sont partagées entre services de soins, pharmacie et laboratoires (virologie, pharmacologie), avec échanges via une messagerie interne.

Chaque élément biologique saisi dans NADIS peut être édité et imprimé sous forme graphique, permettant une visualisation synthétique de son évolution. La saisie codée des résultats du génotype du VIH est facilitée par une interface intuitive. Le module de prescription médicamenteuse permet de pré-enregistrer les prescriptions habituelles. Le profil pathologique du patient (VIH,VHC,VHB ou co-infection) est choisi lors de la création du dossier. Il peut être modifié au cours du temps, permettant la saisie d'éléments spécifiques. Le choix du profil du patient permet en outre de paramétrer les différentes tables de codage (diagnostics, actes, médicaments), facilitant ainsi la saisie des données. NADIS permet aussi l'impression de nombreux documents facilitant la gestion de la consultation (ordonnances de prescriptions médicamenteuses et examens paracliniques, lettre de sortie, résumé de consultation, synthèse immuno-virologique, et certificats divers). Des alertes (pré-inclusion dans des protocoles thérapeutiques, cohérence diagnostic/stade CDC de l'infection à VIH, posologie hors AMM des antirétroviraux prescrits...) permettent une aide à la décision fondée sur des recommandations consensuelles. Des fenêtres d'alertes, non bloquantes, s'affichent en cas d'absence de prescriptions d'examens paracliniques recommandés dans certaines situations de prise en charge (par exemple consultation gynécologique semestrielle pour les femmes infectées).

L'amélioration des prescriptions médicamenteuses se fait grâce à différents outils :

- Outils de prescription
- Contrôles posologiques
- Historique des thérapeutiques antirétrovirales
- Motifs d'arrêts des schémas thérapeutiques
- Au cours du 1er semestre 2005 : utilisation de la Banque Claude Bernard
- Fiches produits en ligne
- Moteur d'interactions médicamenteuses
- Module de pharmacovigilance (en cours de développement)

Les bénéfices secondaires directs en consultation sont nombreux pour les médecins et les patients : ordonnances claires et compréhensibles (contrôles de posologies avec demande de validation en cas d'écart avec la posologie recommandée selon l'âge et le poids), éditions de documents standards (récapitulatif des différentes lignes thérapeutiques avec raison de l'arrêt, suivi des différents marqueurs de la maladie).

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[1] Infectiologie Pitié Salpétrière, Infectiologie CHU Toulouse, CISIH CHU Nantes, Hématologie & Cisih APHM, CH de Tourcoing

Les enjeux scientifiques sont également majeurs dans l'utilisation de cette base. En effet la constitution en temps réel d'une base de données patients :

- Facilite le screening pour essais thérapeutiques
- Permet le suivi rétrospectif et prospectif d'une cohorte
- Autorise l'exploitation multicentrique

La qualité des données saisies est attestée par un contrôle qualité de routine et de façon aléatoire sur échantillonnage.

Un module de Pharmacovigilance est actuellement en développement. Son objectif est de faciliter et d'augmenter l'exhaustivité des déclarations de pharmacovigilance, d'optimiser la qualité des données des études de phase IV issues de NADIS et de faciliter le remplissage des clinical report form (CRF) (dans le cadre d'essais thérapeutiques ou de demandes d'ATU).
Le but de ce module est de permettre le déclenchement d'alertes et de générer des propositions de déclaration de pharmacovigilance en fonction de la saisie ou de la présence d'éléments dans le dossier patient (saisie de signes cliniques, résultats biologiques, et modification d'une ligne thérapeutique). Il doit intégrer les tables des grades OMS des effets indésirables (pour alertes si grade OMS > 2).
Les données déjà saisies auxquelles s'ajouteront les données nécessaires pour compléter la déclaration des effets indésirables graves, permettront d'éditer le formulaire de déclaration.
Ce même formulaire sera accessible en visualisation et/ou saisie par le centre de pharmacovigilance.

Utilisation de NADIS dans le cadre d'une étude de phase IV concernant l'atazanavir :
Cette étude de phase IV du Reyataz (atazanavir) a été réalisée parmi les patients suivis dans les sites pilotes Nadis. Pour être inclus, les patients devaient avoir débuté leur traitement par atazanavir après le 01/03/2004 (date de mise à disposition de l'atazanavir auprès des prescripteurs). Les données pharmacologiques, les paramètres immuno-virologiques, lipidiques et hépatiques étaient colligées, ainsi que l'analyse des arrêts de traitement et de génotypes VIH. Parmi les 6703 (88,6%) patients traités répertoriés dans la base, 570 (88%) ont reçu l'atazanavir après sa mise sur le marché. 72% des patients étaient de sexe masculin, d'âge moyen 42 ans et infectés depuis en moyenne 12 ans. 31,2 % étaient co-infectés par les virus de l'hépatite B ou C. Le nombre moyen de lignes de traitement précédant l'initiation de l'atazanavir était de 6,67 pour une durée totale de traitement de 6,7 ans. 44% des patients avaient été précédemment traités par 2 inhibiteurs nucléosidiques de la transcriptase inverse et 1 inhibiteur de la protéase (IP). 41% des patients avaient arrêté leur précédent traitement pour effets secondaires (effets secondaires digestifs, lipodystrophies, dyslipidémie). Dans 77% des cas l'atazanavir était associé à 2 inhibiteurs nucléosidiques de la transcriptase inverse et 1 IP (166 patient sous Epivir®, Norvir®, Reyataz® et Viread®). 288 patients ont bénéficié d'une analyse du génotype VIH dans leur histoire thérapeutique avant l'introduction de l'atazanavir (soit 47% des patients traités par atazanavir). La posologie de l'atazanavir était principalement de 300 mg, boostée par 100mg de ritonavir (79%), mais d'autres posologies atazanavir/ritonavir étaient également observées (400/100 9,5%; 300/200 2,2%; 400/200 1,8%). 7,5% des patients traités ne recevaient pas d'atazanavir boosté (400mg : 5,1%; 300mg : 2,4%).
6% des patients ont présenté une hyperbilirubinémie de grade supérieur à 2. Chez les patients ayant arrêté leur traitement précédent pour dyslipidémie, à 12 semaines le cholestérol total a diminués (médiane cholestérol –1.38 mmol/L) ainsi que les triglycérides (médiane – 0,89mmol/l).
8% des patients (n=45) ont arrêté leur traitement après un délai médian de 38,5 jours. Dans 4,7% dans cas l'arrêt du traitement était du en raison d'un effet secondaire (principalement cutané).
Au total, ce premier travail a permis d'évaluer la faisabilité d'études de phase IV avec Nadis (rapidité des extractions et analyses, homogénéité des bases, reproductibilité), d'évaluer l'utilisation de l'atazanavir "en grandeur nature", enfin d'évaluer les pratiques thérapeutiques et les comparer aux dernières recommandations "Delfraissy 2004" (Indications hors AMM (résistances aux IP), posologies hors AMM).
L'intérêt de NADIS réside également en une réactivité supérieure à celle du dossier médico-économique de l'immunodéficience humaine (DMI_2) (mise à jour en temps réel vs semestrielle) et par le développement prochain d'un module dédié au couple mère/enfant.

Annexe 3-67

IV – TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Sont signalés les cas d'effets indésirables, de mésusages, d'erreurs et de manque de cohérence de l'information ainsi que les risques potentiels d'effets indésirables, pouvant donner lieu à des mesures (mises en enquête, notes...) ou pouvant faire l'objet d'une mise au point, dans le cadre de la prévention du risque médicamenteux.
La liste complète des cas est jointe en annexe 1.

Effets indésirables avérés :

ORBENINE (cloxacilline) et effet indésirables neurologiques centraux / CRPV d'Amiens
Le CRPV d'Amiens a signalé deux cas d'effets indésirables neurologiques centraux sous ORBENINE (cloxacilline) chez des patients ayant une insuffisance rénale sévère. Dans les deux cas, des taux importants de cloxacilline (et de ses métabolites) ont pu être documentés. Cet antibiotique a une élimination rénale significative. Or, il est indiqué dans le RCP qu'il est inutile de réduire la posologie en cas d'insuffisance rénale.
→ La firme s'est engagée à déposer une demande de modification de l'information médicale pour ORBENINE®.

CORDARONE (amiodarone) et contre-indication à l'Iode / CRPV de Dijon
Le CRPV de Dijon a signalé que dans le RCP de certains médicaments, il est mentionné une contre-indication chez la personne allergique à l'Iode. Cette mention pose le problème de la notion abusive d'allergie à l'iode qui correspond en fait le plus souvent à une allergie à un produit de contraste iodée. Par ailleurs, il n'a jamais été rapporté d'allergie croisée entre amiodarone et produit de contraste iodé ou povidone iodée.
→ La liste des médicaments présentant cette mention d'une contre-indication à l'Iode sera listée par l'Afssaps pour d'éventuelles suites à donner.

DEROXAT (paroxétine) et risque hémorragique chez les nouveaux-nés exposés en fin de grossesse au inhibiteurs de recapture de la sérotonine (IRS) / CRPV de Grenoble
Le CRPV de Grenoble a signalé un cas d'hématome sous-dural et intraparenchymateux chez un nouveau-né de mère traitée par DEROXAT tout au long de la grossesse. Un autre cas d'hématome sous-dural et d'hémorragie intra-parenchymateuse avait été rapporté en 2004 à ce même CRPV chez un nouveau-né de mère traitée par SEROPRAM (citalopram). Deux cas similaires sont décrits dans la littérature. La question du risque hémorragique chez le nouveau-né de mère traitée par IRS a été discuté en Groupe de Travail Grossesse en 2000. Les données animales et cliniques disponibles ont été considérées comme insuffisantes pour permettre de conclure à un risque. Le Groupe de travail est en train de revoir la rubrique grossesse des médicaments utilisés en psychiatrie.
→ Une note sera transmise à la cellule grossesse et allaitement à propos de ces deux observations.

Interaction médicamenteuse sous ZOCOR (simvastatine) et FUCIDINE (acide fusidique) / CRPV de Limoges
Le CRPV de Limoges a signalé une rhabdomyolyse sévère à la suite de l'administration de FUCIDINE® pour une infection urinaire à staphylocoques chez un patient traité depuis 9 ans par ZOCOR®. L'évolution a été favorable après l'arrêt du traitement par ZOCOR®. L'interaction médicamenteuse entre ZOCOR® et FUCIDINE® n'apparaît pas dans les RCP de ces deux spécialités.
→ Une note sera transmise à l'unité interactions médicamenteuses afin de signaler ce cas.

SEROPRAM (citalopram) et glaucome aigu à angle fermé / CRPV de Paris –HEGP
Le CRPV de Paris-HEGP a signalé un cas de glaucome aigu à angle fermé sous SEROPRAM (citalopram). Cet effet n'est pas mentionné dans le RCP de SEROPRAM. A la suite de l'arbitrage européen sur paroxétine, un rectificatif est en cours afin d'ajouter cet effet et une mise en garde sur cet effet pour DEROXAT.
→ Le rapport périodique de pharmacovigilance de SEROPRAM sera transmis au CRPV de Paris – HEGP pour évaluer le risque de glaucome.

MEDIATOR (benfluorex) et hypertension artérielle pulmonaire / CRPV de Montpellier

Le CRPV de Montpellier a signalé un cas d'hypertension artérielle pulmonaire d'évolution fatale chez une patiente de 55 ans traitée par MEDIATOR® comme anorexigène. Quatre autres cas d'hypertension pulmonaire sont signalés dans la base nationale de pharmacovigilance.

→ La mise à jour de l'enquête officielle sur les effets neuropsychiatriques sous MEDIATOR® décidée lors du comité technique de décembre 2004 sera étendue aux cas d'hypertension pulmonaire.

PHYTALGIC (huile de poisson omega 3, vitamine E, zinc) et purpura vasculaire / CRPV de Rouen

Le CRPV de Rouen a signalé un cas de purpura vasculaire sous PHYTALGIC, qui est un produit sans AMM, lequel aurait été utilisé par le patient dans le traitement des douleurs articulaires.

→ Une note sera adressée à la direction de l'inspection pour suite à donner.

ACUPAN® (nefopam) et modalités d'administration / CRPV de Strasbourg

Le CRPV de Strasbourg a signalé la mauvaise tolérance d'ACUPAN® administrée en IV lente de 5 minutes conformément au RCP alors que la pratique habituelle semble être en IV lente d'une heure voire plus.

→ Ce cas sera signalé à l'évaluateur pharmaco-toxico-clinique concerné afin de revoir les modalités d'administration.

CRESOPHENE (dexaméthasone, thymol, parachlorophénol, camphre) solution pour usage dentaire et arthrite dentaire / CRPV de Strasbourg

Le CRPV de Strasbourg a signalé deux cas d'arthrite dentaire sous CRESOPHENE (dexaméthasone, thymol, parachlorophénol, camphre) avec évolution favorable à l'arrêt du traitement. La teneur en camphre (64,9g) et parachlorophénol (30g) dans ce produit est élevée.

→ Ces cas seront signalés à l'évaluateur pharmaco-toxico-clinique concerné afin d'envisager une réflexion plus globale sur ce type de produit en ondotologie.

TEGRETOL (carbamazépine) et infertilité liée à une anomalie du sperme / CRPV de Strasbourg

Le CRPV de Strasbourg a signalé un cas d'anomalie du sperme chez un homme de 32 ans traité par TEGRETOL (carbamazépine), réversible à l'arrêt de ce médicament.

Deux autres cas suspects d'anomalie du sperme sous TEGRETOL® sont signalés dans la Base Nationale de Pharmacovigilance. Cet effet indésirable est mentionné dans le PDR et des petites séries de cas ont fait l'objet de publication par les Scandinaves.

→ Une note sera adressée à la cellule grossesse et allaitement afin de signaler ce cas.

Interaction médicamenteuse entre tramadol et les antivitamines K tels que fluindione, acécoumarol, warfarine / CRPV de Tours

Le CRPV de Tours a signalé une interaction médicamenteuse se manifestant par une hémarthrose du genou avec un INR à 10 après introduction de tramadol chez une femme de 62 ans traitée par PREVISCAN (fluindione). Cette interaction entre tramadol et fluindione n'est pas mentionnée dans le RCP des spécialités à base de fluindione et le risque d'interaction avec les coumariniques ne figure que pour quelques spécialités contenant du tramadol. 8 cas d 'interaction tramadol avec fluindione, 4 cas avec acécoumarol et 2 avec warfarine sont signalés dans la base nationale de pharmacovigilance et il existe plusieurs publications. Le risque d'interaction AVK-tramadol ne figure pas dans le thésaurus récemment mis sur le site de l'Afssaps.

→ Une note sera transmise à l'unité interaction médicamenteuse afin de signaler ce nouveau cas et d'envisager que l'interaction médicamenteuse antivitamine K et tramadol soit mentionnée dans les RCP de toutes les spécialités contenant du tramadol.

Annexe 3-67

Effets indésirables potentiels

Risque de confusion du fait du nouveau conditionnement des ampoules de SUFENTANIL MERCK 50 microgrammes du nouveau conditionnement des ampoules d'ADRENALINE AGUETTANT 5mg/5ml / CRPV de Dijon

→ La notion d'un risque de confusion de SUFENTANIL MERCK 50 microgrammes avec des ampoules de serum physiologique pour solutions injectables réservé à d'autres médicaments, et d'un risque de confusion des ampoules d'ADRENALINE AGUETTANT 5mg/5ml avec les ampoules de NORADRENALINE lié à un changement de conditionnement de ces produits injectables de petit volume, est transmise aux affaires réglementaires.

Documents distribués :

Nouvelles enquêtes officieuses et officielles de pharmacovigilance :

→ La mise à jour de l'enquête officielle MEDIATOR® décidée lors du comité technique de décembre 2004 sera étendue aux effets indésirables d'hypertension pulmonaire.

Annexe 3-67

V - MISE AU POINT SUR LE BON USAGE DES MÉDICAMENTS POUR PRÉVENIR LA IATROGÉNÈSE MÉDICAMENTEUSE CHEZ LE SUJET ÂGÉ

Cette mise au point a été élaborée à partir des évaluations d'un groupe pluridisciplinaire d'experts qui s'est réuni en janvier 2005. Anne CASTOT a indiqué que le document comprenait 10 pages et qu'il serait nécessaire de l'accompagner d'un résumé. Alice ROULEAU (Département CORGRIS) a précisé que cette mise au point n'était pas exhaustive et qu'elle se limitait aux classes pharmacologiques le plus souvent responsables d'effets indésirables sur la base des études publiées, des données de pharmacovigilance et de l'avis des experts. De plus, Anne Castot a indiqué le projet de rédaction d'un cahier « médicaments et sujets âgés » comme cela vient d'être fait pour les interactions médicamenteuses. Pour cela, l'aide des CRPV serait la bienvenue.

Jacques CARON a proposé aux membres du Comité technique de faire les remarques et commentaires sur le document avant le 15 mars 2005, du fait du passage en commission d'AMM prévu le 24 mars 2005.

Catherine SGRO a suggéré de faire apparaître des renvois pour les thèmes ayant déjà été traités dans d'autres documents (médicaments et canicule ; médicaments et grand froid).
Catherine NOBLET a suggéré d'indiquer la formule de Cockcroft & Gault pour l'estimation de la clairance de la créatinine.

Annexe 3-67

VI - PRÉSENTATION DES RÉSULTATS DU REGISTRE FRANÇAIS DES NEUTROPÉNIES CHRONIQUES SÉVÈRES : ÉVALUATION DES EFFETS SECONDAIRES DU G-CSF CHEZ DES PATIENTS PORTEURS DE NEUTROPÉNIES CHRONIQUES

Le Dr DONADIEU, médecin au service d'hémato-oncologie pédiatrique à l'Hôpital Trousseau à Paris, a présenté les résultats de l'évaluation des effets secondaires du G-CSF chez des patients appartenant au registre français des neutropénies.

C'est en 1994 qu'est né le registre français des neutropénies afin de répondre à une question de pharmacovigilance : le risque de survenue de leucémies est-il majoré par l'utilisation du G-CSF ? Il s'agit d'un registre portant sur une maladie et non sur ce médicament.

L'analyse a porté sur 306 patients dont 231 atteints de neutropénie congénitale et 65 atteints de neutropénie sévère chronique de l'adulte (recueil des données : 31 mars 2003).

Treize cas de transformation maligne (leucémies ou syndromes myélodysplasiques, MDS) ont été rapportés parmi les 231 patients atteints de neutropénie congénitale.

Les patients porteurs d'un syndrome de Shwachman Diamond et les patients porteurs de neutropénie congénitale sévère sont les seuls à avoir développé des leucémies secondaires. Chez ces patients, le taux de leucémie est de 10,8% et 18,8% respectivement à l'âge de 10 ans et 20 ans. Cette incidence augmente jusqu'à 36% à 30 ans parmi les patients atteints du syndrome de Shwachman Diamond.

Sur l'ensemble des patients porteurs de neutropénie constitutionnelle, il existe une corrélation entre l'exposition au G-CSF, représentée par la dose moyenne par injection et par la dose cumulée de G-CSF, et le risque de leucémie. Les groupes de patients les plus souvent traités par G-CSF sont les patients atteints de neutropénie congénitale sévère.

Suite à la mise à jour de septembre 2004, l'analyse a dénombré 2 cas supplémentaires de MDS pour un total de 253 patients suivis.

Le registre international répertorie jusqu'en 1999 731 patients. Le taux de leucémies dans ce groupe se rapproche de celui déterminé pour le groupe français à 20 ans d'âge. Contrairement à la France, l'influence de la dose n'a pas été étudiée. Seule, la dose moyenne (TAD : Time Averaged Dose) a été prise en compte : le risque de leucémie est 2,7 fois plus élevé chez les patients ayant reçu une dose supérieure à la TAD.

L'utilisation du G-CSF a transformé le pronostic infectieux des patients porteurs de neutropénie chronique. Chez les patients qui nécessitent les doses les plus importantes de G-CSF et à un rythme le plus intense, le G-CSF est associé à une augmentation du risque de transformation maligne (effet G-CSF) alors que ce risque est déjà important en l'absence de G-CSF (effet maladie). Ainsi, il ne semble pas fondé de contre-indiquer le traitement par G-CSF chez les patients porteurs de neutropénie chronique, en raison de l'effet protecteur du G-CSF vis à vis des infections vitales. La dose minimale doit toujours être recherchée lors d'un usage prolongé. Un suivi médullaire, cytogénétique attentif de ces patients est indispensable, d'autant plus que les besoins en G-CSF sont importants. Il est utile pour les patients chez qui de fortes doses de G-CSF sont nécessaires d'évaluer l'intérêt potentiel d'une greffe de moelle. C'est en effet le seul traitement alternatif disponible aujourd'hui mais qui présente lui aussi des risques.

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VII - MISE A JOUR DES DONNEES DE L'ENQUETE OFFICIELLE SUR LE RISQUE DE LEUCEMIE SECONDAIRE OU DE MYELODYSPLASIE APRES UTILISATION DES G-CSF

Le Pr COQUEREL (CRPV de Caen) a présenté les résultats de l'enquête française ne concernant que le lénograstim. Les conclusions sont similaires à celle faites précédemment par le Dr DONADIEU. Il a cependant été précisé que la relation linéaire effet/dose était soumise à d'importantes variabilités interindividuelles. Une présentation des cas issus de la base nationale de pharmacovigilance a également été effectuée sur la période de 2000 à 2005. Il n'y a pas de cas signalé de MDS ni de leucémie (myéloblastique) ni de cancer avec le GRANOCYTE®. En revanche 3 cas sont signalés avec le NEUPOGEN® (filgrastim).
Les laboratoires pharmaceutiques ont déclaré 2 cas japonais : une leucémie myéloïde (fatale) et une tumeur cérébrale ; et 3 cas français : 2 MDS sous GRANOCYTE® et 1 MDS sous NEUPOGEN® (fatal).
En conclusion, le CRPV de Caen rappelle que toutes les études randomisées publiées qui ont évalué le risque de néoplasie secondaire liée à l'utilisation du G-CSF sont négatives. Il n'y a aucun doute sur les bénéfices à court terme du G-CSF chez les patients atteints de neutropénie congénitale sévère. Il faut cependant recommander l'utilisation de la dose minimale active et la durée la plus courte possible ainsi qu'une surveillance prudente chez les patients qui reçoivent du G-CSF. En outre, il faut renforcer la surveillance lors des chimiothérapies adjuvantes des cancers du sein et des donneurs de cellules souches (Peripheral Blood Precursor Cells : PBPC). Le suivi longitudinal des différents registres des leucopénies sévères est également une nécessité et doit servir de modèles pour le suivi des prescriptions prolongées ou réitérées de G-CSF.

Discussion
Catherine SGRO a fait remarquer que les leucémies induites par la MITOXANTRONE (anthracycline utilisée dans le traitement du cancer du sein) ne sont pas du même type que celles observées sous facteurs de croissance. Ces dernières se rapprochent plus de celles induites par les alkylants.
Laurence MOACHON et Antoine COQUEREL ont soulevé le problème des patients sains qui développent une leucémie à la suite d'un don de cellules souches stimulé par facteurs de croissance.

Françoise BAVOUX pose le problème de l'absence de suivi des enfants nés de mères traitées par G-CSF pour cancer du sein au cours des 2ème et/ou 3ème trimestre de grossesse.
En conclusion, il n'est pas utile de modifier les données du RCP actuel. Une surveillance clinique et hématologique rapprochées des patients recevant de fortes doses de G-CSF semble plus que nécessaire.

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VIII - PEDEA® : IBUPROFEN THAM DANS LE TRAITEMENT DE LA PERSISTANCE DU CANAL ARTERIEL

Le CRPV de Saint-Vincent de Paul a présenté un point sur un nouveau traitement de la persistance du canal artériel : Pedea® ibuprofen THAM IV (laboratoires Orphan).

-Rappel concernant la circulation fœtale et naissance

Circulation fœtale :

D'après les études réalisées chez l'animal (fœtus du mouton), 70% du débit cardiaque total retourne à l'oreillette droite par la veine cave inférieure, 20% par la veine cave supérieure et 4% par le sinus coronaire. Seuls 5% du débit cardiaque empruntent la circulation pulmonaire. Le reste du débit ventriculaire droit (55% du débit cardiaque total) est dévié du poumon en passant dans l'aorte descendante à travers le canal artériel. 35% du débit cardiaque est délivré à l'oreillette gauche par l'intermédiaire du foramen ovale, qui reste ouvert pendant la vie fœtale du fait de la différence des pressions entre les deux oreillettes.

Naissance :

La pression artérielle pulmonaire et les résistances pulmonaires diminuent rapidement après la naissance avec fermeture fonctionnelle du canal artériel (dans les 10 à 96 premières heures chez le nouveau né à terme) puis anatomique (en 2 à 3 semaines).

PERSISTANCE DU CANAL ARTERIEL (PCA)

La fréquence de la PCA est inversement proportionnelle à l'âge gestationnel et au poids de naissance.

L'incidence de la PCA chez le prématuré de poids < 1750g est de 40 à 45%, et de 80% pour un poids<1000g.

Chez le nouveau-né à terme, l'incidence de la PCA est de 1/2000.

- *Facteurs de risque de la PCA* : maladies des membranes hyalines, apports liquidiens, souffrance fœtale, hypoxie à la naissance, certaines pathologies congénitales, malformations cardiaques. Les AINS (les inhibiteurs des prostaglandines) reçus pendant la grossesse peuvent modifier le tissu du canal artériel qui peut se rouvrir après la naissance.
- *Facteurs pouvant diminuer la PCA* : corticoïdes anténataux pour la maturation du surfactant et prévention de la maladie des membranes hyalines et la rupture prolongée des membranes
- Les signes cliniques de la PCA sont : pouls pulsatiles, hypotension, cardiomégalie, détresse respiratoire, hépatomégalie.
- *Le diagnostic* est souvent difficile surtout s'il existe une maladie des membranes hyalines associée. Il repose essentiellement sur l'échographie doppler cardiaque qui apprécie le retentissement hémodynamique et permet la recherche d'une anomalie congénitale associée.
- *La prise en charge thérapeutique de la PCA :* est largement dominée par le traitement médicamenteux, la chirurgie n'étant proposée qu'en deuxième intention en cas d'échec de fermeture pharmacologique du canal artériel.
- *Le traitement médicamenteux* repose sur les inhibiteurs de la synthèse des prostaglandines (AINS). L'indométacine a été le premier AINS utilisé dans cette indication et ce, depuis plus de 20 ans. Bien qu'efficace (70 à 80% de fermeture chez le grand prématuré), est encore mal évaluée et ses effets indésirables restent préoccupants (constriction de la circulation cérébrale et mésentérique, oligurie et rétention hydrosodée).

PEDEA® : IBUPROFEN THAM

Plusieurs données bibliographiques existent sur le traitement de la PCA avec la forme ibuprofène lysine. L'efficacité est similaire à l'indométacine, avec une meilleure tolérance. Les 2/3 des essais cliniques ont été réalisés avec ibuprofen lysine (commercialisé dans plusieurs pays pour l'adulte).

Les données relatives à Ibuprofen tham sont insuffisantes chez le grand prématuré de moins de 28 SA avec des données à 18 mois insuffisantes par rapport aux données dont on dispose pour l'indométacine.

En 2001, l'ibuprofène a été désigné par la Commission des Communautés Européennes comme médicament orphelin pour deux indications: traitement du canal artériel persistant et prévention du canal artériel persistant chez le nouveau-né prématuré de moins de 34 semaine d'age gestationnel.

Une demande d'autorisation de mise sur le marché (AMM) en Europe et d'ATU de cohorte en France a été présentée par le laboratoire Orphan pour une nouvelle formulation de l'ibuprofène avec modification de l'excipient (Tham).
L'usage en prophylaxie de l'ibuprofène Tham a été contre-indiqué en raison d'un arrêt d'essai clinique du fait de la survenue au cours de celui-ci de 3 cas d'hypoxie.
Pedea® a obtenue une AMM européenne selon la procédure centralisée en juillet 2004 (Irlande, rapporteur ; Grande Bretagne, co-rapporteur). Il a été demandé à la firme de réaliser deux études en post-AMM :

- une étude de dose, cinétique, efficacité et tolérance chez le prématuré de moins de 28 semaines d'aménorrhée (SA) avec la forme ibuprofen tham
- une étude de suivi des complications neurologiques et pulmonaires à 18 mois.

Les protocoles de ces deux études seront discutés par le groupe d'experts pédiatres à Londres au Comité des Spécialités Pharmaceutiques du mois avril 2005.

Pedea® a été mis à disposition dans les hôpitaux français en octobre 2004 ce qui a pour conséquence la suspension de l'ATU de l'indométacine et l'ibuprofène.

L'indication retenue est la suivante : traitement curatif de la PCA à la posologie de 10-5-5mg/kg en cure de trois jours.

BILAN DES CRPV

Dix-huit observations ont été retrouvées dans la base nationale de pharmacovigilance à la date du 31 décembre 2004. L'âge gestationnel était de 24 à 29 semaines d'aménorrhée (SA) (dont 11< 27SA).
Quatorze patientes ont eu un traitement curatif par ibuprofène seul, les 4 autres ont eu recours à un traitement par indométacine aprés échec du traitement par ibuprofène. Dans la moitié des cas, le traitement a été interrompu à la suite de l'apparition d'effets indésirables.
Parmi les facteurs de risque, on note : souffrance fœtale aiguë (n=9), maladies des membranes hyalines (n=11), éclampsie ou pré-éclampsie (n=4), infection mère et enfant (n=2).

Les effets indésirables rapportés étaient représentés par :

- les **atteintes digestives** dont 2 perforations digestives à l'emporte pièce, 2 entérocolites nécrosantes, 2 distensions abdominales avec souffrance mésentérique, 2 hémorragies hautes.
- les **atteintes rénales** dont 2 insuffisances rénales aiguës, une rétention hydrosodée et une hyperkaliémie.
- les **atteintes cardio-pulmonaires** représentées par une hypertension artérielle pulmonaire aiguë survenue une heure aprés l' administration de l'ibuprofène et corrigée par le NO.
- les **atteintes cérébrales** représentées essentiellement par des hémorragies intra-ventriculaires dont 2 de grade II, 2 de grade III et une de grade IV.

L'évolution était fatale chez six prématurés (<27SA) sur les 18. Le décès était lié à la grande prématurité et aux pathologies sous jacentes.

COMPARAISON DE DEUX ESSAIS CLINIQUES EN PROPHYLAXIE

L' un des essais a été réalisé avec ibuprofen lysine ne rapportant pas d' HTAP ni d'effets indésirables digestifs dans le groupe ibuprofen lysine.
L' autre essai a été réalisé avec l'ibuprofen tham PEDEA et a été arrêté en raison HTAP. De plus dans cette étude ibuprofen PEDEA, étaient rapportées des perforations digestives : 5/65 contre 1/66 dans le groupe placebo.

PROPOSITIONS DU COMITE TECHNIQUE

Le Comité technique a proposé :

- une mise en suivi du produit qui sera assuré par le CRPV de Saint-Vincent de Paul,
- de demander au laboratoire de réaliser une étude chez le rat pour mieux étudier la toxicité digestive de l'ibuprofène et comparer les deux formes d'excipients lysine et tham (perforation à l'emporte-pièce non observée avec l'ibuprofène lysine).
- de demander au laboratoire de clarifier pour quelle raison a t-il développé une nouvelle formulation de l'ibuprofène avec un nouvel excipient pour le dossier d'AMM, alors que plusieurs essais cliniques ont été conduit avec la forme ibuprofène lysine.

IV - INHIBITEURS DE LA POMPE A PROTONS ET RISQUE D'HYPERTENSION ARTERIELLE

Le Centre Régional de Pharmacovigilance du Languedoc-Roussillon a présenté un point sur les hypertensions artérielles secondaires à la prise d'inhibiteurs de la pompe à protons (IPP). Ce point fait suite à la notification d'un cas d'hypertension artérielle accompagnée de flush et de sueurs chez une femme de 80 ans, sans antécédents notables et traitée par IPP depuis environ 8 ans. Un examen complet à la recherche d'une tumeur endocrinienne a montré que cette patiente présentait une gastrinémie élevée (142ng/l, N<110) et des taux de chromogranine A à 5N. Les autres examens biologiques étaient normaux (sérotonine plasmatique, catécholamines urinaires, acide 5-hydroxy-indole acétique: 5HIAA, neuron specific enolase: NSE, thyrocalcitonine), ainsi que l'ostéoscan (scanner osseux). Le traitement par IPP a été arrêté, ce qui a permis une amélioration de la symptomatologie avec normalisation du taux de chromogranine A 5 jours plus tard. Un cas similaire a été rapporté aux XXIV° Journées de l'hypertension artérielle du 16-17 décembre 2004. Un phéocromocytome, initialement suspecté dans ce cas, avait conduit à la réalisation d'examens complémentaires montrant un taux de chromogranine A à 9N. Une résolution à l'arrêt de l'IPP a été observée (*Lopez-Sublet et coll*).

Dans la base nationale de pharmacovigilance, 12 cas d'augmentation de la tension artérielle ont été rapportés. Ils concernent des patients d'âge moyen 72,4 ans. Dans 1/3 des cas, l'effet indésirable est accompagné de flush et de sueurs. Dans 5 cas, l'effet survient dans les 2 premiers jours de traitement. L'arrêt du médicament a permis la régression de la symptomatologie et il n'y a pas eu d'exploration complémentaire. De plus, 12 autres observations de sueurs et flush ont été retenus. Elles concernent des patients d'âge moyen 60,1 ans. De même, la survenue de l'effet est rapide avec 2/3 des cas survenant dans les premiers jours de traitements. Une régression de la symptomatologie est observée à l'arrêt du traitement.

Dans la littérature, Guisti et al. *(Eur J Endocrinol. 2004 Mar ;150(3) :299-303)* rapportent une série de 9 cas d'augmentation de chromogranine A avec des taux supérieur à 90ng/l chez des patients traités par oméprazole. Dans 6 de ces cas, on note une symptomatologie ou des antécédents d'hypertension. Il est à noter, cependant, qu'aucune corrélation entre le taux de chromogranine A et les chiffres tensionnels n'a pu être établie dans cette étude. Par ailleurs, 4 cas d'hypertension artérielle ont été rapportés dans les essais cliniques avec le lansoprazole. *(Harford W et al. Helicobacter. 1996 Dec;1(4):243-50 et Swarbrick et al. Eur J Gastroenterol Hepatol. 1996 May;8(5):431-8).*

Un mécanisme d'action a été proposé : on observe en effet une augmentation de la gastrinémie en réponse à la réduction de la sécrétion d'acide chlorhydrique lors de traitement par IPP. L'hypergastrinémie peut provoquer au long cours une hyperplasie des cellules entérochromaffines (ECL) avec augmentation de la concentration de chromogranine A, glycoprotéine contenue dans les granules de sécrétion de ces cellules. L'hypergastrinémie pourrait également provoquer une libération de l'histamine, également contenue dans ces vésicules, pouvant expliquer les phénomènes de vasodilatation à type de flush. Takiyyundin et al. (*Hypertension. 1993 ;21(5) :674-9*) ont montré que le taux de chromogranine A était plus élevé chez les patients ayant une hypertension artérielle essentielle que chez les patients normotendus. A l'inverse, une augmentation isolée de chromogranine A n'entraîne pas forcément une hypertension artérielle. Dans leur étude, Giusti et al. concluent qu'il existe, rapidement après l'instauration d'un traitement par oméprazole, une élévation des taux de chromogranine A. Toutefois, les auteurs notent que celle-ci est plus élevée chez les patients ayant un taux de chromogranine A basal élevé. Ce taux est lui-même corrélé à l'âge, aux antécédents d'hypertension artérielle et à la créatininémie. Il a également été rapporté que les patients porteurs d'*Helicobacter pylori* ont des taux de chromogranine A plus élevés que les patients non porteurs d'*Helicobacter pylori*. Un rôle du polymorphisme du cytochrome CYP2C19, impliqué dans la dégradation de l'oméprazole, a été évoqué par Sagar et al. *(Aliment Pharmacol Ther. 2000 ;14(11) :1495-502)*. Les patients mutés sur l'allèle codant le CYP2C19 ont un taux de gastrinémie et de chromogranine A plus élevés. On peut enfin rappeler que la suppression de l'acidité

gastrique a été associée à la constatation de carcinoïdes gastriques à cellules entérochromaffines chez le rat, mais que ces tumeurs n'ont toutefois pas été observées chez l'homme lors d'études évaluant la prise d'IPP au long cours.

Au niveau du résumé des caractéristiques du produit (RCP) des différents IPP, l'augmentation de la gastrinémie est mentionnée en Section 5.1 (Propriétés pharmacodynamiques) pour le pantoprazole, le rabéprazole et l'ésoméprazole. Une augmentation du nombre de cellules ECL en relation possible avec l'hypergastrinémie, lors de traitement au long cours par IPP, est mentionné dans cette section pour le pantoprazole et l'ésoméprazole. Le RCP du rabéprazole mentionne que « des prélèvements, obtenus par biopsie d'estomac humain provenant de l'antre et du fundus chez plus de 500 patients traités par rabéprazole sodique ou comparateur sur une durée allant jusqu'à 8 semaines, n'ont pas permis de déceler de modifications de l'histologie des cellules ECL ».

- **Propositions du Rapporteur :**

- Les IPP entraînent une augmentation de la gastrinémie et de la chromogranine A. Cette notion devrait être précisée au niveau de tous les RCP et éviterait certains examens coûteux.
- Exceptionnellement, les IPP peuvent révéler ou aggraver une hypertension artérielle. Cette hypertension peut s'accompagner de flush et sueurs excessives. Faut-il ajouter cette mention dans le RCP des IPP malgré les arguments limités disponibles à ce jour ?

- **Conclusion :**

On peut rappeler que le dosage plasmatique de chromogranine A occupe une place de choix dans le bilan biologique des tumeurs -. Au niveau des cas rapportés d'hypertension, on constate que, même pour les IPP pour lesquels le risque d' hypergastrinémie et d'hyperplasie des cellules ECL est déjà mentionné dans le RCP, la survenue d'une hypertension avec élévation des taux de chromogranine A a conduit à la réalisation d'un bilan complet à la recherche d'une tumeur neuroendocrinienne.
D'autre part, le nombre de cas rapportés d'hypertension est faible alors que l'utilisation de ces produits est répandue. Très peu de cas sont documentés avec des dosages de chromogranine A. De plus, il n'existe pas de mécanisme suffisamment étayé sur la relation entre élévation initiale des taux de chromogranine A et une hypertension artérielle secondaire induite. Enfin, il n'est pas sûr que les mesures proposées modifieraient la prise en charge d'une hypertension pour laquelle on soupçonne une origine tumorale.
Au vu de ces éléments, le Comité technique de pharmacovigilance considère **qu'il n'est pas justifié de proposer d'éventuelles mesures à ce jour.**

X – PHARMACOVIGILANCE EUROPEENNE

EZETROL® (ézetimibe) est un agent hypolipémiant bénéficiant d'une AMM selon une procédure de reconnaissance mutuelle depuis mars 2003 (Allemagne, Etat membre de référence). Il est commercialisé en France depuis le 10 janvier 2005. L'ézetimibe agit en inhibant l'absorption intestinale du cholestérol et des phytostérols mais son mécanisme d'action est incomplètement élucidé.
Un suivi national a été mis en place en février 2005 sous la responsabilité du CRPV de Paris-HEGP. Un communiqué de presse sera diffusé aujourd'hui sur le site Internet de l'Afssaps afin d'avertir les professionnels de santé et le public sur le risque de survenue de rhabdomyolyse chez les patients traités par Ezétrol®. Des cas de rhabdomyolyse ont en effet été rapportés chez des patients traités par Ezétrol en association avec une statine, mais également lorsque Ezétrol était utilisé seul. Ce communiqué sera accompagné des recommandations concernant la prise en charge thérapeutique du patient dyslipidémique.

PROTOPIC® (tacrolimus) est un immunosuppresseur qui se présente sous la forme d'une crème destinée au traitement de la dermatite atopique modérée à sévère chez l'enfant et l'adulte après échec ou intolérance aux traitements conventionnels. Une étude au long cours (étude APPLES) a été demandée lors de l'octroi de l'AMM afin d'évaluer le risque de cancers cutanés, systémiques et de lymphomes chez les enfants traités par ce médicament pendant au moins 6 semaines. Le protocole est maintenant finalisé et doit être adopté prochainement par la FDA et les autorités compétentes européennes. Cette étude devrait débuter en mai 2005 et inclure 8000 enfants qui seront suivis pendant 10 ans.

EPREX® (époétine alfa) : demande par les laboratoires Janssen-Cilag d'une réintroduction de la voie sous-cutanée
En novembre 2001, la notification de 40 cas mondiaux d'érythoblastopénie chez des insuffisants rénaux chroniques traités avec Eprex® (époétine alfa) avait conduit l'Afssaps à déclencher une mesure de restriction urgente (USR) afin de modifier l'information du Résumé des Caractéristiques du Produit. Devant l'augmentation du nombre de cas, une deuxième USR puis une troisième USR ont été déclenchées avec pour résultat final une contre-indication de l'administration d'Eprex® par voie sous-cutanée chez les patients insuffisants rénaux chroniques (la voie intra-veineuse étant considérée moins immunogène que la voie sous-cutanée).

Les causes de ce problème avaient toujours été considérées comme multifactorielles et aucune étiologie précise n'avait été identifiée.

Les laboratoires Janssen-Cilag ont déposé en juin 2004 une demande de modification du RCP destinée à lever la contre-indication relative à l'utilisation de la voie sous cutanée en développant l'hypothèse suivante pour expliquer la survenue des cas d'érythroblastopénie : en 1998, l'albumine est remplacée par du polysorbate 80 dans la composition du produit. Ce polysorbate 80 agirait comme un détergent au niveau du caoutchouc des pistons des seringues pré-remplies, ce qui provoquerait la libération de substances appelées « leachates » dans le produit fini. Ce serait donc ces « leachates » d'après Janssen-Cilag qui seraient à l'origine des érythroblastopénies observées avec Eprex®. Au vue des données fournies par le laboratoire, le rapport préliminaire de l'Afssaps de février 2005 est resté en faveur du maintien de la contre-indication de la voie sous-cutanée chez l'insuffisant rénal chronique. Cet avis a été suivi en majorité par les Etats membres ayant répondu.

Inhibiteurs de la cyclo-oxygénase II ou « coxibs » : lors de la semaine du 14 février 2005, les membres du CHMP ont discuté de la procédure d'arbitrage commencée en novembre 2004 pour l'ensemble des coxibs. Le CHMP a décidé de déclencher une mesure de restriction urgente (*urgent safety restriction, USR*) permettant de modifier en urgence les RCP (notamment ajout de contre-indications et de mises en garde) au regard du risque cardiovasculaire et d'informer les professionnels de santé par l'envoi d'une lettre (*Dear Doctor letter*). Cette USR a été déclenchée le 16 février et finalisée le 17 février 2005. Un communiqué de presse a été diffusé sur le site Internet de l'Afssaps et l'envoi de la lettre d'information au professionnels de santé a été effectuée le 4 mars 2005 par le laboratoire Pfizer. L'opinion finale du CHMP concernant la procédure d'arbitrage est attendue pour avril 2005.

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XI – QUESTIONS DIVERSES

Groupe qualité

Le groupe qualité mis en place par l'association des CRPV, et représenté par Anne Chiffoleau et Pascale Lainé, souhaite centraliser l'ensemble des fiches d'aide au recueil spécifique d'effets indésirables. Afin de d'effectuer ce travail, le groupe qualité demande aux CRPV de bien vouloir collaborer en leur faisant parvenir les fiches d'aide au recueil.

1891 ADOPTE

Annexe 3-68

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le

COMITE TECHNIQUE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du mardi 7 juin 2005)

Etaient présents :
M. CARON : président
M. ANDREJAK : vice-président
Mme POLARD (suppléante de M. ALLAIN), Mme JONVILLE - BERA (suppléante de Mme AUTRET-LECA), Mme MOACHON (suppléante de Mme BAVOUX), M. BIOUR, Mme PEYRIERE (suppléante de M. BLAYAC), Mme CHICHMANIAN, Mme LACOTTE (suppléante de M. COQUEREL), M. CALVO, Mme ZENUT (suppléante de M. ESCHALIER), Mme PETIT PAIN (suppléante de M. GILLET), Mme HARAMBURU, Mme JEAN-PASTOR, Mme VEYRAC (suppléante de Mme JOLLIET), M. KANTELIP, Mme LAINE-CESSAC, Mme WAROT (suppléante de Mme LEBRUN-VIGNES), M. LE LOUET, Mme LE BELLER (suppléante de Mme LILLO-LE LOUET), M. MERLE, Mme BAGHERI (suppléante de M. MONTASTRUC), Mme GUY (suppléante de M. OLLAGNIER), Mme PERAULT, M. RICHE, Mme DISSON DAUTRICHE (suppléante de Mme SGRO), Mme NOBLET (suppléante de M. THUILLEZ), M. TRENQUE, M. VIAL, Mme ALT (suppléante de Mme WELSCH).
Mme BURNEL (représentant le Directeur de l'Hospitalisation et de l'Organisation des Soins)
Mme DELOFFRE (représentant le Directeur Général de la Santé)
Mme KREFT-JAIS (représentant le Directeur Général de l'Afssaps)

Unité de Pharmacovigilance :
Mme BIDAULT
Mlle BOUTRON
Mme CARDONA-GIORDANO
Mlle DELEAU
Mlle FERARD
Mme GOEBEL
Mme GRENE
M. JACQUET
Mme LAHMAR
Mlle PAGE
Mme POINSARD
Mme POROKHOV
Mlle ROBINE
M. VESQUE

PTC :
Mme CHAMPART
Mme DEGUINES
Mlle MONZON
Mme YOLDJIAN

CRPV :
M. DAVID LAROCHE
Mme EFTEKHARI

Stagiaire :
Mlle DOS SANTOS
Mlle DES RIEUX

Interne :
Mlle GILLES
Mlle BIZIEN

Etaient excusés :
M. le Directeur Général de l'INSERM
M. MALLARET (Président de la Commission Nationale des Stupéfiants et des Psychotropes)
M. le Président de la Commission Nationale de pharmacovigilance vétérinaire

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I - ADOPTION DU PROCES VERBAL DE LA SEANCE DU MARDI 10 MAI 2005

Le procès-verbal de la séance du 10 mai 2005 a été adopté avec les corrections suivantes :

Page 5 : III – Enquête officielle de pharmacovigilance relative aux effets indésirables observés en cas de surdosage accidentel ou volontaire avec le buflomédil (FONZYLANE®)

- Ligne 22 : remplacer « passage du buflomédil de la liste I à la liste II des substances vénéneuses » par « passage du buflomédil de la liste II à la liste I des substances vénéneuses ».

Page 8 : IV – Point relatif aux effets indésirables de l'enfuvirtide (FUZEON®)

- Ligne 19 : ajouter « inhibiteur » après « un analogue non nucléosidique » et après « un analogue nucléosidique ».

Page 10 : V – Tour de table des cas marquants et de la littérature

- Ligne 15 : supprimer « deux ».

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II - TOUR DE TABLE DES CAS MARQUANTS ET DE LA LITTERATURE

Sont signalés les cas d'effets indésirables, de mésusages, d'erreurs et de manque de cohérence de l'information ainsi que les risques potentiels d'effets indésirables, pouvant donner lieu à des mesures (mises en enquête, notes...) ou pouvant faire l'objet d'une mise au point, dans le cadre de la prévention du risque médicamenteux.
La liste complète des cas est jointe en annexe 1.

Effets indésirables avérés :

ACTIFED RHUME et ACTIFED JOUR ET NUIT et accident vasculaire cérébral / CRPV de Caen
Le CRPV de Caen a signalé un cas d'accident vasculaire cérébral chez une adolescente de 14 ans et demi après une automédication par ACTIFED RHUME® et ACTIFED JOUR ET NUIT®. La contre-indication chez l'adolescente n'a pas été respectée.
→ L'unité pharmacovigilance demandera à la firme l'évolution des chiffres de ventes pour ces spécialités et demandera au département publicité de porter son attention sur le contenu de l'information relative à la contre-indication chez l'enfant de moins de 15 ans au niveau des publicités grand public.

VASTEN (pravastatine) et effets malformatifs / CRPV de Clermont-Ferrand
le CRPV de Clermont-Ferrand a rapporté un cas d'interruption médicale de grossesse à 22 semaines d'aménorrhée pour multiples malformations dont holoprosencéphalie chez une femme traitée par VASTEN (pravastatine) en début de grossesse. Deux cas d'effets malformatifs similaires, l'un avec cérivastatine, l'autre avec lovastatine ont été publiés dans la littérature. Les statines sont contre-indiqués pendant la grossesse pour un risque potentiel ; ici, se pose la question de malformations spécifiques des inhibiteurs des HMG-CoA réductase.
→ Une note sera transmise à la cellule grossesse et allaitement afin de signaler ces trois cas avérés de malformations sous statines.

Confusion entre l'acide borique et glucose / CRPV de Marseille
Le CRPV de Marseille rapporte un cas d'erreur de délivrance entre deux poudres blanches, acide borique au lieu de glucose, non étiquetées dans une pharmacie de ville. L'acide borique est utilisé sous forme de topique dans l'hypersudation.
→ Une note sera transmise à l'unité affaires réglementaires afin de signaler cette erreur de délivrance. L'inspection régionale a été informée directement.

CRESTOR (rosuvastatine) et rupture tendineuse / CRPV de Lyon
Le CRPV de Lyon a signalé une cas de rupture tendineuse chez un patient de 50 ans sous CRESTOR®. Deux autres cas sont rapportés dans la base nationale de pharmacovigilance. L'enquête officielle sur les tendinites en présence de statines a été effectuée avant la mise sur le marché de CRESTOR®, spécialité en procédure de reconnaissance mutuelle Pays-Bas Etat membre de référence.
→ L'attention sera portée sur cet effet indésirable dans le prochain PSUR CRESTOR®.

VARILRIX (vaccin varicelleux vivant) et neuronite et ataxie vestibulaire / CRPV de Lyon
Le CRPV de Lyon a signalé un cas de neuronite et ataxie vestibulaire 15 jours après la vaccination par VARILRIX (vaccin varicelleux vivant) chez une femme de 28 ans, avec récidive et persistance de ces effets un mois après la date d'apparition. A cette occasion, il est apparu une divergence de libellé des rubriques sécurité d'emploi entre VARILRIX® et VARIVAX®. Ces deux vaccins varicelleux ont une composition différente et suivent des procédures d'enregistrement différentes.
→ Il sera envisagé une demande de modification de l'information pour VARILRIX®.

HYDROXYCUT complément alimentaire et deux cas d'hépatites aiguës / CRPV de Lyon
Le CRPV de Lyon a signalé un cas d'hépatite aiguë chez une patiente de 23 ans avec HYDROXYCUT complément alimentaire à visée amincissante. Deux cas d'hépatites aiguës ont été publiés récemment. Il contiendrait notamment des plantes (Garcinia cambogia, extraits de guarana, Citrus aurantium), du chrome, de la caféine, de la L-carnitine, de l'acide hydroxycitrique...

→ Une note sera transmise à la Direction de l'Inspection pour informer la Direction Générale de la Consommation, de la Concurrence et de la Répression des Fraudes, une fois l'observation du CRPV de Lyon complétée.

ZYVOXID et acidose lactique / CRPV de Montpellier

Le CRPV de Montpellier a signalé un cas d'acidose lactique chez une femme de 65 ans traitée par ZYVOXID (linézolide), spécialité en procédure de reconnaissance mutuelle, France état membre concerné. ZYVOXID fait l'objet d'un suivi national de pharmacovigilance. Trois autres cas d'acidose sont présents dans la base nationale de pharmacovigilance. Cet effet indésirable est par ailleurs signalé dans les PSURs.

→ La rubrique 4.8 « effets indésirables » du RCP de ZYVOXID® fera état de cet effet.

THALIDOMIDE LAPHAL® et pneumopathie interstitielle diffuse / CRPV de Paris – Fernand-Widal

Le CRPV de Paris – Fernand-Widal a rapporté un article du Journal of Clinical Oncology, vol 23, n°10, 2005 :2425-2426 sur thalidomide et pneumopathie interstitielle diffuse. Aucun cas de pneumopathie interstitielle diffuse n'est signalé dans la base nationale de pharmacovigilance.

→ Il sera envisagé de demander une revue des cas pour cette spécialité à la firme.

TENORDATE (aténolol, nifédipine) et gingivite hyperplasique / CRPV de Reims

Le CRPV de Reims a signalé un cas d'hyperplasie gingivale sous TENORDATE (aténolol, nifédipine), chez un homme de 64 ans. Dans le RCP de TENORDATE, il est juste mentionné « rares cas de gingivite », alors que dans le RCP des autres spécialités contenant de la nifédipine (ADALATE10mg®, CHRONADALATE®), il est mentionné « rarement, gingivite hyperplasique ».

→ Il sera demandé à la firme commercialisant TENORDATE® le dépôt d'une demande de modification de l'information afin de préciser la notion d'hyperplasie gingivale.

POMMADE MAURICE 2,5% (oxyde jaune de mercure) et eczéma / CRPV de Saint-Etienne

Le CRPV de Saint-Etienne a signalé un cas d'eczéma de contact à la deuxième application ophtalmique de la POMMADE MAURICE (oxyde jaune de mercure) chez un enfant de 7 ans et demi pour un orgelets. Les tests de contact, effectués ultérieurement, ont révélé une positivité à l'oxyde de mercure. 15 cas d'effets indésirables dont 5 cas d'eczéma, 5 cas d'œdème, un cas d'œdème de Quincke ont été rapportés dans la base nationale de pharmacovigilance pour les produits à base d'oxyde jaune de mercure, tels que POMMADE MAURICE 2,5%®, OPHTERGINE®, OXYDE MERCURIQUE JAUNE 1% CHAUVIN®. La possibilité d'irritation locale est le seul effet indésirable mentionné dans les RCP de POMMADE MAURICE® et OPHTERGINE®. Le RCP de la spécialité OXYDE MERCURIQUE JAUNE 1% CHAUVIN® mentionne également des réactions d'hypersensibilité cutanéo-conjonctivale en rubrique 4.8.

→ Il sera demandé aux firmes commercialisant ces médicaments le dépôt d'une demande de modification de l'information afin de mettre à jour le libellé de la rubrique 4.8. Il sera signalé à l'AMM que ce type de produit, indiqué dans le traitement local des blépharites infectieuses, notamment parasitaires, risque de sensibiliser les patients traités, aux dérivés mercuriels.

THALIDOMIDE LAPHAL® et aménorrhée / CRPV de Saint-Etienne

Le CRPV de Saint-Etienne a signalé un cas d'aménorrhée sous THALIDOMIDE LAPHAL® . Cet effet indésirable est connu : 6 autres cas dans la base nationale de pharmacovigilance. Cet effet est décrit dans la littérature mais n'est pas mentionné dans le RCP de cette spécialité.

→ Il sera envisagé de demander le dépôt d'une demande de modification de l'information pour cette spécialité en Autorisation Temporaire d'Utilisation afin d'ajouter cet effet indésirable.

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III – ENQUETE OFFICIELLE RELATIVE AUX HYPERTENSIONS ARTERIELLES PULMONAIRES ET AUX TROUBLES NEURO-PSYCHIATRIQUES OBSERVES AVEC MEDIATOR® (BENFLUOREX).

Lors du Comité Technique de Pharmacovigilance du 7 décembre 2004, plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique ayant été rapportées avec MEDIATOR® (chlorhydrate de benfluorex), une actualisation des données relatives aux troubles neuro-psychiatriques observés avec cette spécialité pharmaceutique a été décidée. Par la suite, du fait d'une notification d'un cas d'hypertension artérielle pulmonaire rapportée lors du Comité Technique du 8 mars 2005, l'enquête a été étendue aux hypertensions artérielles pulmonaires.

MEDIATOR® (chlorhydrate de benfluorex) appartient à la classe des amphétamines et est commercialisé en France depuis 1976, par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés, dosés à 150 mg.

Ses indications sont :
- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Historique

Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables et avec les restrictions de délivrance de ces produits, le Comité Technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène. Ainsi, le benfluorex a été inscrit sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes le 10 mai 1995.

Le dossier relatif aux effets indésirables du benfluorex a été présenté lors de différentes réunions du Comité Technique de Pharmacovigilance en 1998 et au groupe de travail européen de Pharmacovigilance le 30 novembre 2000, entraînant les modifications de la rubrique « effets indésirables » du Résumé des Caractéristiques du Produit (en gras) :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, **confusion**, somnolence, état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles ;
- très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke ;
- élévation des enzymes hépatiques, hépatite (très rare).

Résultats de l'enquête officielle de pharmacovigilance du CRPV de Besançon relative aux hypertensions artérielles pulmonaires et aux troubles neuro-psychiatriques observés avec MEDIATOR® (benfluorex)

1. Troubles neuro-psychiatriques

A. Troubles psychiatriques pendant le traitement :

35 cas ont été rapportés dont 10 déclarés depuis l'enquête présentée en juillet 1999.
Ils concernent 18 hommes (âge moyen : 58,5 ans) et 17 femmes (âge moyen : 60 ans).

Les troubles psychiatriques sont divers :

- agressivité (4), nervosité (3), irritabilité (1)
- cauchemars (2), angoisse (1), stupeur (1), dépression (1)
- désorientation (7), confusion (5), aggravation des troubles cognitifs (1)
- agitation (3), trouble du comportement (3)
- délire (2), bouffée délirante aiguë (1)

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Les cas graves ayant nécessité une hospitalisation sont :

- 4 cas de confusion (dont un provenant de la littérature) chez des patients ayant des traitements associés ;
- 3 cas de désorientation temporo-spatiale ;
- 2 cas de bouffées délirantes aiguës, avec d'autres troubles associés, d'évolution rapidement favorable après traitement symptomatique par neuroleptiques.

B. Troubles psychiatriques au sevrage :

10 notifications de troubles psychiatriques apparaissant lors du sevrage ont été rapportés.

Ils concernent 2 hommes et 8 femmes, dont les âges varient respectivement de 27 à 34 ans (âge moyen : 30,5 ans) et de 30 à 65 ans (âge moyen : 45,25 ans)

Le délai d'apparition des troubles après l'arrêt du MEDIATOR® est très variable : de 1 jour (après un traitement de 8 ans) à 3 semaines (après un traitement de 4 à 15 mois).

La durée de traitement par MEDIATOR® est très variable : de 1 mois à 8 ans.

Trois cas ont nécessité une hospitalisation, chez des femmes ayant par ailleurs des antécédents de troubles psychiatriques. Une évolution favorable a été constatée dans un des cas après traitement symptomatique par neuroleptiques, les deux autres cas sont d'évolution inconnue.

C. Autres troubles neurologiques :

12 notifications ont été rapportées.
Elles concernent 8 hommes et 4 femmes :

- 2 cas de convulsions d'évolution favorable ;
- 2 cas de neuropathie, chez deux patients diabétiques présentant de multiples autres étiologies possibles ;
- 7 cas de paresthésies, d'apparition rapide et d'évolution favorable en quelques heures, dont deux mésusages ;
- 1 cas de tremblement des mains.

D. Abus

2 cas d'abus ont été rapportés :

- chez un homme augmentant les doses de MEDIATOR® à 10 comprimés par jour pendant 11 mois, sans effet indésirable associé ;
- chez un sportif, consommant (sur prescription médicale) des doses croissantes (1comprimé/semaine au début et jusqu'à 9 comprimés/jour) de MEDIATOR® comme « dopant » et présentant une excitation lors du sevrage.

2. Hypertension artérielle pulmonaire (HTAP) :

16 notifications dont 1 doublon ont été rapportées.

A. Notifications où MEDIATOR® est associé à un anorexigène :

Lors de la présentation du rapport MEDIATOR® en décembre 1998, 11 notifications d'«hypertension artérielle pulmonaire » avaient été rapportées.
9 d'entre elles ont été présentées lors de l'enquête « Anorexigènes et hypertensions artérielles pulmonaires » au Comité Technique du 28 avril 1995 :

- 6 ont été classées en HTAP d'allure primitive
- 2 en HTAP post-capillaire
- 1 en HTAP post-embolique

Le MEDIATOR® n'était jamais prescrit seul : il était associé à un ou plusieurs anorexigènes :

- ISOMERIDE® : 7 fois

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- ISOMERIDE® + PONDERAL® : 2 fois
- ISOMERIDE ®+ FENPROPOREX® : 1 fois
- DININTEL® + TENUATE DOSPAN® + FRINGANOR® : 1 fois

La durée de traitement par MEDIATOR® était précisée dans 7 cas sur 11 et allait de plusieurs mois à 5 ans.

Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® était :
- concomitante dans 5 cas,
- antérieure dans 2 cas,
- postérieure dans 3 cas,
- imprécise dans 1 cas.

Sur les 3 cas où la prise de MEDIATOR® était postérieure à la prise d'anorexigènes, 2 cas présentaient une dyspnée et un cas une double atteinte valvulaire aortique et mitrale.

B. Notifications où MEDIATOR® n'est pas associé à un anorexigène :

5 notifications ont été rapportées chez des femmes (dont une présentait une HTAP post capillaire sur valvulopathie et une autre une HTAP sur embolies pulmonaires) n'ayant pas de traitement anorexigène associé. Il est à noter que l'un des cas rapportés est très succinct.

C. Fréquence

Depuis le début de la commercialisation de MEDIATOR®, le nombre de boites de 30 comprimés vendues est de : 110 693 331, correspondant à 45 515 349 mois de traitement*.

Après élimination des HTAP post-emboliques (2) et post-capillaires (3), il reste 11 cas d'HTAP idiopathique (ou primitive) soit :
- 1 cas pour 10 063 030 boites vendues
- ou 1 cas pour 4 137 759 mois de traitement.

(*mois de traitement : estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés (mois de 30,4 jours).

Discussion

La prévalence de l'hypertension artérielle pulmonaire primitive est de 100 cas par an.

Si on considère uniquement, parmi les cas rapportés, les diagnostics d'hypertension artérielle pulmonaire d'allure primitive et si l'on exclut les cas associés aux anorexigènes et les antécédents d'embolie pulmonaire et de valvulopathie, il reste 2 cas soit une incidence très faible de :
- 1 cas pour 55 346 666 boites vendues
- 1 cas pour 22 757 675 mois de traitement

Les résultats de cette enquête officielle seront présentés en Commission Nationale de Pharmacovigilance.

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IV - POINT RELATIF AUX ANTI-TNF α ET CANCER : BIBLIOGRAPHIE ET DONNEES DE LA BASE NATIONALE DE PHARMACOVIGILANCE

1/ Risque carcinogène des anti-TNF α : données bibliographiques

Le Centre Régional de Pharmacovigilance (CRPV) de Paris Saint-Vincent-de-Paul a présenté les données bibliographiques relatives au risque carcinogène des anti-TNF. A ce jour, trois anti-TNFα sont commercialisés en France :

- l'infliximab (REMICADE®),
- l'adalimumab (HUMIRA®),
- l'étanercept (ENBREL®),

Il ressort de cette analyse que :

- l'adalimumab et l'infliximab sont associés, dans la partie contrôlée des essais cliniques, à une augmentation du risque de cancers, par comparaison aux patients atteints de la même affection et recevant un placebo ;
- il existe des augmentations statistiquement significatives des cancers de la peau, hors mélanomes et basocellulaires, avec les trois anti-TNF α ;
- des cas de lymphomes ou autres cancers, d'évolution fulminante, survenus d'emblée ou après une rémission, ont été rapportés dans un délai pouvant être très court ;
- il semble enfin qu'il existe un risque carcinogène variable, en fonction de l'immunosuppresseur associé, toutefois seul le méthotrexate a été correctement étudié dans les essais cliniques.

Le CRPV de Saint-Vincent-de-Paul a souligné que :

- le rapport bénéfice/risque des anti-TNFα dans les formes sévères de polyarthrite rhumatoïde (PR) ou de maladie de Crohn n'est pas remis en question,
- des données des essais cliniques ont été occultées, dans leur partie contrôlée, sont insuffisamment discutées,
- à court et moyen terme, la chronologie suggère que les anti-TNFα viendraient révéler ou favoriser le développement de cancers pré-existants,
- le risque différentiel qualitatif et quantitatif en fonction de l'anti-TNFα est encore inconnu,
- l'association aux immunosuppressseurs, autres que le méthotrexate, en attendant d'autres données, devrait être considérée comme hasardeuse.

2/ Données de la base nationale de pharmacovigilance

a/ REMICADE® (infliximab)

Le CRPV de Nice a présenté les données de la base nationale de pharmacovigilance (BNPV) relatives au risque d'apparition de cancers solides lié à l'utilisation de REMICADE®.

Cet anti-TNF α a obtenu une autorisation de mise sur le marché selon la procédure centralisée le 13 août 1999.

22 cas de cancers solides ont été retrouvés dans la BNPV :

- 9 cas concernent l'appareil digestif (3 cancers de l'œsophage, 5 cancers coliques, 1 cancer du pancréas),
- 5 cas concernent la peau (2 epithélioma basocellulaires, 2 epithélioma spinocellulaire, 1 epithélioma de la verge),
- 4 cas concernent des cancers génito-urinaires (3 cancers du col utérin, 1 cancer de la prostate),
- 3 cancers bronchopulmonaires,
- 1 cancer de la thyroïde.

Ces cancers concernent 10 femmes et 12 hommes, dont les âges varient de 27 à 82 ans (âge moyen : 58 ans). Le délai moyen de survenue est de 10 mois.
Les traitements associés sont représentés par du méthotrexate et des corticoïdes dans 16 cas, et par de l'azathioprine dans 6 cas.
Parmi les 22 cas retrouvés dans la BNPV, 2 ont évolué vers un décès, les 20 autres sont en cours.

b/ ENBREL® (étanercept)

Le CRPV de Toulouse a présenté les données de la BNPV relatives au risque d'apparition de cancers solides lié à l'utilisation d' ENBREL®.

Cet anti-TNF a obtenu une autorisation de mise sur le marché selon la procédure centralisée en février 2000, mais a été commercialisé en France dès avril 1999, sous autorisation temporaire d'utilisation (ATU).

15 cas de cancers solides ont été retrouvés dans la BNPV et la base industrie :

- 3 cancers du poumon, avec dans 2 cas, des antécédents de tabagisme,
- 3 cancers du sein,
- 2 mélanomes,
- 1 cancer de l'ovaire,
- 1 cancer de l'endomètre,
- 1 myélome,
- 1 méningome,
- 1 cancer de la langue, 1 cancer colique et 1 cancer hépatique.

Ces cancers concernent 11 femmes et 3 hommes, dont l'âge moyen est de 54,5 ± 8,2 ans. Le délai de survenue est supérieur à 1 an dans 6 cas et inférieur à 1 an dans 8 cas.
L'imputabilité est douteuse dans tous les cas.

c/ HUMIRA® (adalimumab)

Le CRPV de Nancy a présenté les cas notifiés relatifs au risque d'apparition de cancers solides lié à l'utilisation d'HUMIRA®, dans la BNPV.

Cet anti-TNFα est un anticorps monoclonal humanisé qui a obtenu une autorisation de mise sur le marché selon la procédure centralisée en mai 2003.

7 cas de cancers solides ont été rapportés entre novembre 2003 et mai 2005 :

- 2 cas concernent l'appareil respiratoire (1 carcinome bronchique et 1 adénocarcinome pulmonaire chez des patients fortement tabagiques),
- 1 cancer du rectum,
- 3 cas concernent l'appareil génito-urinaire (2 cancers du sein dont 1 observé chez une patiente aux antécédents familiaux de cancer du sein , 1 tumeur de la vessie),
- 1 myélome multiple.

Ces cancers concernent 3 femmes et 4 hommes, dont les âges varient de 48 à 82 ans (âge moyen : 56,1 ans). Le délai entre le début du traitement par HUMIRA® et l'apparition des premiers symptômes varie de 1,5 et 14,5 mois (moyenne à 7 mois).

Le méthotrexate était associé dans 6 cas, des corticoïdes dans 6 cas, le léflunomide (ARAVA®) dans 2 cas et l'étanercept (ENBREL®) dans 1 cas.
Sur les 7 cas retrouvés, 1 cas a évolué vers un décès, 1 autre a évolué vers une guérison avec séquelles et 5 sujets sont encore non -rétablis.
Dans tous les cas, l'imputabilité a été déterminée douteuse l1.

3/ Conclusions

Au vu de ces différentes présentations, le Comité technique propose que ce dossier soit attentivement suivi.

Il a été rappelé par l'unité de pharmacovigilance que le Résumé des Caractéristiques du Produit (RCP) de l'infliximab (REMICADE®) et de l'adalumimab (HUMIRA®) ont fait l'objet de récentes mises à jour (variations) en ce qui concerne le risque de cancer. Les libellés adoptés sont les suivants :

- rubrique « mises en garde et précautions d'emploi » :

Tumeurs malignes et troubles lymphoprolifératifs

Dans la partie contrôlée des essais cliniques avec des anti-TNF, il a été observé plus de cas de lymphomes chez les patients traités par un anti-TNF que chez les patients du groupe contrôle. Cependant, l'incidence a été rare et la période de suivi des patients sous placebo était plus courte que celle des patients sous traitement anti-TNF. De plus, il existe un contexte de risque accru de lymphome chez les patients atteints d'une polyarthrite rhumatoïde ancienne, inflammatoire et hautement active, ce qui complique l'estimation du risque. Dans l'état actuel des connaissances, la possibilité d'un risque de développer des lymphomes ou autres maladies malignes chez les patients traités par anti-TNF ne peut être exclue.

Il n'existe pas d'études chez des patients avec antécédents de tumeurs malignes ou chez des patients qui continuent leur traitement alors qu'ils développent une tumeur maligne sous Humira. En conséquence, une prudence accrue devra être observée lorsqu'on envisage un traitement de ces patients par Humira (voir rubrique 4.8).

- rubrique « **effets indésirables** » : ajout de
Tumeurs malignes et troubles lymphoprolifératifs.

Par ailleurs, l'unité de pharmacovigilance a également rappelé qu'une réunion européenne constituée d'un groupe d'experts allait avoir lieu à Londres le 16 juin prochain. Le Comité technique sera tenu informé des conclusions de cette réunion.

Au total, les effets indésirables des anti-TNFα, et tout particulièrement le problème de survenue de cancers, font l'objet d'une surveillance étroite au niveau national, comme au niveau européen. Ceci se manifeste par les nombreuses variations en cours et à venir concernant ces produits. De ce fait, les RCP sont très régulièrement enrichis et complétés.

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V - POINT RELATIF A RISPERDAL CONSTA® (RISPERIDONE) ET RESURGENCES DES DELIRES

Le Centre Régional de Pharmacovigilance (CRPV) de Montpellier a présenté un point concernant les résurgences de délire, hallucinations et échecs thérapeutiques observés chez des patients traités par Risperdal Consta® (rispéridone).

Risperdal Consta® est le premier antipsychotique atypique à action retard, indiqué dans le *« traitement des psychoses, en particulier des psychoses schizophréniques, en relais d'un traitement antipsychotique par rispéridone par voie orale »* ; il a obtenu une AMM en octobre 2003 en France (procédure nationale). Il s'agit d'une suspension aqueuse de microsphères constituées d'une matrice de rispéridone et d'un copolymère biodégradable (contrairement aux antipsychotiques conventionnels à action prolongée dont la libération s'effectue par l'intermédiaire d'un véhicule huileux).
Risperdal Consta® est administré par injection intramusculaire, toutes les deux semaines, à des posologies variant de 25 à 50 mg. Une couverture par rispéridone par voie orale doit être assurée durant les trois premières semaines de traitement par Risperdal Consta®. Un tableau d'équivalence posologique entre la voie orale et la voie intramusculaire figure dans le Résumé des Caractéristiques du Produit (RCP) et recommande une dose de Risperdal Consta® de 25 mg, ou comprise entre 25 et 37,5 mg, ou de 50 mg lorsque la dose de rispéridone orale est respectivement de 2 mg, comprise entre 2 et 4 mg, ou bien de 4 mg et plus. La même posologie de 50 mg sera donc proposée, que le patient soit traité auparavant par une posologie de rispéridone orale de 4 mg, ou de 16 mg.

Eléments de pharmacocinétique du Risperdal Consta®
La rispéridone est métabolisée par le cytochrome P450 2D6 en 9-hydroxy-rispéridone qui constitue, avec la rispéridone, la fraction active du médicament. Le métabolisme dépendant du CYP 2D6 est soumis à un polymorphisme génétique.
Après injection intra-musculaire, la phase de libération principale débute à partir de la 3ème semaine, rendant nécessaire la prise orale de rispéridone pendant cette période. Cette phase se poursuit ensuite pendant 4 à 6 semaines et se termine à la 7ème semaine. L'état d'équilibre survient après la quatrième injection. Risperdal Consta® présente donc à la fois une action prolongée et une action retardée.

Eléments de pharmacodynamie
Les antipsychotiques atypiques se caractérisent par une action antagoniste sur les récepteurs D2 à la dopamine. Une occupation des récepteurs au moins égale à 60% est nécessaire pour assurer une efficacité antipsychotique. Une étude récente a étudié l'occupation des récepteurs D2 à la suite de l'injection de Risperdal Consta®[1]. Le taux d'occupation des récepteurs D2 a été de 25-48% chez les patients traités par 25 mg, de 59-83% pour une posologie de 50 mg, et de 62-72% pour une posologie de 75 mg. Cette étude a été réalisée après la 5ème injection chez 7 patients et après la 3ème chez un patient. Le taux d'occupation des récepteurs D2 à l'état d'équilibre après administration de Risperdal Consta® est équivalent à celui obtenu chez des patients traités efficacement par des doses de 2 à 6 mg par jour de rispéridone par voie orale.

Données de notifications spontanées
Entre mars et octobre 2004, 16 cas (dont 13 graves) de résurgence de délire ou d'échec thérapeutique ont été rapportés en France chez des patients, d'âge moyen 38 ans, traités par Risperdal Consta®.
Dans 11 cas, les patients avaient bénéficié de la couverture par rispéridone voie orale, comme recommandé dans le RCP. Dans 6 cas, les patients étaient bien équilibrés sous traitement oral par rispéridone à des posologies de 6 à 16 mg/j.
La rechute est survenue entre la première et la troisième injection dans 8 cas, et après la troisième injection dans 5 cas. Le délai de rechute par rapport à l'injection (et non par rapport au début du traitement) n'est connu que dans un cas (12-13 jours après la 4ème injection).

[1] Gefvert O, Eriksson B, Persson P, et al. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Constatrade mark) in patients with schizophrenia. Int J Neuropsychopharmacol 2005; 8: 27-36.

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L'évolution a été favorable, ou une amélioration a été observée après réintroduction de la rispéridone par voie orale dans 4 cas. Dans deux cas, le traitement par Risperdal Consta® a été poursuivi en augmentant la dose sans que le patient ait été amélioré. Dans un autre cas, le traitement a été poursuivi et l'évolution est inconnue. Dans trois cas, la rechute a amené à interrompre l'arrêt du Risperdal Consta® et à administrer d'un autre traitement neuroleptique. Dans deux cas, Risperdal Consta® a été arrêté et un traitement par rispéridone par voie orale a été repris.

Données de l'étude DEPIST

En décembre 2004, les laboratoires Janssen ont débuté une étude de phase IV, l'étude DEPIST (Diagramme de l'Etat Psychotique utilisable par l'Infirmier dans la Schizophrénie Traitée au Long Cours), visant à permettre la poursuite du traitement par Risperdal Consta® chez des patients déjà traités, dans l'attente de la fixation du prix de la spécialité.
A la date du 15 avril 2005, 823 patients avaient été inclus, et 40 observations d'effets indésirables avaient été colligées ; 25 cas (tous graves) faisaient mention d'une résurgence de la symptomatologie. Les observations sont peu documentées ; l'existence de la couverture par rispéridone par voie orale ou la notion de médicaments antérieurs sont peu renseignées.

Données dans d'autres pays européens

Une information non urgente, envoyée à l'ensemble des Etats membres de l'Union européenne, a permis d'être informé de l'existence de 62 cas de rechute de psychose, d'échec thérapeutique, de résurgence de délire, rapportés aux Pays-Bas (25 cas), au Royaume-Uni (25 cas), en Irlande (6 cas), Espagne (4 cas), Finlande (2 cas).
La couverture par rispéridone voie orale n'est encore une fois pas bien documentée. A noter, dans deux observations anglaises, que la rechute a eu lieu juste avant l'injection suivante de Risperdal Consta®.

Au total, un nombre non négligeable de rechutes et d'échecs thérapeutiques ont été rapportés en France mais aussi dans d'autres pays européens avec Risperdal Consta®.
Dans la plupart des cas, ces rechutes ont nécessité l'hospitalisation des patients, dont certains étaient correctement équilibrés avant la mise sous Risperdal Consta®.
Plusieurs hypothèses peuvent être émises pour expliquer ce phénomène :

- une variabilité inter-individuelle,
- un polymorphisme génétique au niveau de la métabolisation,
- une modification des récepteurs,
- une durée trop courte (3 semaines) de la couverture par rispéridone orale.

Par ailleurs, le rapporteur et le Comité technique ont souligné la difficulté des modalités de préparation et d'administration de Risperdal Consta® (préparation longue et compliquée, administration devant être faite en intra-musculaire profonde dans le muscle fessier), pouvant être à l'origine d'une inefficacité du produit.

Le Comité technique souhaite que ce dossier soit revu par le Groupe de travail sur les médicaments de neurologie, psychiatrie, anesthésie, et antalgie, en apportant une attention particulière sur l'aspect pharmacocinétique.
Ce dossier sera ensuite présenté en Commission nationale de pharmacovigilance.

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VI - ENQUETE OFFICIELLE DE PHARMACOVIGILANCE RELATIVE AUX EFFETS INDESIRABLES HEPATIQUES AVEC LE PROGUANIL ET LA CHLOROQUINE

Les résultats de l'enquête officielle de pharmacovigilance relative aux effets indésirables hépatiques rapportés avec la chloroquine et le proguanil ont été présentés par le Centre Régional de Pharmacovigilance (CRPV) d'Angers. Cette enquête fait suite à la notification d'un cas d'atteinte hépatique mixte, survenu chez une patiente traitée par l'association chloroquine-proguanil pour une prophylaxie du paludisme.

La chloroquine est un dérivé amino-4-quinoléine qui exerce une action essentiellement schizonticide sur les formes érythrocytaires du plasmodium. Son métabolisme hépatique fait intervenir le CYP2C8, le CYP3A4 et dans une moindre mesure le CYP2D6. Le métabolite principal, la monodéséthylchloroquine, a une activité in vitro, un profil de distribution et une fixation tissulaire analogue à la chloroquine. La demi-vie de la chloroquine s'échelonne entre 30 et 60 jours.

Le proguanil ou chloroguanide n'a pas par lui-même d'activité mais son métabolite, le cycloguanil, produit via le CYP2C19, inhibe assez spécifiquement la dihydrofolate réductase du plasmodium et empêche sa division. Du fait d'un polymorphisme génétique du CYP2C19, certains patients sont métaboliseurs lents, à hauteur de 6 à 10 % de la population caucasienne mais pouvant atteindre 20 % dans le sud-est asiatique. La demi-vie d'élimination est d'environ 14 heures pour le proguanil et 19 heures pour le cycloguanil.

Cinq spécialités, contenant l'un et/ou l'autre des principes actifs sont concernées par cette enquête : NIVAQUINE® (chloroquine, laboratoire Sanofi-Aventis), PALUDRINE® (proguanil, laboratoires Astra Zeneca), SAVARINE® (chloroquine/proguanil, laboratoires Astra Zeneca), NOPALU® (chloroquine/proguanil, Pharmacie Centrale des Armées), MALARONE® (atovaquone/proguanil, laboratoires GSK).

Ces cinq spécialités sont indiquées dans la prophylaxie du paludisme. Par ailleurs, NIVAQUINE® et MALARONE® sont également indiqués dans le traitement curatif de l'accès palustre. Enfin, la forme dosée à 100 mg de NIVAQUINE® est aussi indiquée dans le traitement symptomatique de la polyarthrite rhumatoïde, du lupus discoïde, du lupus érythémateux subaigu et le traitement préventif des rechutes de lupus et des lucites.

METHODOLOGIE

Les observations, issues des CRPV et des laboratoires, appartenant à la classe-organe "foie" ont été sélectionnées puis ont fait l'objet d'une première analyse visant à exclure : les cas trop peu informatifs, les intoxications par la chloroquine qui peuvent s'accompagner d'une perturbation du bilan biologique hépatique par bas débit en cas de défaillance cardiaque, les atteintes musculaires, les cas pour lesquels une étiologie non médicamenteuse était démontrée.

Les observations retenues pour l'enquête ont été imputées selon la méthode française et classées en 4 groupes en fonction des résultats des tests biologiques : les atteintes hépatiques cytolytiques (ALAT/PAL $\geq$ 5), les atteintes hépatiques mixtes (2 < ALAT/PAL < 5), les atteintes cholestatiques (ALAT/PAL $\leq$ 2), les anomalies biologiques hépatiques isolées.

En raison du faible nombre d'observations, la période de recueil débute en 1985 pour la chloroquine, molécule la plus anciennement utilisée, et à la date de commercialisation pour les autres médicaments dont la commercialisation est postérieure à 1985. La fin de la période de recueil a été fixée au 30 juin 2004.

L'incidence des notifications a été estimée par mois (4 semaines) de traitement prophylactique en utilisant le nombre d'unités vendues et les posologies quotidiennes ou hebdomadaires conseillées pour un usage préventif. Cette estimation a été réalisée pour chaque produit. L'intervalle de confiance bilatéral à 95 % (IC95) a été calculé selon la loi de Poisson.

RESULTATS

Un total de 69 observations a été inclus dans l'enquête, se répartissent comme suit :

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Principes actifs	Nombre total de cas		Nombre de cas inclus dans l'enquête			
	CRPV	Industrie	CRPV	Industrie	Doublons	Total
Chloroquine	36	18	21	12	5	28
Proguanil	0	0	0	0	0	0
Chloroquine + Proguanil	31	24	20	14	4	30
Atovaquone + Proguanil	4	12	4	10	3	11

• Les atteintes hépatiques associées à la chloroquine utilisée seule sans proguanil sont au nombre de vingt-huit notifications se répartissant en :

- Atteinte cytolytique : 12 cas
- Atteinte mixte : 4 cas
- Atteinte cholestatique : 2 cas
- Anomalies biologiques isolées : 10 cas

Les atteintes cytolytiques touchent 9 femmes et 3 hommes, d'âge moyen 36 ± 13 ans [20-60]. Les indications du traitement par chloroquine sont les suivantes : prophylaxie du paludisme (6 cas), accès palustre (1 cas), porphyrie cutanée tardive (PCT) (1cas), tentative de suicide par absorption de chloroquine et de lorazépam sans atteinte cardiotoxique (1cas), injection par erreur de chloroquine au lieu d'héroïne chez un toxicomane (1cas) et indication inconnue (2 cas).
Lorsqu'elle est connue, la posologie est conforme à l'indication sauf dans deux cas où elle est jugée excessive par rapport aux recommandations de l'AMM.
Le délai de survenue de l'effet indésirable après le début du traitement par chloroquine est variable allant de quelques minutes (injection par erreur de chloroquine) à 120 jours. Dans 9 cas, l'atteinte hépatique survient dans le premier mois du traitement. Dans 2 cas, le délai est inconnu.

La cytolyse hépatique, marquée par une élévation des transaminases (les ALAT varient de 2 N à 100 N), s'associe à des troubles digestifs à type de douleurs abdominales et/ou nausées et/ou vomissements dans 4 cas, à un ictère dans 5 cas, à une asthénie dans 3 cas, à une fièvre dans 3 cas (en dehors de tout accès palustre) et à une éruption cutanée dans 2 cas. Aucune cytolyse n'a été documentée au plan anatomo-pathologique. L'évolution a été majoritairement favorable (12 cas), inconnue (2 cas). Au vu des éléments du dossier, il est difficile d'appréhender le mécanisme.

La chloroquine est le seul médicament suspect dans 7 cas. Dans les 5 autres cas, la chloroquine est associée à d'autres médicaments de même imputabilité et dont certains sont connus pour leur hépatotoxicité. Dans un seul cas d'imputabilité C2S2, la chloroquine est le seul médicament suspect (porphyrie sous-jacente méconnue suspectée).

Les atteintes mixtes touchent 1 femme et 3 hommes dont les âges varient de 48 à 77 ans. Les indications du traitement par chloroquine sont les suivantes : suspicion d'accès palustre (1 cas), lupus (1 cas), sclérodermie (1 cas), inconnue mais probablement prophylaxie du paludisme (1 cas). Lorsqu'elle est connue, la posologie est conforme aux recommandations de l'AMM.
Le délai de survenue de la symptomatologie après le début du traitement par chloroquine varie de 2 à 21 jours. Dans un cas, le délai de survenue est non précisé mais il s'agit d'une cirrhose hépatique évoluant chez un patient atteint de sclérodermie.

Outre le cas de cirrhose hépatique dont l'étiologie est inconnue, trois cas d'atteinte mixte sont enregistrés avec des ALAT comprises entre 2 et 10,6 N et des PAL entre 1,3 et 2,4 N. La symptomatologie clinique associe des douleurs abdominales (2 cas), des urines foncées (1 cas), une fièvre chez un patient (suspicion d'accès palustre non confirmée). Dans un cas, une atteinte pancréatique est associée à l'atteinte hépatique sans mise en évidence d'une lithiase biliaire à l'échographie. Enfin un cas, dont le bilan étiologique infectieux était négatif, s'est accompagné d'une thrombopénie, d'une neutropénie et d'une insuffisance rénale.

La chloroquine est le seul médicament suspect dans 2 cas. Dans le seul cas d'imputabilité C2S2, la chloroquine est le seul médicament suspect.

Les atteintes cholestatiques touchent deux hommes de 56 et 68 ans. Aucune de ces observations ne permet de retenir formellement le rôle de la chloroquine dans la cholestase du fait dans un cas de

l'association à un autre médicament de même imputabilité et dans l'autre d'un suivi évolutif et d'un bilan étiologique incomplets.

Les anomalies biologiques hépatiques isolées touchent 7 hommes et 3 femmes dont l'âge varie de 1 à 62 ans (3 patients d'âge inconnu). Ces cas sont très peu informatifs, d'évolution inconnue dans 6 cas, et ne permettent aucune conclusion.

• Les atteintes hépatiques observées lors d'une association chloroquine et proguanil

Trente notifications d'atteinte hépatique survenue à l'occasion d'un traitement associant chloroquine et proguanil ont été retenues pour l'enquête. Ils se répartissent en :

- Atteinte cytolytique : 17 cas
- Atteinte mixte : 7 cas
- Atteinte cholestatique : 4 cas
- Anomalies biologiques isolées : 2 cas

Huit cas sont survenus sous NIVAQUINE® associé à PALUDRINE®. Un cas est associé à un traitement en alternance NIVAQUINE® puis SAVARINE®. Les 21 autres cas sont survenus sous SAVARINE®. Aucun cas n'est associé à la prise de NOPALU®.

Dénombrement des cas en fonction du type d'atteinte hépatique et des spécialités

Spécialités	Atteinte cytolytique	Atteinte mixte	Atteinte cholestatique	Perturbations biologiques	Total
SAVARINE®	11	5	3	2	21
NIVAQUINE® + PALUDRINE	5	2	1	0	8
NIVAQUINE® + SAVARINE®	1	0	0	0	1
NOPALU®	0	0	0	0	0
Total	17	7	4	2	30

Les atteintes cytolytiques touchent 12 femmes et 5 hommes d'âge moyen 39 ± 16 ans [10-67]. L'association chloroquine et proguanil est dans tous les cas utilisée pour une prophylaxie du paludisme à une posologie classique de 100 mg de chloroquine et 200 mg de proguanil par jour (la posologie est inconnue dans 5 cas).
Le délai de survenue de la symptomatologie après le début de la chimioprophylaxie est variable de 8 à 63 jours. Dans 9 cas l'atteinte hépatique survient dans le premier mois du traitement. Ce délai est inconnu dans 4 cas.

La cytolyse hépatique, marquée par une élévation des transaminases (les ALAT varient de 1,5 N à 25 N), s'accompagne de troubles digestifs à type de douleurs abdominales (5 cas), de nausées et/ou vomissements (5 cas), de diarrhée (5 cas). Une fièvre est présente dans trois cas en dehors de tout accès palustre. Une éruption cutanée est présente dans un cas, associée à d'autres manifestations évocatrices d'un syndrome d'hypersensibilité. Enfin, un cas dont le bilan étiologique infectieux est négatif, s'est accompagné d'une thrombopénie et d'une neutropénie. Aucune cytolyse n'a été documentée au plan anatomo-pathologique en raison de la bénignité de l'atteinte et d'une évolution rapidement favorable à l'arrêt des médicaments suspects.

L'association chloroquine et proguanil est le seul traitement suspect dans 13 cas. Dans les 4 autres cas, d'autres médicaments de même imputabilité sont associés. Certains sont connus pour leur hépatotoxicité tel Augmentin®, paracétamol ou fénofibrate. Dans les deux cas d'imputabilité C2S2, SAVARINE® est le seul médicament suspect.

Les atteintes mixtes touchent 4 femmes et 3 hommes dont les âges varient de 43 à 50 ans (une patiente est d'âge inconnu). L'association chloroquine et proguanil est dans tous les cas utilisée pour prophylaxie du paludisme à posologie classique.
Le délai de survenue de la symptomatologie après le début de la chimioprophylaxie est variable de 5 à 40 jours. Un cas, d'imputabilité C1S1 a été découvert 25 jours après l'arrêt du traitement alors que le sujet était en plein accès palustre.

Les perturbations du bilan biologique hépatique sont modérées : ALAT entre 4 et 29,5 N, PAL entre 1,5 et 7 N quand les valeurs sont connues. Elles s'accompagnent de troubles digestifs (3 cas), d'un

ictère (2 cas). Quelques observations notent des manifestations évocatrices d'un mécanisme immuno-allergique. Aucune ponction biopsie hépatique n'a été réalisée. L'évolution est favorable dans 4 cas et inconnue dans 3.

L'association chloroquine et proguanil est le seul traitement suspect dans 5 cas. Dans les 3 cas d'imputabilité C2S2, SAVARINE® est le seul médicament suspect.

Les atteintes cholestatiques touchent 3 femmes et un homme âgés de 29 à 79 ans. L'association chloroquine et proguanil est dans tous les cas utilisée en prophylaxie.
Le délai de survenue de la symptomatologie après le début de la prophylaxie est inférieur à 1 mois dans 3 cas, et imprécis dans 1 cas mais d'environ 1 mois.

La cholestase est marquée par une élévation des PAL entre 5,5 et 9 N ou un ictère. Il s'y associe trois fois une cytolyse modérée (ALAT entre 2,7 et 12 N). Des manifestations évocatrices d'une réaction immuno-allergique sont présentes dans trois observations. L'évolution est dans tous les cas favorable. Elle est signalée comme lente avec persistance d'une cholestase à 10 mois avec PAL à 2 N dans un cas.

La chimioprophylaxie est le seul traitement suspect dans deux cas. Dans deux autres cas, il existe un autre médicament suspect de même imputabilité (simvastatine d'une part, contraceptif oestroprogestatif d'autre part).

Les anomalies biologiques isolées touchent 2 hommes de 48 et 55 ans. Il s'agit d'une simple élévation de la GGT (C2S1) dans un cas et d'une élévation modérée des transaminases et de la GGT d'évolution inconnue (C1S1) dans l'autre cas.

- Les atteintes hépatiques observées lors d'une association atovaquone et proguanil

Onze notifications d'atteinte hépatique survenue à l'occasion d'un traitement associant atovaquone et proguanil (MALARONE®) ont été retenues pour l'enquête. Ils se répartissent en :

- Atteinte cytolytique : 7 cas
- Atteinte mixte : 1 cas
- Atteinte cholestatique : 1 cas
- Anomalies biologiques isolées : 2 cas.

Les atteintes cytolytiques sont majoritaires avec cette spécialité et concernent 2 femmes et 5 hommes dont l'âge varie de 16 à 57 ans. Les indications du traitement par atovaquone et proguanil sont les suivantes : prophylaxie du paludisme (4 cas), accès palustre (2 cas) et suspicion d'accès palustre (1 cas).
Le délai de survenue est très variable de 2 à 28 jours. Un cas est de découverte tardive environ 3 mois après l'arrêt du traitement.

La cytolyse est marquée par une élévation des transaminases (les ALAT varient de 2,6 à 119 N). Elle s'associe dans un cas à d'autres effets évoquant une possible réaction immuno-allergique. L'évolution est favorable dans 5 cas et inconnue dans les 2 autres.

Dans 5 cas, MALARONE® est le seul médicament suspect. Dans le seul cas C2S2, la prophylaxie antipalustre est associée à un traitement par ibuprofène de même imputabilité.

Les atteintes mixtes sont survenues dans un seul cas chez une femme de 24 ans, hôtesse de l'air, traitée par MALARONE® pour un accès palustre à *Plasmodium falciparum* confirmé.

Les atteintes cholestatiques sont survenues dans un seul cas chez une femme de 50 ans traitée en prophylaxie antipalustre par MALARONE®.

Les anomalies biologiques hépatiques isolées sont représentés par deux cas peu informatifs et d'imputabilité C1S1.

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ESTIMATION DU TAUX DE NOTIFICATION

Le taux de notification des effets hépatiques sous chloroquine ou proguanil peut être qualifié de "très rare" ou "exceptionnel".

Taux de notification des atteintes hépatiques

Spécialités	Nb. d'unités de vente vendues (période) *Nb. de mois de prophylaxie*	Nb. de cas notifiés pendant la période	Incidence des notifications pour 10^6 mois de prophylaxie [IC95]
NIVAQUINE® (toutes unités des variétés PO)	236 453 395 (01/01/1994 au 31/12/2003) ***9 060 213***	21	2,3 [1,4-3,5]
SAVARINE® (boîte de 28 comprimés)	2 229 731 (01/02/2000 au 30/06/2004) ***2 229 731***	12	5,3 [2,8-9,4]
PALUDRINE® (boîte de 56 comprimés)	275 646 (01/02/2000 au 30/06/2004) ***275 646***	0	[0-13,4]
NOPALU® (flacons de 14 gélules)	26 682 (01/02/2004 au 30/06/2004) ***13 341***	0	[0-277]
MALARONE® (boîtes de 12 comprimés)	590 354 (01/01/2001 au 30/06/2004) ***253 008***	11	43,5 [21,7-77,8]

RESULTATS DE LA NOTIFICATION SPONTANEE HORS DE FRANCE

Les données internationales des différents laboratoires sont peu nombreuses et difficilement exploitables du fait d'un manque fréquent d'informativité en particulier sur le suivi évolutif. Ainsi, les seules données retenues pour l'enquête sont extraites de la base ASTRA ZENECA.

Il s'agit de neuf cas associés à : chloroquine seule (1 cas) ; proguanil seul (3 cas) ; association chloroquine et proguanil (5 cas).

Le cas survenu sous chloroquine seule concerne un ictère attribué à une hépatite subfulminante. Le cas est peu détaillé tant au plan clinique que paraclinique. L'évolution est favorable sans greffe hépatique.

Trois atteintes hépatiques survenues sous chloroquine et proguanil sont intéressantes à considérer car elles s'intègrent dans un tableau clinique plus large évoquant un problème d'hypersensibilité grave : un érythème polymorphe, un syndrome de Stevens Johnson et un syndrome d'hypersensibilité (DRESS syndrom).

Les deux autres atteintes hépatiques, d'évolution favorable, survenues sous chloroquine et proguanil sont : une atteinte mixte et une atteinte cholestatique associée à une stomatite.

Enfin trois atteintes hépatiques sont survenues sous proguanil utilisé seul en prophylaxie : une atteinte mixte, une atteinte cholestatique (récidive de moindre intensité un an après lors d'une nouvelle cure de proguanil) et une hépatite avérée au plan anatomo-pathologique (quelques éléments évoquent une participation immuno-allergique).

DISCUSSION

Chloroquine

L'analyse des cas notifiés associés à la chloroquine utilisée seule n'apporte pas beaucoup d'arguments pour valider l'existence d'effets indésirables hépatiques induits par ce médicament. Seules, deux observations où la chloroquine est le seul médicament suspect avec une imputabilité plausible sont disponibles. Aucun cas avec réintroduction positive n'a été recueilli.

En revanche, l'analyse bibliographique montre que la chloroquine présente une toxicité hépatique expérimentale lorsqu'elle est administrée à dose unique forte (970 mg/kg) chez le rat (peroxydation lipidique conséquence d'un stress oxydatif). In vitro, la chloroquine démontre une toxicité sur des hépatocytes de rat en culture à des concentrations 2 à 10 fois plus importantes que les concentrations plasmatiques retrouvées en thérapeutique humaine.

Un autre problème soulevé par l'analyse bibliographique est celui de la toxicité hépatique de la chloroquine lorsqu'elle administrée à des patients atteints de porphyrie cutanée tardive (PCT). La PCT est la plus fréquente des porphyries. Elle peut être familiale (type II ou III) ou sporadique (type I). Les réactions cutanées phototoxiques en sont la principale manifestation clinique. Un des traitements de la PCT réside dans l'administration de faibles doses de chloroquine (125 mg x 2/semaine). Ce traitement s'accompagne classiquement de fièvre, de douleurs abdominales, d'une élévation des transaminases de façon d'autant plus importante que la dose de chloroquine est forte. Le mécanisme de l'hépatotoxicité de la chloroquine dans ces conditions est mal connu mais pourrait être le fait d'une destruction sélective des mitochondries responsables de la surproduction de porphyrines. Une seule notification analysée dans l'enquête fait état d'une PCT chez un patient atteint de cytolyse. Ce problème est vraisemblablement mal connu et ne figure pas de façon explicite dans le RCP de la chloroquine ce qui justifie en conséquence un ajout dans le RCP.

Proguanil

Aucun des cas français inclus dans l'enquête ne concerne le proguanil utilisé seul. Cependant au vu des conclusions précédentes concernant la chloroquine et en raison de trois cas issus de la base ASTRA ZENECA impliquant le seul proguanil (un cas avec réintroduction positive, un cas publié), il est logique de conclure que le proguanil peut exceptionnellement être responsable d'atteinte hépatique. Ces atteintes sont le plus souvent cytolytiques ou mixtes. Elles sont d'évolution rapidement favorable à l'arrêt du traitement. La gravité de certains cas est souvent le fait d'autres manifestations associées qui évoquent parfois de véritables syndromes d'hypersensibilité (DRESS syndrom) comportant une atteinte hépatique. Une étude de la tolérance de l'association chloroquine-proguanil réalisée par une surveillance clinique et biologique rigoureuse de 131 militaires ayant séjourné 4 mois en République Centrafricaine montre une élévation franche des transaminases dans 3 cas (2,3 %) alors que les sérologies des hépatites virales sont négatives. L'interruption du proguanil a été suivie d'une normalisation de ces enzymes.

Les cas français rapportés avec l'association atovaquone-proguanil, inclus dans l'enquête, n'apportent pas d'argument supplémentaire pour valider l'existence d'atteinte hépatique induite par le proguanil, ce d'autant que des effets indésirables hépatiques sont également décrits avec l'atovaquone. Une communication récente au congrès annuel de l'American College of Gastroenterology décrit une hépatite fulminante, d'évolution favorable après greffe de foie (la biopsie hépatique montrait une nécrose hépatocytaire massive compatible avec une étiologie toxique ou médicamenteuse).

PROPOSITIONS

La rareté des effets hépatiques notifiés, et l'absence de cas particulièrement sévères justifient que les propositions se limitent à délivrer auprès des professionnels de santé une simple information.

A l'heure actuelle, aucune mention d'effet indésirable hépatique ne figure dans les RCP de NIVAQUINE®, SAVARINE®, PALUDRINE® et NOPALU®. Le RCP de MALARONE® signale la possibilité d'élévation des enzymes hépatiques liée plus spécifiquement à l'atovaquone.

La rubrique "Mises en garde" de NIVAQUINE® signale que la chloroquine est susceptible de déclencher une crise de porphyrie aiguë chez les patients atteints de porphyrie intermittente. L'indication porphyrie cutanée tardive ne figure pas dans l'AMM et aucune mention de l'hépatotoxicité de la chloroquine dans cette pathologie n'est signalée.

Au vu des données de l'enquête, il serait souhaitable de faire figurer à la rubrique "effets indésirables" les mentions suivantes :

- au RCP des spécialités contenant de la chloroquine : *"très rares cas d'élévation des enzymes hépatiques ou d'atteinte hépatique survenant notamment chez les patients porteurs d'une porphyrie cutanée tardive, et ce de façon dose-dépendante ".*
- au RCP des spécialités contenant du proguanil : *"très rares cas d'élévation des enzymes hépatiques ou d'hépatite survenant principalement dans un contexte d'hypersensibilité".*

Les résultats de cette enquête officielle seront présentés en Commission nationale de pharmacovigilance.

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VII – PRESENTATION DU PROJET « OBSERVATOIRES INTERREGIONAUX DES MEDICAMENTS ET DES INNOVATIONS THERAPEUTIQUES (OMIT) EN CANCEROLOGIE »

Madame Muriel Dahan, de l'Institut National du Cancer, a présenté en présence du Professeur Christian Riché, chargé de mission du projet, les grandes lignes d'un cahier des charges intervenant dans le cadre de la mise en place d'observatoires des médicaments et des innovations thérapeutiques (OMIT) en cancérologie, sur l'ensemble du territoire français. Ces observatoires viseront à assurer un suivi et à analyser des pratiques de prescription observées au niveau régional ou interrégional : l'analyse des données contribuera à améliorer le bon usage du médicament, la qualité et la sécurité des soins et à réduire les inégalités d'accès aux thérapeutiques appropriées. Ces OMIT en cancérologie seront sous la responsabilité des Agences Régionales d'Hospitalisation (ARH) des inter-régions, correspondant aux zones géographiques des cancéropoles. L'institut National du Cancer assurera leur coordination et la synthèse nationale des données.

Afin de définir le type de données à collecter auprès des prescripteurs, et les conditions dans lesquelles elles seront recueillies, exploitées et synthétisées, il convient d'élaborer un cahier des charges commun à l'ensemble des OMIT en cancérologie. Le but est de pouvoir le transposer aux médicaments hors cancer et aux dispositifs médicaux.

Afin d'apporter des solutions et de faire des propositions concernant la création de ce cahier des charges, le Comité technique a proposé la constitution d'un groupe de travail : 4 CRPV (Brest, Limoges, Marseille, Clermont-Ferrand et Reims) se sont proposés afin d'y participer. La première réunion de travail est prévue fin juin 2005.

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VIII - QUESTIONS DIVERSES

13ème cas de nouveau variant de la maladie de Creutzfeldt-Jakob en France

12 cas certains* ou probables* identifiés en France, dont 9 décédés.

Ces 9 décès présentent les caractéristiques suivantes :

- décédés en 1996 (1 cas), 2000 (1 cas), 2001 (1 cas), 2002 (3 cas), 2004 (2 cas) et 2005 (1 cas.
- 5 hommes et 4 femmes
- médiane des âges lors de leur décès est de 36 ans (entre 20 et 58 ans),
- 4 cas franciliens et 5 cas provinciaux,
- tous homozygotes Met-Met pour le codon 129 du gène de la protéine prion (PRP) et ne présentent aucun facteur de risque identifié pour les autres formes reconnues de MCJ.

Le 31 mai, un 13ème cas probable* de nvMCJ est notifié en France. Il est caractérisé par :

- Patient de 47 ans, vivant
- IRM évocatrice d'un nvMCJ
- EEG non caractéristique
- Ponction lombaire normale, recherche de la protéine 14-3-3 dans le LCR et examen génétique de la PRP en cours
- 17 dons connus pour ce patient effectués en Rhône Alpes entre 1991 et 2004 (17 CGR et 17 plasma).

Un rappel des lots en cours de validité a été effectué le 9 juin 2005. Un message destiné au professionnel de santé est en ligne sur le site de l'Afssaps avec la liste des lots retirés.

(*) Critères d'imputabilité :

- **vMCJ possible** : patient présentant un trouble neuropsychiatrique progressif pendant plus de 6 mois, sans examen de routine en faveur d'un autre diagnostic, sans argument pour une exposition à une source iatrogène potentielle ni pour une forme familiale de MCJ, avec au moins 4 des 5 signes suivants : symptômes psychiatriques précoces, symptômes sensitifs douloureux persistants, ataxie, myoclonies ou chorée ou dystonie, démence et absence d'un EEG typique de MCJ sporadique.
- **vMCJ probable** : vMCJ possible avec soit un "signe du pulvinar*" bilatéral sur l'IRM soit une biopsie d'amygdales positive (présence de PrPres en immunohistochomie et Western blot).
- **vMCJ certaine** : présence de lésions caractéristiques du vMCJ à l'examen neuropathologique cérébral et présence dans le tissu cérébral de protéine prion de type 4 (Western blot).

Annexe 3-68

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Saint-Jacques – 25030 BESANCON Cedex

MEDIATOR® (benfluorex)

ENQUETE OFFICIELLE

Troubles neuropsychiatriques

Hypertensions artérielles pulmonaires

Comité Technique du 7 juin 2005

Confidentiel

Lors du Comité Technique de Pharmacovigilance du 7 décembre 2004, plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique ayant été rapportés, il a été décidé d'actualiser les données relatives aux troubles neuro-psychiatriques avec MEDIATOR®.

Suite à une notification d'hypertension pulmonaire rapportée lors du Comité Technique du 8 mars 2005, l'enquête a été étendue aux hypertensions artérielles pulmonaires.

Le MEDIATOR® (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés, dosés à 150 mg.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité Technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène. (Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Historique :
Une première mise au point des effets indésirables du benfluorex a été présentée lors du Comité Technique du 11 juillet 1995, suivie d'une enquête officieuse dont les rapports ont été présentés aux Comités Techniques:

- du 30 avril 1998 sur les effets indésirables du benfluorex, rapportés aux CRPV
- du 10 septembre 1998 sur le métabolisme et les chiffres de ventes du benfluorex

et de l'enquête officielle présentée aux Comités Techniques des 17 décembre 1998 et 20 juillet 1999.

Le Résumé des Caractéristiques du Produit a été modifié suite à une Demande de Modification de l'Information Médicale expertisée par le CRPV de Besançon en juin 2000 d'une part, et une réunion de Pharmacovigilance à l'EMEA le 30 novembre 2000 d'autre part (pour choc et effets hépatiques).
(Les modifications sont inscrites en gras dans le paragraphe ci-dessous)

Les effets indésirables sont :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, **confusion**, somnolence, état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles
- **très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke**
- **élévation des enzymes hépatiques, hépatite (très rare)**

Métabolisme :

- In vivo : Chez l'homme, le MEDIATOR® est hydrolysé très rapidement au niveau plasmatique et hépatique par des estérases en S422 (dérivé alcool), puis transformé en 8 métabolites majeurs identifiés dont, par oxydation (S1475, dérivé acide) ou désalkylation (S585, norfenfluramine).
  Le métabolite majoritaire est le dérivé carboxylique : S1475.
  Le métabolite primaire S422 et la norfenfluramine sont retrouvés à des taux très inférieurs.

Après administration de benfluorex radioactif, on retrouve 87 à 99% de la radioactivité après 72 heures dans les urines.
L'absence de quantité significative dans les fécès montre que le produit est bien absorbé.
Il n'existe donc pas de phénomène d'accumulation.

L'élimination se fait en 2 phases :
- une première phase rapide (60% en 3 ou 4 heures)

- une seconde phase lente de 96 heures environ

- *In vitro* : Les travaux faits *in vitro* après incubation d'hépatocytes frais humains montrent que les principaux cytochromes P450 jouent un rôle très minoritaire dans le métabolisme du benfluorex.

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I – TROUBLES NEUROPSYCHIATRIQUES

A. Asthénie, somnolence ou états vertigineux sont mentionnés dans les RCP.

B. Troubles psychiatriques lors du traitement

35 cas ont été rapportés dont 10 déclarés depuis l'enquête présentée en juillet 1999.
Elles concernent 18 hommes (âge moyen : 58,5 ans) et 17 femmes (âge moyen : 60 ans).

Les troubles psychiatriques sont divers :

- agressivité (4), nervosité (3), irritabilité
- cauchemars (2), angoisse, stupeur, dépression
- désorientation (7), confusion (5), aggravation des troubles cognitifs
- agitation (3), trouble du comportement (3)
- délire (2), bouffée délirante aiguë

La responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue, dans la plupart des notifications.

1. Imputabilité :

Remarque : Les nouveaux cas (9) notifiés depuis le rapport de juillet 1999 sont inscrits **en gras**.

4 cas sont imputés « vraisemblable » :

- NC9500171 : nervosité et nausées chez une femme de 50 ans, 1 à 2 h après la prise de 1 comprimé de MEDIATOR®

- S10010345 : désorientation et obnubilation, chez une femme de 80 ans. Le traitement a été arrêté après 13 jours. Une réadministrationn ultérieure a été positive (traitement associé : KERLONE® et MOGADON®)

- **CN0000093** : désorientation temporo-spatiale et agitation chez un homme de 76 ans. Le délai d'apparition des troubles est inconnu, mais les signes cliniques se sont améliorés à l'arrêt du MEDIATOR® et la réadministration est positive. Les autres médicaments ne sont pas arrêtés (DAONIL®, LASILIX®, SINTROM®, MONICOR L.P®. et FOZIRETIC®).

- **128E22** : chez un homme de 72 ans , traité pour démence, prenant pendant plusieurs années MEDIATOR® pour troubles métaboliques et MODOPAR® pour maladie de Parkinson, est observée une amélioration de ses troubles cognitifs lors d'un arrêt fortuit du MEDIATOR® et une aggravation lors de la reprise du MEDIATOR®.

5 cas sont imputés « plausible »

- NC9700094 : accès d'agitation et agressivité, chez une femme de 74 ans, pendant la prise de MEDIATOR®, pendant 6 jours. Disparition des symptômes 12 heures après l'arrêt du MEDIATOR®.

- NC9300347 : irritabilité chez un homme de 39 ans, traité pendant 11 mois par MEDIATOR®. L'évolution est favorable à l'arrêt du médicament.

- MA9100069 : angoisse et palpitation, chez un homme de 40 ans, 2 heures après avoir ingéré 4 comprimés de MEDIATOR®.

- NC9300349 : dépression, chez un homme de 50 ans, traité pendant 9 mois par MEDIATOR®. L'évolution est favorable à l'arrêt du médicament.

- CF9000137 : désorientation chez une femme de 79 ans, traitée par MEDIATOR®, HALDOL®, SERESTA®, ZESTRIL®, CATAPRESSAN®, PRAXILENE®, SERMION®. L'évolution est favorable à l'arrêt de tous les médicaments.

26 cas ont été imputés « douteux » dont 13 (C2, S1).

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Les effets indésirables ont nécessité une hospitalisation dans 9 cas

SE9500017 : Un **état confusionnel** ayant duré 12 h est survenu, chez une femme de 41 ans après 83 jours de traitement par MEDIATOR® (1cp/j) et INCITAL® et 2 ans par LEXOMIL®. Elle avait été retrouvée errante sur la voie publique après une dispute avec son mari. (Imputabilité : C1,S1)

010326 : Un homme de 61 ans, traité par MEDIATOR® (dose et durée inconnues), FONZYLANE® et SINTROM® est hospitalisé pour déshydratation avec fièvre et **confusion**. L'évolution est favorable après rehydratation et arrêt du MEDIATOR®.

120M85 : Un homme de 69 ans, traité par MEDIATOR®, 2 cp/j pendant 11 jours pour désordre métabolique est admis à l'hôpital pour malaises avec **confusion** et amnésie. Le MEDIATOR® est arrêté, mais les troubles de mémoire continuent. Le scanner cérébral montre une atrophie cortico-souscorticale.
Le traitement associé est PREVISCAN® et CORDARONE®.

10345 : Une femme de 80 ans, avec des séquelles d'accident vasculaire cérébral, traité pur hypercholestérolémie par MEDIATOR® 3cp/j pendant 13 jours est hospitalisée pour **désorientation temporo-spatiale et obnubilation** avec hypotension artérielle. L'évolution est favorable à l'arrêt du MEDIATOR®. Le rechallenge est positif.
Le traitement associé est: KERLONE®, MOGADON®.

RE037148 : Une patiente de 66 ans, obèse et grabataire, est amenée à l'hopital en raison de l'apparition d'un syndrome confusionnel avec état stuporeux et une hyperthermie à 40°. Ses antécédents sont assez chargés avec entre autres, un état dépressif, un asthme et une cardiopathie hypertensive. Le traitement par MEDIATOR® (3cp/j) avait débuté 10 à 12 jours avant son hospitalisation à raison de 3 cp/j. Après l'arrêt du MEDIATOR®, on note une amélioration en quelques jours de la **désorientation temporo-spatiale**. Le traitement habituel de la patiente est : ASPEGIC®, COAPROVEL®, CORVASAL®, DIFFU K®, MONOTILDIEM®, MOVICOL®, SEROPRAM®, TRINIPATCH®, MEDIATENSYL®, VASTEN®, SERETIDE® et VENTOLINE®. (Imputabilité : C2,S1)

CN0000093 : Chez un homme de 76 ans, traité depuis 2 ans par 3cp/j de MEDIATOR®, est apparu une **désorientation temporo-spatiale** et agitation, dont le délai d'apparition des troubles est inconnu, mais les signes cliniques se sont améliorés à l'arrêt du MEDIATOR et la réadministration a été positive. Les autres médicaments ne sont pas arrêtés (DAONIL®, LASILIX®, SINTROM®, MONICOR L.P. ® et FOZIRETIC®) *(dossier imputé «C3,S1 » décrit ci-dessus).*

RN9500096 : Une patiente de 59 ans, sans antécédent psychiatrique, en cure d'amaigrissement (perte de 10 kg) depuis 3 mois avec MEDIATOR® (3cp depuis 73j), LIPANTHYL®, AMFEPRAMONE®, Craetegus 100mg, PILOSURYL®, CANOL®, STRESAM®, OLIVIASE®, RELVENE® et TOP MAG® est hospitalisée pour **bouffée délirante aiguë** avec confusion, désorientation temporo-spatiale et agitation. L'évolution est favorable 8 jours après l'arrêt de tout le traitement et la mise sous neuroleptiques. (Imputabilité : C1,S2)

TO041306 : Une **bouffée délirante aiguë** à thème de persécution et de complot avec agitation extrême et opposition des soins a nécessité une hospitalisation sous contrainte chez un homme de 50 ans qui était traité par MEDIATOR® (1cp/j) depuis 29 mois, associé à COTAREG® et ZYLORIC®. Les troubles ont disparu en 24 h sous SOLIAN IM®, TERCIAN IM® ET RIVOTRIL®. Le patient est sorti de l'hôpital avec SOLIAN® 400mg 2 fois par jour. (Imputabilité : C1,S2)

S01000031 : Un homme de 63 ans a été hospitalisé à plusieurs reprises pour confusion mentale inexpliquée. Une recherche des médicaments sur l'urine par technique de polarisation de fluorescence révèle une réponse positive pour les

dérivés amphétaminiques et une chromatographie gazeuse couplée à une spectrométrie de masse ne confirmant pas l'abus d'amphétaminiques (Jordan, Pennsy).

Cependant, la norfenfluramine est retrouvée à des concentrations de 587 ng/ml dans l'urine et 3,4 ng/mg dans les cheveux.

La présence de norfenfluramine et l'absence de fenfluramine sont en faveur d'un abus illicite de MEDIATOR® (dose inconnue). L'évolution est inconnue. (Imputabilité : C1,S1)

(Cas publié :Norfenfluramine : usage thérapeutique ou toxicomanie ? V.CIRIMELE et coll. Journal de Médecine Légale Droit Médical, 2001, Vol.44, N°1, 23-26.

3. Tableau récapitulatif des observations : (voir pages suivantes)

Les nouveaux cas (9) notifiés depuis le rapport de juillet 1999 sont inscrits **en gras**.

Troubles psychiatriques lors du traitement (1)

N°	S/Age	Durée TTT	Posologie/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables
S01001236	**M ,54**	**17 jours**	**450 mg**	**C2,S1**	**TRANDATE, C1,S1**		**A**	**N**	**Agressivité,irritabilité, insomnie**
LY9600963	M,45	1 mois	450 mg	C1,S1	LEXOMIL, C2,S1		A	N	agressivité
NC9700094	F,74	6 j	225 mg	C2,S2			A	N	agressivité
541173	F,45	8j	300 mg	C2,S1	CORENITEC,C1,S1 LYSANXIA		A		Agressivité + hallucination
NC9300347	M,39	11 mois	150 mg	C2,S2			A	N	Irritabilité
NC9500171	F,50	1 cp	150mg	C3,S2			A	N	Nervosité
MP9800179	F,47	11j	300 mg	C2,S1	LIPANOR, C1,S1		A	N	Nervosité
124G84	F,35	20 j	300 mg	C2,S1	MAXEPA LEVOTHYROX HYDROCORTISONE	Hypothyroïdie Insuffisance surrénale	A	N	Nervosité +excitation
MA9100069	M,40	1 j	600 mg	C2,S2			A	N	Angoisse
TS9500338	F,69	8 j	150 mg	C2,S1	DAONIL, C1,S1 ALPRESS BITILDIEM DIAMICRON…		A	N	Stupeur
LY8900392	M,52	20 j	450 mg	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1		A	N	Cauchemars
10540O46	M, ?	qq semaines	450 mg	C1,S1	ZOCOR, C1,S1 PERSANTINE MAXEPA TILDIEM DAONIL		A	N	Cauchemars
NC9300349	M,50	9 mois	450 mg	C2,S2	LOPRIL, C1,S1		A	N	Dépression Paresthésie, asthénie
SE9500017	F,41	84 j	150 mg	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1		A	O	confusion
010326	M,61	?	?	C1,S1	FONZYLANE, C1,S1 SINTROM, C1,S1		A	O	Confusion Autre cause !

120M85	M,70	11j	300 mg	C2,S1	PREVISCAN , C1,S1 CORDARONE, C1,S1	Scanner cérébral : atrophie cortico souscorticale	A	O	Confusion Troubles de la mémoire
000031	**M ,63**	**?**	**?**		**Drogue ?**		**U**	**O**	**Confusion**
127V18	**M,70**	**1 jour !**	**150 mg**	**C2,S1**	**TERALITHE LEXOMIL NOCTRAN**	**Syndrome dépressif**	**A**	**N**	**Confusion Somnolence**
128E22	**M,72**	**+ années**	**?**	**C3,S1**	**MODOPAR**	**Démence**	**A**	**N**	**Aggravation des troubles cognitifs**

Troubles psychiatriques lors du traitement (2)

N°	S/Age	Durée TTT	Posologie/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables
CF9000137	F,79		450 mg	C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2 SERMION, C2,S2		A	N	désorientation
010345	F,80	13 j	450 mg	C3,S1	MOGADON, C1,S1 KERLONE, C1,S1		A	O	Désorientation Obnubilation
060J96	F,80	?	?	C1,S1	RENITEC ADALATE HEMIDAONIL TILDIEM		A	N	Désorientation
060J13	F,82	1 mois	450 mg	C2,S1	DAONIL		A	N	Désorientation
120M52	M,60	2 j	150 mg	C2,S1	LIPANTHYL, C1,S1 ASPEGIC, C1,S1		A	N	Désorientation Somnolence
RE037148	**F,66**	**13 j**	**450 mg**	**C2,S1**		**Syndrome dépressif**	**A**	**O**	**Désorientation temporospatiale Etat stuporeux**
CN0000093	**M,76**	**2 ans**	**450 mg**	**C3,S1**	**DAONIL, C1,S1 SINTROM, C1,S1 LASILIX, C1,S1 MONICOR L.P., C1,S1 FOZIRETIC, C1,S1**		**A**	**O**	**Désorientation temporospatiale Agitation**
MA8900523	F,40		150 mg	C1,S1	ISOMERIDE, 1j, C2,S1		A	N	Agitation
DJ9800349	M,74	3 mois	450 mg	C2,S1			A	N	Agitation

PA0200221	**F,70**	**1 j**	**3 cp en 1 prise**	**C1,S1**			**A**	**N**	**Agitation, paresthésie**
10060560	M,75	Plusieurs mois	450 mg	C2,S1	DAONIL		A	N	Trouble du comportement
GR0100547	**F,44**	**4 mois**	**450 mg**	**C2,S1**	**OLIGOSOL, C2,S1**	**Syndrome dépressif**	**F**	**N**	**Trouble du comportement Hallucination, vertige**
GR0100594	**F, ?**	**9 mois**	**450 mg**	**C1,S1**			**U**	**N**	**Trouble du comportement**
RN9500096	F,59	73 j	450 mg	C1,S2	LIPANTHYL, C1,S2 PILOSURYL, C1,S2 CANOL, C1,S2 OLIVIASE, C1,S2 Amfépramone, C1,S2		A	O	délire
GR8700216	M,45	16 j	450 mg	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1		A	N	délire
TO041306	**M,50**	**29 mois**	**150 mg**	**C1,S2**	**COTAREG, C1,S1 ZYLORIC, C1,S1**		**B**	**O**	**Bouffée délirante aiguë**

Les nouveaux cas notifiés depuis le rapport de juillet 1999 sont inscrits en gras.

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3. Troubles psychiatriques apparaissant lors du sevrage

10 notifications de troubles psychiatriques apparaissant lors du sevrage ont été rapportés, 6 par les CRPV, 4 par le laboratoire.

Ils concernent 2 hommes et 8 femmes, dont la moyenne d'âge est respectivement 30,5 ans (27-34) et 45,25 ans (30-65).

Le délai d'apparition des troubles après l'arrêt du MEDIATOR® est très variable : de 1 jour (après un traitement de 8 ans) à 3 semaines (après un traitement de 4 à 15 mois).

La durée de traitement par MEDIATOR® est de 1 mois à 8 ans.

Dans les 3 observations qui ont nécessité une hospitalisation (gravité = O), il existe un terrain ou des antécédents prédisposants :

- **LY0200303** : une femme de 36 ans, traitée par MEDIATOR® pendant 6 mois pour obésité avec hypercholestérolémie et PROZAC pendant 6 semaines pour syndrome dépressif est hospitalisée en psychiatrie pour **état anxiodépressif aigu** avec crise de panique 2 à 3 semaines après l'arrêt des 2 médicaments.
L'état de la patiente s'améliore rapidement sous SOLIAN® et STABLON®. (Imputabilité : C1,S1)

- **LY0200036** : chez une femme de 34 ans, avec des troubles dysthymiques, suivie pour difficultés psychologiques de type border line, en rupture de traitement neuroleptique depuis plusieurs mois, apparaît une **décompensation avec délire persécutif et anxiété**, environ 3 semaines après un traitement de 4 mois par MEDIATOR®.
La patiente sera traitée pour troubles psychotiques, l'évolution est inconnue. (Imputabilité : C1,S1)

- **LY0200037** : une femme de 53 ans, diabétique non insulino-dépendante, ayant fait 2 épisodes maniaques en 1985 et 1996 (ce deuxième épisode étant survenu à la suite d'un régime amaigrissant accompagné peut-être au benfluorex) est hospitalisée pour **accès maniaque atypique** environ 3 semaines après l'arrêt d'un traitement de 15 mois par MEDIATOR®. Il est a noté un amaigrissement de 20 kg en 1 an.
La patiente sera traitée pour troubles psychotiques, l'évolution est inconnue. (Imputabilité : C1,S1)

Les autres troubles sont identiques à ceux décrits pendant le traitement par MEDIATOR® :

- vertige (4), somnolence (2)
- cauchemar, angoisse (2)

Dans 1 cas, l'imputabilité de MEDIATOR® est « vraisemblable » :

- PA97355052 : il s'agit d'un syndrome de sevrage avec **excitation** chez un homme de 27 ans, sportif, qui consomme (sur prescription médicale) à doses croissantes (1cp/semaine au début jusqu'à 9 cp/j) du MEDIATOR® comme "dopant ».
Ce patient avait eu un épisode similaire quelques mois plus tôt. (Imputabilité : C3,S1)

Troubles psychiatriques apparaissant lors du sevrage

Les nouveaux cas (8) notifiés depuis le rapport de juillet 1999 sont inscrits **en gras.**

N°	S/Age	Durée TTT	Poso/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables	sevrage
MP0300791	**F,58**	**8 ans**	**450 mg**	**C2,S2**	**LIPANTHYL ,C2,S1 LEVOTHYROX, C1,S1 EUPRESSYL, C1,S11**		**A**	**N**	**Vertige, somnolence**	24h
060141	**M,34**	**2 mois**	**300 mg**	**C2,S1**			**A**		**Vertige, sueur**	2 jours
TO001223	**F,30**	**3 mois**	**450 mg**	**C1,S1**	**SURGAM CLAMOXYL**		**A**	**N**	**Céphalalgie, malaise, somnolence**	9 jours
S02000276	**F,34**	**1 mois**	**450 mg**	**C2,S1**	**XENICAL ESBERIVEN**		**A**		**Nausée, vertige , fatigue, cauchemar, tremblement**	
LY0200303	**F,36**	**6 mois**	**300 mg**	**C1,S1**	**PROZAC, C1,S1**	**Syndrome dépressif**	**B**	**O**	**Etat anxiodépressif**	2 à 3 semaines
S03000265	**F,52**	**+ années**	**450 mg**	**C1,S1**	**LEVOTHYROX LIPANTHYL**		**U**	**N**	**Angoisse, nervosité, vertiges**	Quelques jours
10060219	F,65	2 ans		C1,S1			A		Bouffées d'angoisse	
PA9735052	M,27	6 mois		C3,S1	« 9 cp/j (dopant) »		U		Excitation	
LY0200036	**F,34**	**4 mois**		**C1,S1**		**Troubles dysthymiques sur personnalité pathologique**	**U**	**O**	**Bouffées délirantes**	3 semaines
LY0200037	**F,53**	**15 mois**		**C1,S1**	**GLUCOR, C1,S1 STAGID, C1,S1 LEVOTHYROX, C1,S1**	**Troubles dysthymiques**	**U**	**O**	**Exaltation maniaque atypique**	3 semaines

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Les nouveaux cas (4) notifiés depuis le rapport de juillet 1999 sont inscrits en gras.

12 notifications ont été rapportées, 9 par les CRPV, 3 par le laboratoire :
Elles concernent 8 hommes et 4 femmes :

- Convulsions : 2 cas

PA9223988 : Chez un homme de 60 ans, survient une **crise convulsive généralisée**, alors qu'il est traité par MEDIATOR 1cp/j (durée inconnue), TENSIONORME® depuis 10 ans et DIFFU K®. L'évolution est favorable à l'arrêt des 3 médicaments.

10060J47 : Une femme de 36 ans traitée par MEDIATOR® depuis 2 mois et DAONIL®, fait une **crise comitiale**, dont l'évolution est favorable.

- Neuropathies : 2 cas

MA8700716 : Chez un homme de 73 ans traité pour un diabète léger par MEDIATOR® pendant 9 ans apparaît une **neuropathie sensitivomotrice** des membres inférieurs. Une autre étiologie peut être envisagée. L'évolution est inconnue.

TS9300183 : Une **neuropathie** est rapportée chez un homme de 68 ans traité depuis 3 mois par MEDIATOR® et GLUCOPHAGE®, et 5 mois par AZANTAC®. Le traitement habituel est DIAMICRON®, SURBRONC® et CYCLOSPASMOL®.

- Paresthésies : 7 cas

Dans 3 cas (**PA0200221,** NC9300349, **MA03P0355**), il existe des symptômes associés cités ci-dessus : agitation, dépression, vertige et asthénie.

Le délai d'apparition est très court : de 1 à 8 jours dans la majorité des cas. Dans 1 cas, où la neuropathie est associée à une dépression et asthénie le délai est de 9 mois (NC9300349).

L'évolution, quand elle est connue, est favorable rapidement en quelques heures.

A noter que dans 2 cas, il s'agit de mésusage :

- **MA03P0355 :** prise de 6 comprimés en 1 fois, par une femme de 26 ans, qui a présenté des douleurs abdominales, des vertiges, une asthénie et des paresthésies au niveau des membres inférieurs.
- MA9700170 : automédication chez une femme de 42 ans, qui après le deuxième comprimé de MEDIATOR est survenue une sensation de chaleur accompagnée de picotements des extrémités et des palpitations. L'évolution est inconnue.

- Tremblements des mains

128F60 : un patient de 72 ans ayant débuté depuis 5 jours un traitement par MEDIATOR®, LIPANTHYL®, MONO-TILDIEM® et HYPERIUM® développe un **tremblement des mains.**
HYPERIUM® est remplacé par diltiazem puis trandolapril, LIPANTHYL® remplacé par atorvastatine et les doses de MEDIATOR® de 300 mg/j sont diminuées de moitié. Les tremblements régressent.
Le MEDIATOR® est arrêté ensuite.

Autres troubles neurologiques

N°	S/Age	Durée TTT	Poso/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Commentaires
CONVULSION									
PA9223988	M,60	?	150 mg	C2,S1	TENSIONORME, C2,S1 DIFFU K		A	N	Tensionorme : B3
10060J47	F,36	2 mois		C1,S1	DAONIL		A		Crise comitiale
NEUROPATHIE									
MA8700716	M,73	9 ans	?	C1,S1	HEMOCLAR TORENTAL		U	N	Autre étiologie
TS9300183	**M,68**	**3 mois**	**?**	**C2,S1**	**AZANTAC, 1j, C2,S1** **GLUCOPHAGE, C2,S1**		**A**	**N**	**Imputabilité Azantac : B2**
PARESTHESIE									
BX8800193	M,36	8 j	300 mg	C1,S1	PRAXINOR, 8j, C1,S1		F	N	
LM9500090	M,61	4 j	150 mg	C2,S1	Traitement associé inconnu		A	N	
10051683	M,65		450 mg	C2,S1	DAONIL GLUCOPHAGE LIPANOR ANGIOXINE		A	N	
MA9700170	F,42	1 j	150 mg	C2,S2	TAMIK, C1,S1		U	N	Mésusage
MA03P0355	**F,26**	**6 cp en 1 j**	**900mg**	**C2,S2**			**A**	**N**	**Mésusage Vertige, asthénie**
PA0200221	**F,70**	**1 j**	**3 cp en**	**C1,S1**			**A**	**N**	**Agitation, paresthésie**

			1 prise						
NC9300349	M,50	9 mois	450 mg	C2,S2	LOPRIL, C1,S1		A	N	Dépression Paresthésie, asthénie
128F60	**M,72**	**5 j**	**450 mg**	**C2,S1**	**LIPANTHYL, C2,S1** **HYPERIUM, C1,S1** **MONOTILDIEM, C1,S1**		A	N	**Tremblements des mains**

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2 cas d'abus ont été rapporté :

- 1 cas rapporté par le laboratoire sans effet indésirable :

  Un homme de 42 ans, traité par MEDIATOR® 150 mg 2 fois par jour pour hypertriglycéridémie depuis décembre 1999, augmente les doses à 10 comprimés par jour de janvier à novembre 2001, puis retourne à une dose normale à 2 comprimés par jour ensuite.
  Le traitement associé était TERCIAN® et LEPTICUR®.
  Aucun effet indésirable n'est rapporté.

- 1 cas rapporté par un CRPV avec effet indésirable : (déjà cité page 7, paragraphe sevrage)

  - PA97355052 : il s'agit d'un syndrome de sevrage avec **excitation** chez un homme de 27 ans, sportif, qui consomme (sur prescription médicale) à doses croissantes (1cp/semaine au début jusqu'à 9 cp/j) du MEDIATOR® comme "dopant ».
  Ce patient avait eu un épisode similaire quelques mois plus tôt. (Imputabilité : C3,S1)

II – HYPERTENSIONS PULMONAIRES :

Suite à une notification d'hypertension artérielle pulmonaire (HTAP) rapportée par le CRPV de Montpellier lors du Comité Technique du 8 mars 2005 (MP0300189), l'enquête sur MEDIATOR® a été étendue aux hypertensions artérielles pulmonaires.

16 notifications (5 CRPV et 11 laboratoire) dont 1 doublon ont été rapportées :

1. Notifications où MEDIATOR® est associé à un anorexigène :

Lors de la présentation du rapport MEDIATOR® en décembre 1998, 11 notifications d'«hypertension artérielle pulmonaire » avaient été rapportées.
9 d'entre elles, expertisées par le Professeur WEITZENBLUM (Strasbourg) faisaient partie de l'enquête « Anorexigènes et hypertensions artérielles pulmonaires » présentée au Comité technique du 28 avril 1995 :

- 6 ont été classées en HTAP d'allure primitive
- 2 en HTAP post-capillaire
- 1 en HTAP post-embolique

Le MEDIATOR n'était jamais prescrit seul : il était présent en association à un ou plusieurs anorexigènes :

- ISOMERIDE® : 7 fois
- ISOMERIDE® + PONDERAL® : 2 fois
- ISOMERIDE ®+ FENPROPOREX® : 1 fois
- DININTEL® + TENUATE DOSPAN® + FRINGANOR® : 1 fois

La durée de traitement par MEDIATOR® est précisée dans 7 cas sur 11 : elle est de plusieurs mois à 5 ans.

Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® est :

- concomitante dans 5 cas,
- antérieure dans 2 cas,
- postérieure dans 3 cas
- imprécise dans 1 cas.

840255 : Une femme, 57 ans, obèse depuis longtemps, ayant pris PONDERAL pendant 2 mois en 1978 et ISOMERIDE en 1986 (durée inconnue) est hospitalisée en janvier 1993 pour suspicion d'embolie pulmonaire. La scintigraphie pulmonaire est normale.
Le traitement habituel est VOLTARENE, FELDENE et DOLIPRANE pour lombalgies.

[illegible] d'insuffisance tricuspidienne. Des signes d'hypertrophie ventriculaire droite sont retrouvées à l'électrocardiogramme
La dyspnée s'aggravant progressivement, la patiente est hospitalisée en novembre 1993.
A noter que la patiente aurait pris MEDIATOR , VEINOBIASE, STILNOX et XANAX au cours du mois de septembre.
A l'échodoppler cardiaque, la PAP systolique est estimée à 73 mmHg.
Le cathétérisme cardiaque confirme l'HTAP précapillaire.
En février , l'échodoppler montre une aggravation de la PAPs à 95 mmHg, mais létat clinique de la patiente est légèrement amélioré début juin 1994..

840663 : Chez un homme de 48 ans, dont les antécédents sont une hypertension artérielle traitée par FLUDEX, des glycémies, cholestérolémie et uricémie aux limites supérieures de la normale, un syndrome restrictif post-traumatique, un tabagisme interrompu depuis 1987 et une obésité traitée par ISOMERIDE de septembre 1990 à avril 1991 est hospitalisé en février 1992 pour syndrome obstructif post-tabagique sévère et aggravation du syndrome restrictif. Une dyspnée d'effort est cotée stade 3-4.
Le traitement de sortie est : MEDIATOR, VECTARION, BRONCHODUAL et BRONILIDE. FLUDEX est remplacé par ECAZIDE puis LUMITENS.
Après une amélioration, la dyspnée s'est aggravée et le patient est hospitalisé à nouveau en mai 1993 pour bilan de l'hypoxémie.
A l'échocardiographie, les cavités droites sont très dilatées, comprimant les cavités gauches. La PAPs est estimée à 50 mmHg.
Le cathétérisme droit effectué en juin 1993 pose le diagnostic d'HTAP précapillaire avec une PAP systolique à 90 mmHg.
Le patient décède 24 mois plus tard.

840B19 : Une femme de 51 ans, ayant une HTA, une obésité après une première grossesse en 1966, traitée par PONDINIL en 1974 puis par ISOMERIDE de 1985 à 1989 (2 fois 3 mois), une hyperlipidémie traitée par MEDIATOR de 1989 à janvier 1995, est hospitalisée en août 1994 pour bilan d'un syndrome sec.
Une échocardiographie met en évidence une double atteinte aortique et mitrale et une HTAP. Le traitement antérieur comporte : LIPUR, SECTRAL, DEBRIDAT, PRAGMAREL, ENDOTELON.
En décembre 1994, lors d'une échocardiographie de contrôle, la PAPs est estimée à 60-65 mmHg.
Le traitement de la patiente est alors : SECTRAL, MODURETIC, KALEORID, RANIPLEX, PREPULSID.
En janvier 1995, l'état de la patiente est stable avec une PAPs évaluée à 55 mmHg.

2. Notifications où MEDIATOR® n'est pas associé à un anorexigène : 5 notifications

4 dossiers ont été expertisés par le Professeur WEITZENBLUM, le 5° étant trop succinct.

➢ PS9900385 :
Chez une femme de 50 ans, ayant comme antécédent une hypertension artérielle traitée par LOGIRENE®, 0,5 cp/j et TRIATEC® 2,5 cp/j et une hypercholestérolémie traitée par LIPANTHYL® 1 cp/j et MEDIATOR®, 1 cp/j, est découvert une hypertension artérielle pulmonaire.
Le début des symptômes remontent à décembre 1998 avec l'installation d'une dyspnée d'effort, qui s'est majorée après un an d'évolution.
Lors d'un bilan en mai 1999, la pression artérielle pulmonaire systolique (PAPs) est estimée à 91 mmHg à l'échographie cardiaque.
Un bilan en juin 1999 confirme une hypertension artérielle pulmonaire avec une coronarographie, une angiographie et une scintigraphie pulmonaire normales.
Au cathétérisme droit, la pression artérielle pulmonaire moyenne (PAPm) est à 51 mmHg.
Un traitement par FLOLAN® est instauré (21 juin 1999).

Un bilan réalisé à trois mois montre une réelle amélioration et la patiente reste stable cliniquement jusqu'en septembre 2001 où elle constate une réaggravation de la dyspnée d'effort mais la PAPm est alors stable à 55mmHG.

➢ **TO040278 :**

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Une femme de 36 ans traitée pendant 2 ans par MEDIATOR®, Depa, LEVOTHYROX®, ADIPOR Fort®, PRAXINOR®, PROZAC®, HEPTAMYL® et CANOL® est hospitalisée le 25 novembre 2003 suite à une détresse respiratoire aiguë. Le diagnostic est un syndrome alvéolo-interstitiel bilatéral. Il n'y a pas de syndrome inflammatoire.
Les antécédents sont une hypothyroidie, un tabagisme, un surpoids et une insuffisance aortique de grade 2 découverte un an auparavant.
L'échographie montre une fonction systolique ventriculaire gauche à 65%, avec un ventricule gauche dilaté, une insuffisance mitrale de grade 2 et une insuffisance aortique de grade 2.
Le doppler veineux ne montre pas de thrombose veineuse des membres inférieurs.
L'état de la patiente s'améliore sous ALDACTONE®, LASILIX® et RENITEC®. Le traitement associé est LEVOTHYROX®, PROZAC® et CANOL®.
Une échographie de contrôle réalisée après normalisation clinique et radiologique montre une oreillette gauche dilaté, des cavités droites non dilatées sans HTAP.
Conclusion du cardiologue: *« décompensation cardiaque associée à une probable infection virale broncho-pulmonaire ».*

Le 5 janvier, la patiente est hospitalisée à nouveau pour récidive d'un subOAP sur valvulopathies aortique et mitrale à la faveur d'une virose.
La valvulopathie est recontrôlée par échographie par voie transthoracique : il existe alors une élévation des pressions artérielles pulmonaires avec une PAPs estimée à 50mmHg (N :15 mmHg), le ventricule et l'oreillette gauches sont dilatées.
Le 23 janvier 2004, le remplacement des valves est effectué. On ne note aucun problème dans les suites de l'opération.
L'anatomopathologie des valves montre une lésion dégénérative aspécifique.

Le diagnostic différentiel élimine :
- une maladie rhumatismale : l'aspect échographique n'est pas en faveur ? ? ?
- une endocardite : la recherche est négative
- une maladie auto-immune : les autoanticorps et la recherche des phospholipides sont négatifs

Il est à noter que la soeur de la patiente est suivie pour valvulopathie.
Le traitement de sortie est PREVISCAN®, RENITEC®, PROZAC®, LEVOTHYROX®.

L'avis de l'expert est : *« cardiopathie valvulaire sévère, l'OAP ayant entrainé une HTAP post-capillaire. »*

➢ **MP0500189** :

Une femme de 55 ans, traitée par MEDIATOR®, 1cp/j, depuis 31 mois est hospitalisée en janvier 2005 pour suspicion d'embolie pulmonaire avec dyspnée d'effort importante, progressivement croissante depuis plusieurs mois.
A l'échographie cardiaque, une hypertension pulmonaire oscille entre 75 et 80 mmHg
L'angioscanner thoracique ne met pas en évidence de signe d'embolie pulmonaire, mais il semble exister un caillot dans l'artère sous segmentaire gauche.
Les D Dimères sont élevés à 12000.
La scintigraphie pulmonaire de ventilation perfusion montre des troubles perfusionnels avec vraisemblablement un petit épanchement pleural gauche, faisant suspecter des épisodes emboliques multiples partiellement reperfusés
Conclusion du cardiologue : *« possible embolie pulmonaire compliquée d'HTA pulmonaire importante avec à la scintigraphie des défects périphériques disséminés. Il s'agit possiblement de micro-embols d'installation progressive mais on ne peut exclure formellement une HTAP primitive de type veino-occlusif. »*

Dans les antécédents de la patiente, on note une embolie pulmonaire en 1981, suite à un accident de la voie publique, compliquée d'une phlébite, traitée par antivitamines K pendant un an, une HTA ancienne traitée par COTAREG et un tabagisme modéré.
Le 31 janvier, l'échographie cardiaque de contrôle met en évidence une diminution de la PAPs à 65 mmHg, le ventricule droit est dilaté, l'insuffisance tricuspide est relativement importante.

Le 1 février 2005, la patiente est sortie avec une HTAP à 65 mmHg, le traitement de sortie étant PREVISCAN® (en prévention d'une embolie pulmonaire), COTAREG® et MOPRAL®.
Le 22 février 2005, elle est hospitalisée à nouveau avec altération de l'état général, des douleurs thoraciques, des vomissements et une dyspnée.

La patiente [illegible] la nuit suivante à 6/5.
La patiente fait une asystolie et décède le lendemain par arrêt cardiocirculatoire.

L'avis de l'expert pneumologue : *« vraisemblable HTAP post-embolique »*

➢ **S02001877** :
Une patiente de 55 ans est traitée pendant un an (juillet 2001-septembre 2002) par MEDIATOR pour un diabète non insulino-dépendant et une dyslipidémie, associé à ALDACTONE®, LASILIX® et TERALITHE®.
En juin 2002, un cathétérisme cardiaque droit montre une hypertension précapillaire avec une PAP à 51 mmHg. L'échographie montre des cavités droites dilatées.
L'échodoppler des membres inférieurs et la scintigraphie pulmonaire sont normaux.

En octobre 2002, la patiente est hospitalisée avec une dyspnée de grade 3. Au cathétérisme cardiaque droit, la PAPm est à 40 mmHg.
Les différents traitements pris par la patiente sont :
PREVISCAN®, LESCOL®, AMAREL®, STABLON®, ATARAX®, TEMESTA®, LIPANTHYL®, LIPUR®, TOCO®, GLUCOPHAGE®.
L'évolution est inconnue.

➢ **S02001046** :
Une femme de 59 ans traitée par MEDIATOR® 450 mg/j pour un désordre métabolique lipidique depuis novembre 1992 associé à de nombreux médicaments est hospitalisée en mars ou avril 2002 pour dyspnée et malaise.
Une hypertension pulmonaire est diagnostiquée. Le MEDIATOR® est alors arrêté.
Les différents traitements associés sont : CAPTEA®, LOPRIL®, PROGYNOVA®, UTROGESTAN®, HUMORYL® et PRAXINOR®
L'évolution est inconnue et le dossier succinct.

3. Fréquence :

Depuis le début de la commercialisation de MEDIATOR®, le nombre de boites de 30 comprimés vendues est de : 110 693 331, correspondant à 45 515 349 mois de traitement*.

Après élimination des HTAP post-emboliques (2) et post-capillaires (3), il reste 11 cas HTAP idiopathique soit :
- 1 cas pour 10 063 030 boites vendues
- ou 1 cas pour 4 137 759 mois de traitement.

(*mois de traitement : estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés (mois de 30,4 jours).

Hypertensions artérielles pulmonaires (1)

N°	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
PP890081	F,42	1 an	DININTEL TENUATE DOSPAN FRINGANOR	5 ans 5 ans 5 ans	Concomitant	U	
NC9300007 = 052454	M,48	4 ans	ISOMERIDE ZYLORIC LIPANTHYL	3 ans 6 ans	Concomitant	D	
10052455	F,46	25 mois	ISOMERIDE CORGARD BUSPAR VELITEN ALDACTONE	580 jours	Concomitant	F	
10052733	F,71	60 mois	ISOMERIDE	45 jours	Antérieur	F	HTA post-capt
10840193	F,47	?	ISOMERIDE COVERSYL LASILIX GLUCOPHAGE	730 jours	Concomitant	F	
10840255	F,57	?	ISOMERIDE PONDERAL STILNOX XANAX VEINOBIASE	? 2 mois	Postérieur	F	
10840663	M,48	+ mois	ISOMERIDE FLUDEX	210 jours	Postérieur	F	
10840770	F,66		ISOMERIDE FENPROPOREX	1 mois	Antérieur	F	HTA post-emb
10840954	F,54		ISOMERIDE STAGID DIAMICRON	1-2 semaines	Inconnu	A	HTA post-capil
10840B19	F,51	5 ans ?	ISOMERIDE SECTRAL MODURETIC	6 mois	Postérieur	F	

			KALEORID LEXOMIL RANIPLEX PREPULSID				
10840D01	F,59	4 ans	ISOMERIDE PONDERAL ZOCOR PROGESTOGEL SPIROCTAN	Environ 12 mois Environ 6 mois	Concomitant	D	

Hypertensions artérielles pulmonaires 2)

N°	S/Age	Durée TTT	TTT associé	Evolution	Commentaires
PS9900385	**F,50**	**4 à 5 ans**	**LOGIRENE TRIATEC Fenofibrate**	**U**	
MP0500189	**F,55**	**31 mois**	**MOPRAL PREVISCAN COTAREG VIOXX**	D	**HTAP post-embolique**
S02001877	**F,55**	**1 an**	**TERALITHE ALDACTONE LASILIX LESCOL PREVISCAN LIPANTHYL, LIPUR GLUCOPHAGE…**		
TO040278	**F,36**	**2 ans**		B	**HTAP post-capillaire**
S02001046	**F,59**	**9.5 ans**	**CAPTEA LOPRIL**	U	

HUMORYL PRAXINOR PROGYNOVA UTROGESTAN

COXIBS : L'EMEA LÉNIFIANTE

L'Agence européenne du médicament (EMEA) avait annoncé un réexamen des données de l'ensemble des coxibs pour janvier 2005 ; les conclusions ont été finalement rendues publiques fin juin 2005 (1,2). Selon l'EMEA, « *la balance bénéfices-risques reste positive pour ces inhibiteurs de la Cox-2 quand ils sont prescrits en accord avec les contre-indications et précautions d'emploi* », sauf pour le *valdécoxib* (Bextra°, jamais commercialisé en France), qui n'est plus autorisé sur le marché (2).

Une nouvelle contre-indication en cas de maladie artérielle périphérique s'ajoute à la liste précédente : angor, infarctus du myocarde, insuffisance cardiaque, antécédent d'accident vasculaire cérébral ou d'accident ischémique transitoire.

Au 21 juillet 2005, l'EMEA n'a publié aucune synthèse résumant les données étayant sa position.

Ces demi-mesures confirment que, pour l'EMEA, l'intérêt des firmes passe avant l'intérêt des patients, qui restent exposés aux dangers de médicaments qui n'apportent aucun progrès thérapeutique (3).

1- Prescrire Rédaction "Coxibs et risques cardiovasculaires (suite)" *Rev Prescrire* 2005 ; **25** (258) : 109.
2- European Medicines Agency "Press release : European medicines agency concludes action on COX-2 inhibitors + Questions and answers on COX-2 inhibitors" 27 juin 2005. Site internet http://www.emea.eu.int consulté le 7 juillet 2005 (sortie papier disponible : 5 pages).
3- Prescrire Rédaction "Le célécoxib encore sur le marché : au profit de qui ?" *Rev Prescrire* 2005 ; **25** (263) : 512-513.

GABAPENTINE : RISQUE SUICIDAIRE ?

En mai 2005, un réseau de pharmacovigilance allemand a mis en garde quant à l'apparition d'idées suicidaires sous *gabapentine* (Neurontin° ou autre) (1). Une observation d'épisodes répétitifs d'idées suicidaires de survenue brutale, pouvant durer 10 minutes, a été signalée à ce centre, chez une femme de 63 ans prenant de la *gabapentine* pour des douleurs neuropathiques (1). Ces symptômes ont duré pendant plus de 2 ans et demi avant que le rôle de la *gabapentine* soit évoqué.

Selon le résumé des caractéristiques (RCP) étatsunien, dans des essais cliniques comparatifs chez des enfants de 3 ans à 12 ans, la fréquence de la labilité émotionnelle a été 6 % sous *gabapentine* versus 1,3 % sous placebo, celle de l'hostilité 5,2 % versus 1,3 %, celles des "troubles de la pensée" 1,7 % versus aucun cas sous placebo (2).

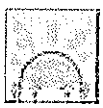
Au cours des essais dans les névralgies postzostériennes, des pensées anormales ont été rapportées chez 2,7 % des patients sous *gabapentine* versus aucun sous placebo (2).

La Food and Drug Administration étatsunienne a reçu 17 notifications de décès par suicide sous *gabapentine*, entre janvier et juin 2003 (3).

En pratique, la surveillance des effets indésirables psychiques chez les patients sous *gabapentine* est souhaitable.

1- "Suizidalität unter Gabapentin (Neurontin u.a.)" *Arznei-Telegramm* 2005 ; **36** (5) : 50-51.
2- "Neurontin°". In : "Physicians' Desk Reference" Thomson-PDR, Montvale 2005 : 2589-2593.
3- Altman K "Citizen petition to request addition of postmarketing suicide reports to the Neurontin (Pfizer/Parke-Davis) labeling" 17 mai 2004 : 14 pages.

VÉRALIPRIDE : RETRAIT DU MARCHÉ EN ESPAGNE



Fin mai 2005, l'Agence espagnole du médicament a annoncé le retrait du marché du *véralipride* (Agréal°), qui a pris effet le 15 juin 2005 (1).

Le *véralipride* est en fait un neuroleptique (voisin du *sulpiride* (Dogmatil° ou autre)), commercialisé en France, comme il l'était en Espagne, pour le traitement symptomatique des bouffées de chaleur de la ménopause.

Des troubles psychiatriques, parfois graves, ont été notifiés en Espagne : dépression, anxiété, symptômes de sevrage. S'y ajoutent des troubles neurologiques : dyskinésies, troubles extrapyramidaux, syndromes parkinsoniens ; de tels effets indésirables ont aussi été observés en France, y compris des dyskinésies tardives (2).

La mise en évidence récente des effets indésirables, notamment cardiovasculaires et de cancer du sein, des traitements hormonaux substitutifs de la ménopause, ne doit pas être l'occasion d'utiliser des médicaments dont la balance bénéfices-risques est, elle aussi, défavorable.

1- Agencia española del medicamento "Suspensión de comercialización de veraliprida (Agreal°) (efectiva el 15 de junio 2005)" 20 mai 2005. Site internet http://www.agemed.es consulté le 30 juin 2005 (sortie papier disponible : 2 pages).
2- Prescrire Rédaction "Effets indésirables extrapyramidaux du véralipride" *Rev Prescrire* 2004 ; **24** (255) : 750.

BENFLUOREX INTERDIT EN ESPAGNE

En juin 2005, l'Agence espagnole du médicament a annoncé une interdiction de préparations magistrales à base de divers produits amaigrissants, dont le *benfluorex* (Mediator°) (1).

Le *benfluorex* est commercialisé en France, comme traitement adjuvant des hypertriglycéridémies et du diabète avec surcharge pondérale, sans preuve d'efficacité clinique en terme de morbimortalité (2,3). C'est un dérivé de la *fenfluramine* (ex-Pondéral°) et de la *dexfenfluramine* (ex-Isoméride°), deux anorexigènes amphétaminiques retirés du marché du fait d'effets indésirables graves : hypertensions artérielles pulmonaires et valvulopathies cardiaques.

Une observation de valvulopathies multiples sous *benfluorex*, ayant conduit à la pose de prothèses mitrale et aortique chez une femme de 50 ans, a été publiée en Espagne en 2003 (1,2). Les lésions histologiques valvulaires étaient du même type que celles observées avec d'autres anorexigènes tels que la *fenfluramine* ou la *dexfenfluramine*. L'autorisation de mise sur le marché du *benfluorex* a été retirée en Espagne le 28 mars 2003.

Les autorités françaises seraient bien avisées de suivre l'exemple de l'Espagne.

1- Agencia española de medicamentos y productos sanitarios "Prohibición de formulas magistrales con productos anorexígenos y estimulantes del sistema nervioso central : benfluorex, prolintano, pemolina, fenilpropanolamina y tiratricol" 30 juin 2005. Site internet http://agemed.es consulté le 10 juillet 2005 (sortie papier disponible : 3 pages).
2- Prescrire Rédaction "Les amphétaminiques cachés : du sevrage tabagique au diabète" *Rev Prescrire* 2003 ; **23** (243) : 677-679.
3- Prescrire Rédaction "La saga des anorexigènes amphétaminiques" *Rev Prescrire* 2003 ; **23** (243) : 672-676.

Annexe 3-69

DIRECTION DE L'EVALUATION DES MÉDICAMENTS ET DES PRODUITS BIOLOGIQUES

Unité de Pharmacovigilance
Dossier suivi par Céline Dos Santos et Béatrice Porokhov

Saint-Denis, le 05 septembre 2005

Note pour Monsieur Jean MARIMBERT
Directeur Général de l'AFSSaPS

Objet : Eléments de réponse à l'article de PRESCRIRE concernant la spécialité MEDIATOR® (benfluorex)

MEDIATOR® (chlorhydrate de benfluorex), classe des amphétamines, a obtenu une AMM lors d'une procédure nationale en 1974, modifiée en 1987. Les indications acuelles sont :

- adjuvant du régime adapté dans les hypertriglycéridémies ;
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Ce médicament est commercialisé en France depuis 1976, par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés, dosés à 150 mg.

En France, une mise au point des effets indésirables au Comité Technique du 11 juillet 1995 a conduit à une restriction de délivrance du produit classant le benfluorex comme une substance interdite dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes par crainte de mésusage.
Une présentation sur les données de cinétique et de ventes est faite au Comité Technique de Pharmacovigilance du 10 septembre 1998.
Une enquête officielle est mise en place lors du Comité Technique du 17 décembre 1998 et les résultats de celle-ci sont présentés en Comité Technique le 20 juillet 1999.
Cette enquête a entraîné des modifications de la rubrique « effets indésirables » du Résumé des Caractéristiques du Produit.

En décembre 2004 la notification de plusieurs cas d'effets indésirables pouvant évoquer un effet de type amphétaminique avec MEDIATOR®, a conduit à une actualisation des données relatives aux troubles neuro-psychiatriques observés avec cette spécialité pharmaceutique.
Par ailleurs, la notification d'un cas d'hypertension artérielle pulmonaire rapportée lors du Comité Technique du 8 mars 2005, a entraîné une extension de l'enquête aux hypertensions artérielles pulmonaires (HTAP).
Les résultats de l'actualisation de cette enquête officielle, présentés par le CRPV de Besançon en Comité Technique de Pharmacovigilance le 07 juin 2005 sont :
Neuf cas graves de troubles neuro-psychiatriques ont été rapportés pendant le traitement : confusion (4), désorientation temporo-spatiale (3), bouffées délirantes aiguës (2). Dix notifications de syndromes de sevrage ont été rapportées dont 3 graves ainsi que 2 cas d'abus, un sans effet indésirable et l'autre présentant un excitation lors du sevrage.

Onze cas d'hypertension artérielle pulmonaire ont été notifiés. Seuls deux cas ont été retenus comme étant d'allure primitive, non associés à la prise d'anorexigènes et/ou à des antécédents d'embolie pulmonaire ou de valvulopathie. Le taux de notification est donc très faible correspondant à 1 cas pour 55 346 666 boites vendues, soit 1 cas pour 22 757 675 mois de traitement.

En ce qui concerne le reste de l'Europe, MEDIATOR® est toujours commercialisé en Grèce, au Luxembourg et au Portugal.
En Italie, lors du programme de réévaluation des produits anciens en juillet 2003, la firme s'est retirée devant l'importance des données complémentaires requises.
En Espagne, le titulaire de l'AMM n'a pas demandé le renouvellement de l'AMM en 2003.

Les résultats de l'actualisation de cette enquête officielle seront présentés lors de la Commission Nationale de Pharmacovigilance de novembre 2005.

Prescrire EN QUESTIONS

L'Agence française des produits de santé est-elle avant tout au service des patients, ou au service des firmes pharmaceutiques ?

Le numéro de septembre de votre revue, et tout particulièrement l'éditorial intitulé « le mot de Gaspard » comporte un certain nombre d'affirmations et d'insinuations qui relèvent du procès d'intention et mettent gravement en cause tant la qualité du travail de l'Afssaps au service de la santé publique que l'honneur professionnel et les motivations de service public des agents et experts participant à l'évaluation des médicaments et à la prise de décision qui en découle.

La gravité de ces imputations développées selon des procédés qui ne sont pas à la hauteur d'un débat de santé publique comme des règles du débat scientifique, me conduit à exercer auprès de vous le droit de réponse en application de l'article 13 de la loi du 29 juillet 1881.

L'éditorial met en avant le cas de 4 produits ou groupes de produits dont au moins un, celui du Di-Antalvic®, n'est assorti d'aucune argumentation de fond faisant écho à celle que l'Agence a exprimée au soutien de sa position récente, et semble avoir été ajouté en « dernière minute », comme pour faire masse dans le tableau qu'entendait dresser le rédacteur.

Amalgame. *Par l'effet d'un amalgame, l'éditorial distille l'image d'une Agence dont les décisions seraient marquées ou tout le moins inhibées par le souci de ménager les ventes des laboratoires pharmaceutiques.*

Ne reculant devant aucun paradoxe pour nourrir cette vision, l'éditorial et l'article auquel il renvoie sur ce point vont jusqu'à présenter la décision de l'Agence sur l'arrêt de commercialisation des antibiotiques locaux par voie orale comme une illustration de sa pusillanimité et de sa complaisance supposées vis-à-vis des firmes concernées ! Comme le sens même de cette décision peut difficilement passer par une bonne manière faite aux firmes, le rédacteur croit pouvoir trouver des indices de la « faiblesse » de l'Agence dans la répartition entre les deux vagues de retrait de 2003 et 2005 et dans le délai d'instruction de cette décision par vague. Sur le premier point, l'Agence a explicitement formulé au moment de la première vague le critère de santé publique qui l'avait conduite à traiter en priorité le cas des produits susceptibles de présenter le plus de risques pour les patients parce que contenant des antibiotiques également administrés par voie générale, ce qui n'est pas le cas du Locabiotal® cité comme exemple par l'article. Quant au délai, les laboratoires pharmaceutiques peuvent, comme il se doit dans un État de droit, faire valoir leur point de vue en invoquant de nouveaux arguments et en produisant des études. En l'absence de risque immédiat pour la santé des patients, ces argumentations successives ont été examinées dans les règles du débat scientifique contradictoire par le groupe de travail compétent et la commission d'AMM. Cela n'a pas emporté la conviction de l'Agence ni entamé sa détermination de faire cesser la consommation de ces antibiotiques au nom d'un raisonnement de santé publique qui a d'ailleurs été salué par nombre de consommateurs impartiaux et peu suspects de complaisance chronique à l'égard des autorités sanitaires.

Di-Antalvic®. *S'agissant du Di-Antalvic®, l'Agence récuse tout automatisme selon lequel l'appréciation portée par une autre autorité nationale devrait la conduire à prendre une décision similaire sans évaluer sa pertinence dans le contexte sanitaire français. Et elle s'est expliquée clairement sur les raisons qui l'ont conduite à tenir ses propres conclusions sur la base des données relatives à l'utilisation de ces médicaments en France (cf. communiqué de presse du 28 juillet 2005 disponible sur le site internet de l'Agence).*

Agréal®. *S'agissant des deux produits retirés par l'Agence espagnole en 2003, je précise tout d'abord que pour la spécialité Agréal® (véralipride), l'Afssaps a lancé une enquête de pharmacovigilance en février 2005 et que la commission d'AMM a donné le 21 juillet dernier un avis favorable au maintien de l'AMM sous réserve d'une série de modifications du RCP (durée du traitement limitée à 3 mois, contre-indication de l'association aux neuroleptiques, antipsychotiques et anti-émétiques, mises en garde renforcées sur les risques de dyskinésies et de syndrome parkinsonien exigeant l'arrêt du traitement, mention de la possible survenue de troubles de l'humeur et d'anxiété, notamment entre deux cures ou à l'arrêt du traitement).*

Mediator®. *En ce qui concerne Mediator® (benfluorex), la notification en décembre 2004 de plusieurs cas d'effets indésirables pouvant évoquer un effet de type amphétaminique a conduit l'Agence à actualiser les données relatives aux troubles neuro-psychiatriques observés avec cette spécialité. Les résultats de l'enquête étendus dans l'intervalle aux hypertensions artérielles pulmonaires, ont été examinés par le Comité technique de pharmacovigilance en juin dernier et font ressortir des taux d'incidents notifiés très faibles, de l'ordre de 1 cas pour 55 millions de boîtes vendues en ce qui concerne les cas retenus d'hypertension artérielle pulmonaire. Ces résultats seront soumis en novembre prochain à la Commission nationale de pharmacovigilance.*

Coxibs. *Enfin, comment ne pas réagir à l'affirmation lapidaire selon laquelle l'Agence aurait « veillé à ne diffuser qu'au compte-gouttes » l'information sur les risques des coxibs. Le rédacteur semble ne pas avoir remarqué que c'est l'Afssaps qui a demandé à la mi-2002 une réévaluation à l'échelon européen. Il ne semble* ▷▷

pas non plus avoir gardé en mémoire les messages d'information et de mise en garde publiés par l'Agence entre juillet 2002 et aujourd'hui : pas moins d'une dizaine de communiqués, cinq lettres aux professionnels de santé et trois mises au point ou questions/réponses.

Secret. *Enfin, s'il est exact que la tradition pharmaceutique est fortement marquée par des préoccupations de secret et de confidentialité qui ont eu des répercussions sur le fonctionnement des agences compétentes dans le monde entier, l'Afssaps se prépare activement à la mise en oeuvre des nouvelles obligations de la Directive européenne de 2004. L'Afssaps avait en partie anticipé ces nouvelles obligations de transparence en commençant à publier des rapports publics d'évaluation, volontairement synthétiques pour être accessibles à un public éclairé mais pas nécessairement spécialiste.*

Ces obligations de transparence constitueront dans toute l'Europe un progrès. Elles ne changeront rien aux priorités de fond de l'Agence, exprimées notamment au travers de son projet d'établissement rendu public au printemps 2004, et sous-tendues par le souci d'assurer aux patients la satisfaction de leurs besoins thérapeutiques dans les meilleures conditions de sécurité. On trouve notamment parmi les axes de travail principaux le développement de l'effort déjà bien amorcé pour développer en continu l'information émanant de l'Afssaps sur les produits de santé, leurs effets et leur bon usage.

Ainsi, l'Agence travaille « au grand jour » au service de la santé publique et des patients. Elle ne se considère pas pour autant comme seule détentrice et émettrice d'une information pertinente sur le médicament, dont l'évaluation est par nature un processus évolutif, qui appelle pluralisme de l'expertise et contradiction. C'est dans cet esprit que beaucoup de ses agents et responsables savent être attentifs aux analyses d'une revue comme Prescrire. Ils pourront le rester pour peu qu'ils y trouvent en retour l'écho d'une décision prise sur la base d'un travail scientifique de qualité, et en tout cas qu'ils y lisent autre chose qu'une mise en cause systématique de leur volonté de servir la cause des patients et de la santé publique.

Jean Marimbert
Directeur général de l'Agence française de sécurité sanitaire des produits de santé

« *L'Afssaps au service de la santé publique* », « *les motivations de service public des agents et experts participant à l'évaluation des médicaments et à la prise de décision qui en découle* » : c'est bien là en effet que les résultats de l'action de l'Agence sont attendus par les citoyens, les patients, et les professionnels de santé.

Dextropropoxyphène + paracétamol. Des données d'évaluation ont été rappelées par la *revue Prescrire* : l'association *dextropropoxyphène + paracétamol* est illogique du point de vue pharmacologique (du fait de la grande différence de demi-vie d'élimination plasmatique entre les deux composants) ; l'évaluation clinique comparative n'a pas démontré de supériorité de l'association sur le *paracétamol* seul ; au Royaume-Uni, des centaines de morts chaque année par intoxication sont recensées (la toxicité du *dextropropoxyphène* s'ajoutant à celle du *paracétamol*), dont 20 % n'ont pas lieu dans un contexte d'intoxication volontaire, et ce malgré la limitation des conditionnements à 20 unités de prise, comme en France ; le constat est de même nature en Suède, des restrictions de conditions de prescription n'ont pas réglé le problème, et le retrait du marché est programmé là aussi ; discrètement mais efficacement, les autorités suisses ont retiré l'association en 2003 (1à5).

En somme, voilà un médicament pas plus efficace que le *paracétamol* mais plus dangereux : la balance bénéfices-risques est défavorable, sans ambiguïté.

Dans ces conditions, les données cliniques françaises devraient être fort probantes pour faire pencher la balance dans l'autre sens. Quelles sont-elles ? Au 30 septembre 2005, l'étude effectuée à partir des données des Centres antipoison mise en avant par le Directeur général de l'Afssaps n'est toujours pas publiée en détail. On ne sait pas combien de décès ont été étudiés en l'absence de contexte évident d'intoxication, en particulier chez les personnes âgées, qui sont nombreuses à être amenées à prendre cet antalgique banal, et sont aussi parmi les plus à risque de surdosage involontaire (par ralentissement de l'élimination du médicament). Combien de décès de patients âgés traités par *dextropropoxyphène* ont paru de cause « *naturelle* » ou ont été imputés à une affection cardiaque, sans que soit effectué un dosage sanguin de *dextropropoxyphène* ?

Surtout, quand bien même le résultat de cette étude serait exempt de toute sous-estimation, comment justifier ces 7 morts par an pour un médicament qui n'a pas d'avantage démontré sur l'antalgique de premier choix, le *paracétamol* ?

Où est le service public rendu quand les autorités laissent la population exposée aux risques avérés d'un médicament qui n'apporte aucun progrès thérapeutique ?

Véralipride. Au sujet de l'efficacité de ce neuroleptique en traitement des bouffées de chaleur de la ménopause, le résumé des caractéristiques (RCP) version dictionnaire Vidal 2005 reste laconique, faisant allusion à des propriétés in vitro, sans aucune donnée clinique (6). Le Martindale, ouvrage de référence en pharmacologie clinique, constate que le *véralipride* a été « *essayé* », sans mentionner de résultat probant (7). Le RCP version dictionnaire Vidal 1983 indique déjà que les effets indésirables sont « *ceux d'un neuroleptique* » (8). Le risque de troubles assez intenses pour motiver une dopathérapie au long cours est établi aussi (9). Les données et la décision espagnoles confirment que la balance bénéfices-risques du *véralipride* dans cette situation est suffisamment défavorable pour justifier le retrait du marché (10).

Dans ces conditions, quels résultats d'enquête de pharmacovigilance pourraient faire pencher la balance dans l'autre sens ? Quels changements du RCP pourraient supprimer tout risque de syndrome extrapyramidal, mentionné clairement par le RCP depuis plus de 20 ans ?

Où est le service public rendu quand les autorités laissent la population exposée aux risques avérés d'un médicament qui n'apporte aucun progrès thérapeutique ?

Benfluorex. Le *benfluorex* est un anorexigène amphétaminique (11). Il a été mis sur le marché français en 1976, « *proposé dans les hypercholestérolémies et hypertriglycéridémies* » et « *le diabète asymptomatique* », « *proposé dans* » signifiant que « *les indications thérapeutiques n'ont pu être mises en évidence par des essais cli-*

niques » (12). Près de 30 ans plus tard, son RCP version dictionnaire Vidal 2005 mentionne toujours que « *l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée* » (13). Les anorexigènes amphétaminiques sont impliqués dans la survenue d'hypertensions artérielles pulmonaires graves depuis la fin des années 1960 (14). Les risques de valvulopathies sont établis depuis la fin des années 1990 (14). Le *benfluorex* a été impliqué dans la survenue d'une valvulopathie motivant une chirurgie cardiaque (11,14). Les décisions espagnoles de 2003 et de 2005 confirment que la balance bénéfices-risques du *benfluorex* est assez défavorable pour justifier le retrait du marché et l'interdiction de préparations magistrales (15).

Dans ces conditions, quels résultats d'enquête de pharmacovigilance, même si elle incluait les valvulopathies qui ne sont pas évoquées par le Directeur général de l'Afssaps, pourraient faire pencher la balance dans l'autre sens ?

Où est le service public rendu quand les autorités laissent la population exposée aux risques avérés d'un médicament qui n'apporte aucun progrès thérapeutique ?

Coxibs. Les premières données cardiovasculaires inquiétantes de l'essai Vigor concernant le *rofécoxib* ont été publiées au printemps 2000 ; la *revue Prescrire* en a fait état en juillet 2000 (16). Des données détaillées ont été rendues publiques par la Food and Drug Administration en février 2001, de même que des données permettant de mettre à jour les manipulations des résultats de l'"essai Class" concernant le *célécoxib* (17). Le premier communiqué de presse de l'Afssaps concernant ces deux coxibs date d'août 2001 (18). C'est deux ans après les premiers signaux publiés que l'Afssaps a demandé une réévaluation au niveau européen fin juin 2002, demande que la *revue Prescrire* a signalée dans son numéro de septembre 2002 (19). L'Afssaps elle-même n'avait publié aucun rapport d'évaluation au moment de l'octroi d'AMM. Au 30 septembre 2005, l'Afssaps n'a pas publié de données françaises de pharmacovigilance détaillées concernant ces coxibs, ni d'estimation de l'incidence des dégâts cardiovasculaires du *rofécoxib* en France. Alors que l'essai APPROVe (mis en avant par la firme Merck Sharp et Dohme-Chibret pour justifier le retrait mondial du marché en 2004) s'est déroulé en partie en France, l'Afssaps a communiqué encore moins de données à ce sujet que l'Agence britannique (20,21,22).

Opacité. *Dextropropoxyphène, véralipride, benfluorex* : persévérant dans ses habitudes, l'Afssaps n'a publié aucun compte rendu des études évoquées par son Directeur général. Le rapport annuel 2004 de l'Afssaps fait état de 2 940 rapports périodiques de surveillance des effets indésirables d'un médicament (PSUR) transmis à l'Agence française, 43 dossiers présentés au Comité technique de pharmacovigilance, 18 dossiers présentés en Commission nationale de pharmacovigilance : elle n'en a rendu aucun public (23).

Alors que les déclarations de liens d'intérêts des experts sollicités par l'Afssaps occupent des dizaines et des dizaines de pages en annexe du bilan annuel d'activité 2004, l'Afssaps n'a publié aucun compte rendu de réunion de Commission d'AMM ni de pharmacovigilance, pas même de simple liste des participants ni d'ordre du jour qui permettraient à chacun de vérifier que les experts en situation de conflits d'intérêts sont exclus des réunions (24).

Est-ce cela travailler « *au grand jour* » ?

Lenteur. La *revue Prescrire* signale et salue des travaux et décisions de l'Agence qui vont dans le sens du service public, ainsi par exemple, et pour s'en tenir à 2005, en ce qui concerne la matériovigilance, la cosmétovigilance, les commercialisations sans AMM, les modifications de RCP motivées par la pharmacovigilance, le conditionnement des médicaments (25à31). Mais ce qui frappe en général dans ces décisions, c'est une lenteur impressionnante.

Ainsi, en septembre 2005, le Directeur général a annoncé le retrait du marché de plusieurs "immunostimulants", effectif fin octobre 2005 (lire dans ce numéro page 747). C'est une mesure très bienvenue. La *revue Prescrire* avait rendu compte en novembre 2001 de la présentation par le Centre régional de pharmacovigilance de Saint-Étienne de l'enquête de pharmacovigilance menée à ce sujet sur les notifications effectuées en France jusqu'en 1998, enquête qui montrait le risque d'effets indésirables rares mais graves (32).

Mais, alors que ces médicaments n'étaient pas plus efficaces qu'un placebo, comment expliquer que le retrait du marché soit annoncé 7 ans après les dernières notifications prises en compte par l'enquête, et 4 ans après les résultats de l'enquête ?

Dans le cas des antibiotiques locaux pris par voie orale, pourquoi avoir mis à part les quelques antibiotiques non utilisés par voie générale, alors qu'ils correspondent à seulement 12 spécialités, si ce n'est pour laisser un sursis supplémentaire aux firmes concernées ? Quel délai fallait-il accorder encore à celles-ci alors que par exemple Locabiotal° figurait déjà dans la liste des médicaments à service médical rendu insuffisant publiée en juin 2001 par la Commission de la transparence (33) ?

Au service de qui ? Dans chacun de ces exemples récents, le premier bénéficiaire de la lenteur excessive de l'Afssaps, de sa pusillanimité et de son opacité, c'est la firme pharmaceutique qui commercialise le médicament en cause, et dont les ventes continuent. Les premières victimes, ce sont les patients, qui restent exposés aux effets indésirables avérés de médicaments qui n'apportent aucun progrès thérapeutique ; viennent ensuite les soignants mal informés, et, parmi les personnels de l'Afssaps, ceux qui ont une réelle motivation de service public mais voient, au final, leurs efforts servir d'abord les intérêts particuliers de firmes pharmaceutiques qui repoussent durant des années les décisions qui leur sont défavorables, même quand ces décisions sont justifiées par la santé publique.

Dans un État de droit, l'Agence du médicament n'a pas à se laisser imposer les vues des lobbies industriels, ni celles des commissions consultatives d'experts, parfois sous influence, souvent timorés. La décision finale, au service du public, peut être contraire à celle suggérée par des commissions mal avisées. Ainsi au printemps 2005, une commission d'experts réunie par la FDA s'est prononcée notamment pour le maintien sur le marché du *valdécoxib* ; experts dont bon nombre avaient des liens financiers avec les firmes détenant des AMM pour des coxibs ; la FDA a cependant décidé du retrait de ce coxib (34). ▶▶

Prescrire EN QUESTIONS

Changer résolument. Une agence réellement au service premier de la santé publique et soucieuse du droit a tout intérêt à appliquer, dès le 30 octobre 2005, la Directive 2004/27/CE (transposée ou non en droit national) et notamment son article 126 ter : « *En outre, les États membres veillent à ce que l'autorité compétente rende accessibles au public son règlement interne et celui de ses comités, l'ordre du jour de ses réunions, les comptes rendus de ses réunions, assortis des décisions prises, des détails des votes et des explications de vote, y compris les opinions minoritaires* ». C'est une opportunité exceptionnelle de montrer sans ambiguïté que l'on œuvre pour une Agence qui choisit fermement le service aux patients, qui travaille visiblement pour eux, sans faux-semblants, opacités ni lenteurs qui profitent d'abord aux firmes les plus influentes. Et à long terme, cette exigence de règles du jeu claires est l'intérêt bien compris des firmes autant que des patients.

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22- Prescrire Rédaction "Coxibs, suite : demi-mesures et maintien sur le marché" *Rev Prescrire* 2005 ; **25** (260) : 281.
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30- Prescrire Rédaction "Quelques mesures de pharmacovigilance qui vont dans le bon sens" *Rev Prescrire* 2005 ; **25** (258) : 143-145.
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Texte complet sur www.prescrire.org
(ou sur demande à la revue Prescrire)

Prévention du BAA : quelle stratégie dans les "pays démunis" ?

Dans les pays démunis, l'incidence du staphylocoque doré résistant à la méticilline et des infections nosocomiales reste élevée. Il existe donc un problème de traiter les infections à staphylocoque doré résistant à la méticilline, dès lors que les signes cliniques sont en faveur d'une origine à staphylocoque doré et que les conditions locales le justifient (1 page + références).

Annexe 3-70

Direction de l'Evaluation
des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 31 janvier 2006

COMMISSION NATIONALE DE PHARMACOVIGILANCE
(Procès-verbal de la réunion du mardi 29 novembre 2005)

Etaient présents :

M. CARON (président),
M. ANDREJAK (vice-président),
Mme AUTRET-LECA, Mme BARBAUD, M. BONNETERRE, M. BOULU, Mme BRUNET, M. CARLIER, Mme COSTAGLIOLA, M. DOUARD, M. ESCHALIER, M. BENICHOU (suppléant de Mme FOURRIER-REGLAT), M. GIROUD, M. HANSLIK, M. IMBS, M. JACQUES, Mme JEAN-PASTOR (suppléante de Mme JOLLIET), Mme JOUAN-FLAHAULT, M. LAGIER, Mme LAINE-CESSAC, Mme LEMER-MALLE, M. LIOTE, M. MERLE, M. MONTASTRUC, M. MUNERA, M. PELLETIER, M. SCHMITT, Mme SGRO, M. VIAL
Mme GUYOT (Représentant la Direction Générale de la Santé)
Mme CASTOT (Représentant le Directeur général de l'Agence Française de Sécurité Sanitaire des Produits de Santé).

Déclaration publique d'intérêts :

M. BOULU, ayant un conflit d'intérêts majeur avec les laboratoires SANOFI-AVENTIS, est sorti de la séance lors du traitement du dossier concernant l'enquête officielle relative aux atteintes hépatiques sous chloroquine et/ou proguanil

LABORATOIRES :

ASTRA ZENECA

Enquête officielle relative aux atteintes hépatiques sous chloroquine et / ou proguanil

GLAXO SMITH KLINE

Enquête officielle relative aux atteintes hépatiques sous chloroquine et / ou proguanil

JANSSEN CILAG

Enquête officielle relative aux effets indésirables neurologiques observés avec la spécialité VESADOL® (halopéridol, buzépide métiodure)

Résurgences de délires / échecs thérapeutiques sous RISPERDAL CONSTA® (rispéridone)

SANOFI AVENTIS

Enquête officielle relative aux atteintes hépatiques sous chloroquine et / ou proguanil

SERVIER

Enquête officielle relative aux hypertensions artérielles pulmonaires et aux troubles neuro-psychiatriques observés avec MEDIATOR® (benfluorex)

WYETH LEDERLE

Suivi national intensif et enquête de pharmacovigilance relatifs aux effets indésirables observés avec PREVENAR® (vaccin conjugué pneumococcique heptavalent)

Annexe 3-70

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ANNEXES 16

I – ADOPTION DU PROCES-VERBAL DE LA SEANCE DU MARDI 27 SEPTEMBRE 2005

Le procès-verbal de la séance du mardi 27 septembre 2005 a été adopté sans modification.

II - ENQUETE OFFICIELLE RELATIVE AUX HYPERTENSIONS ARTERIELLES PULMONAIRES ET AUX TROUBLES NEURO-PSYCHIATRIQUES OBSERVES AVEC MEDIATOR® (BENFLUOREX).

Lors du Comité Technique de Pharmacovigilance du 7 décembre 2004, plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique ont été rapportées avec MEDIATOR® (benfluorex). Une actualisation des données relatives aux troubles neuro-psychiatriques observés avec cette spécialité pharmaceutique a alors été décidée. Par la suite, du fait d'une notification d'un cas d'hypertension artérielle pulmonaire associée à la prise de MEDIATOR® rapportée lors du Comité Technique du 8 mars 2005, l'enquête menée par le CRPV de BESANCON a été étendue aux hypertensions artérielles pulmonaires.
MEDIATOR® est commercialisé en France depuis 1976 par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés dosés à 150 mg.
Ses indications sont :
- adjuvant du régime adapté dans les hypertriglycéridémies ;
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

HISTORIQUE

Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables de ces produits et étant donné les restrictions de leur délivrance, le Comité Technique de Pharmacovigilance a craint une dérive de l'utilisation du benfluorex comme anorexigène. Ainsi, le benfluorex a été inscrit sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes le 10 mai 1995.

Le dossier relatif aux effets indésirables du benfluorex a été présenté lors de différentes réunions du Comité Technique de Pharmacovigilance en 1998 et au groupe de travail européen de Pharmacovigilance le 30 novembre 2000, entraînant les modifications de la rubrique « effets indésirables » du Résumé des Caractéristiques du Produit (RCP) (ajout des effets indésirables en *italique* ci-dessous) :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, *confusion*, somnolence, état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles ;
- *très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke ;*
- *élévation des enzymes hépatiques, hépatite (très rare).*

RESULTATS DE L'ENQUETE

1.Troubles neuro-psychiatriques

A. Troubles psychiatriques pendant le traitement

Trente cinq cas ont été rapportés dont 10 déclarés depuis l'enquête présentée en juillet 1999. Ils concernent 18 hommes (âge moyen : 58,5 ans) et 17 femmes (âge moyen : 60 ans).

Les troubles psychiatriques sont variés :
- agressivité (4), nervosité (3), irritabilité (1) ;
- cauchemars (2), angoisse (1), stupeur (1), dépression (1) ;
- désorientation (7), confusion (5), aggravation des troubles cognitifs (1) ;
- agitation (3), troubles du comportement (3) ;
- délire (2), bouffées délirantes aiguës (1).

Les cas graves ayant nécessité une hospitalisation sont :
- 4 cas de confusion (dont un provenant de la littérature) chez des patients ayant des traitements associés ;
- 3 cas de désorientation temporo-spatiale ;
- 2 cas de bouffées délirantes aiguës, avec d'autres troubles associés, d'évolution rapidement favorable après traitement symptomatique par neuroleptiques.

B. Troubles psychiatriques au sevrage

Dix notifications de troubles psychiatriques apparaissant lors du sevrage ont été rapportés. Ils concernent 2 hommes de 27 et 34 ans et 8 femmes de 30 à 65 ans (âge moyen : 45,25 ans).

Le délai d'apparition des troubles après l'arrêt du MEDIATOR® est très variable : de 1 jour (après un traitement de 8 ans) à 3 semaines (après un traitement de 4 mois, 6 mois ou 15 mois).
La durée de traitement par MEDIATOR® est très variable : de 1 mois à 8 ans.

Trois cas ont nécessité une hospitalisation chez des femmes ayant par ailleurs des antécédents de troubles psychiatriques. Une évolution favorable a été constatée dans un des cas après traitement symptomatique par neuroleptiques, les deux autres cas sont d'évolution inconnue.

C. Autres troubles neurologiques

Douze notifications ont été rapportées. Elles concernent 8 hommes et 4 femmes :
- 2 cas de convulsions d'évolution favorable ;
- 2 cas de neuropathie, chez deux patients diabétiques présentant de multiples autres étiologies possibles ;
- 7 cas de paresthésies, d'apparition rapide et d'évolution favorable en quelques heures, dont deux mésusages ;
- 1 cas de tremblement des mains.

D. Abus

Deux cas d'abus ont été rapportés :
- chez un homme augmentant les doses de MEDIATOR® à 10 comprimés par jour pendant 11 mois, sans effet indésirable associé ;
- chez un sportif, consommant (sur prescription médicale) des doses croissantes (1comprimé/semaine au début et jusqu'à 9 comprimés/jour) de MEDIATOR® comme « dopant » et présentant une excitation lors du sevrage.

2. Hypertension artérielle pulmonaire (HTAP) :

Dix-sept notifications dont 2 doublons ont été rapportées.

A. Notifications où MEDIATOR® est associé à un anorexigène :

Lors de la présentation du rapport MEDIATOR® en décembre 1998, 11 notifications d'«hypertension artérielle pulmonaire » avaient été rapportées (9 d'entre elles avaient été présentées lors de l'enquête « Anorexigènes et hypertensions artérielles pulmonaires » au Comité Technique du 28 avril 1995) :
- 7 ont été classées en HTAP idiopathique
- 3 en HTAP post-capillaire
- 1 en HTAP post-embolique

Le MEDIATOR® n'était jamais prescrit seul : il était associé à un ou plusieurs anorexigènes :
- ISOMERIDE® : 7 fois ;
- ISOMERIDE® + PONDERAL® : 2 fois ;
- ISOMERIDE ®+ FENPROPOREX® : 1 fois ;
- DININTEL® + TENUATE DOSPAN® + FRINGANOR® : 1 fois ;

La durée de traitement par MEDIATOR® était précisée dans 7 cas sur 11 et allait de plusieurs mois à 5 ans.

Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® était :
- concomitante dans 5 cas ;
- antérieure dans 2 cas ;
- postérieure dans 3 cas ;
- imprécise dans 1 cas.

Sur les 3 cas où la prise de MEDIATOR® était postérieure à la prise d'anorexigènes, 2 cas présentaient une dyspnée avant la prise de MEDIATOR, et un cas une double atteinte valvulaire aortique et mitrale.

B. Notifications où MEDIATOR® n'est pas associé à la prise d'un anorexigène

Six notifications ont été rapportées chez des femmes (dont 2 présentaient une HTAP post capillaire sur valvulopathie et une autre une HTAP sur embolie pulmonaire) n'ayant pas de traitement anorexigène associé. Il est à noter que l'un des cas rapportés est très succinct et ne peut, dans ces conditions, être retenu.

C. Incidence des cas notifiés

Depuis le début de la commercialisation de MEDIATOR®, le nombre de boites de 30 comprimés vendues est de : 110 693 331, correspondant à 45 515 349 mois de traitement (estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés).

Après élimination des HTAP post-emboliques (2) et post-capillaires (5), il reste 10 cas d'HTAP idiopathique soit :
- 1 cas notifié pour 11 069 333 boîtes vendues ;
- ou 1 cas notifié pour 4 551 534 mois de traitement.

Si on considère uniquement les diagnostics d'hypertension artérielle pulmonaire idiopathique en excluant les cas associés aux anorexigènes et les antécédents d'embolie pulmonaire et de valvulopathie, il reste 2 cas soit une incidence très faible de :
- 1 cas notifié pour 55 346 666 boîtes vendues ;
- 1 cas notifié pour 22 757 675 mois de traitement.

Conclusion du rapporteur :

Troubles neuro-psychiatriques : cette enquête confirme la réalité du risque de survenue de « confusions » en présence de Médiator®. Il est proposé que cet effet, déjà mentionné dans le RCP soit détaillé comme suit :
« troubles des fonctions cognitives : désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception : hallucinations. »

Hypertensions artérielles pulmonaires : compte-tenu de l'incidence des HTAP idiopathiques (1 à 2 de cas par million et par an), le nombre de cas d'HTAP idiopathique rapportés dans l'enquête ne constitue pas un signal significatif de toxicité du MEDIATOR® dans la classe organe cardio-vasculaire.

DISCUSSION

Les ventes de MEDIATOR® en Europe sont réalisées en quasi totalité en France. Les données DOREMA d'avril 2005 montrent une utilisation dans 46,3% dans les dyslipidémies, dans 33,5% dans le diabète, dans 9,6% dans l'obésité, dans 2,3% dans la régulation métabolique et dans 8,3% dans d'autres indications. L'effet anorexigène du benfluorex n'a pas été démontré. Toutefois, les membres de la Commission nationale craignent un mésusage, en particulier dans l'obésité. Dans ce contexte, une étude d'utilisation/ de prescription serait utile.
Il est à noter que le renouvellement quinquennal du produit intervient dans 2 ans et que des données d'efficacité dans le diabète de type 2 existent mais restent limitées et mériteraient d'être réévaluées.

Le bilan de pharmacovigilance confirme les données de sécurité d'emploi du MEDIATOR® déjà connues. Les effets neuro-psychiatriques décrits actuellement dans le RCP sous le terme « confusion » doivent être détaillés. Il n'y a pas actuellement assez de données pour affirmer l'existence de syndrome de sevrage. Le faible nombre de cas décrits d'HTAP idiopathique associées au MEDIATOR® doit être interprété par rapport à la sous-notification habituelle en pharmacovigilance.

Afin d'évaluer au mieux les risques potentiels de l'utilisation de MEDIATOR®, la Commission nationale de pharmacovigilance a demandé la réalisation de :
- une étude d'utilisation / prescription de MEDIATOR® ;
- une étude expérimentale sur un modèle animal permettant d'évaluer le potentiel de MEDIATOR® à engendrer des HTAP ;

- une étude au niveau des Centres d'évaluation et d'information sur la pharmacodépendance (CEIP) afin d'évaluer un éventuel problème de pharmacodépendance. A ce titre, une saisine de la Commission nationale des stupéfiants et psychotropes sera effectuée.

Enfin, il a été proposé d'étudier la possibilité d'interroger les registres d'HTAP existant dans 17 centres, afin de rechercher, dans une étude rétrospective cas-témoins, le rôle éventuel du benfluorex.

CONCLUSION

Devant les différentes questions posées par l'enquête de pharmacovigilance, plusieurs membres de la commission ont souhaité un réévaluation du rapport bénéfice/risque du produit. La Commission s'est prononcée en faveur de cette réévaluation par 13 voix pour, 10 voix contre et 5 abstentions.

III - SUIVI NATIONAL INTENSIF ET ENQUETE DE PHARMACOVIGILANCE RELATIFS AUX EFFETS INDESIRABLES OBSERVES AVEC PREVENAR® (VACCIN CONJUGUE PNEUMOCOCCIQUE HEPTAVALENT)

Conformément à l'avis du Conseil Supérieur d'Hygiène Publique de France (CSHPF) du 14 septembre 2001 relatif à la vaccination des enfants par le vaccin conjugué pneumococcique heptavalent Prévenar®, l'unité de Pharmacovigilance de l'Afssaps a confié au CRPV de Tours la coordination d'un suivi national intensif de pharmacovigilance de ce vaccin.

Méthodologie

Ce suivi était basé sur une sollicitation de l'ensemble des pédiatres libéraux français à notifier systématiquement durant 19 mois (28 février 2003 – 30 septembre 2004), tout effet indésirable grave et/ou inattendu post-vaccinal. Cette étude avait pour objectif la détection d'effets indésirables non encore identifiés pouvant modifier le rapport bénéfice/risque du Prévenar®.

Le 28 février 2003, un total de 2462 pédiatres français ont reçu de l'Afssaps une lettre présentant l'étude accompagnée d'une demande de participation. Seuls 349 (14%) d'entre eux ont renvoyé leur accord de participation. Plus de 91% de ces pédiatres (n=319) ont indiqué le nombre de vaccinations par Prévenar® et par jour qu'ils estimaient effectuer, soit un total de 274 511 actes vaccinaux pendant la période d'étude.

Le CRPV de Tours a présenté une analyse globale du suivi national intensif de pharmacovigilance et des cas de pharmacovigilance notifiés au réseau national des CRPV et à la firme entre le 2 avril 2001 (date de commercialisation du Prévenar® en France) et le 30 septembre 2004.

Résultats

La répartition des cas graves et inattendus non graves rapportés durant l'enquête de pharmacovigilance et le suivi national intensif est présenté dans le tableau ci-dessous :

	ENQUETE (02/04/2001 – 30/09/2004)	SUIVI NATIONAL INTENSIF (28/02/2003 – 30/09/2004)
Durée	3,5 ans	19 mois
N° cas graves ou jugés graves	107	24
N° cas inattendus non graves	46	8
Total cas graves ou inattendus non graves	153	32*

* Enfants âgés entre 2 et 28 mois (médiane :13 mois)

Par ailleurs, 340 cas non graves et attendus ont été notifiés.

L'incidence des notifications d'effets indésirables graves rapportés après administration de Prevenar® seul est de l'ordre de 5.5/ 100 000 actes vaccinaux [IC $_{95\%}$: 2.7 – 8.7] pour le suivi national et, de 2.5 [IC $_{95\%}$: 1.9 – 3.2] pour l'enquête.

L'incidence des effets indésirables attendus rapportés durant le suivi national et l'enquête, à savoir fièvre élevée (> 38°C), éruption cutanée, urticaire, œdème de Quincke, érythème polymorphe, convulsions fébriles ou non et hypotonie (pouvant être assimilée au syndrome d'hypotonie-hyporéactivité) est inférieure à celle mentionnée dans le Résumé des Caractéristiques du Produit (RCP).

Les effets indésirables inattendus étaient :
- une hypertonie isolée (5 cas dont 4 après Prévenar® seul) ;
- des cris anormaux (5 cas dont 1 après Prévenar® seul) ;
- un œdème aigu hémorragique (3 cas dont 1 après Prévenar® seul) ;
- un purpura vasculaire (3 cas) ;
- un purpura thrombopénique (3 cas) ;
- une érythrose palmo-plantaire (2 cas dont 1 après Prévenar® seul) ;

- un eczéma (2 cas) ;
- un abcès (1 cas) et une cellulite (1 cas).

Leur incidence est également inférieure à celle mentionnée dans l'article de Wise RP et Coll. relatif à l'analyse globale des données de pharmacovigilance du Prévenar® recueillies aux Etats-Unis durant deux années (JAMA, 2004; 292 : 1702-10).

Parmi les 10 cas d'infections invasives à pneumocoque rapportés durant le suivi national et l'enquête, le sérotype est non vaccinal ou inconnu dans 7 cas.

Dans le cadre de l'enquête de pharmacovigilance, un total de trois cas de syndrome de Kawasaki ont été notifiés au réseau national des CRPV. Un bilan actualisé de pharmacovigilance fait état de quatre observations supplémentaires peu documentées rapportées dans le monde depuis mars 2000 jusqu'à ce jour. Le pronostic vital de cette vascularite artérielle infantile est liée à la constitution d'anévrismes coronaires dans 15 à 25% des cas.

Limites de ce suivi

Le suivi a concerné 13% des pédiatres libéraux et 14% des doses vendues pendant cette période en France (total = 2 002 386 doses) ce qui lui confère une représentativité a priori satisfaisante.
L'estimation du nombre d'actes vaccinaux réalisés par les pédiatres participant au suivi intensif (274 511 actes) permet d'estimer que seuls les effets indésirables graves apparaissant avec une fréquence supérieure à 0,001% ont pu être détectés.
Par ailleurs, le niveau d'exhaustivité du recueil n'a pas été parfait dans la mesure où certains pédiatres ne déclaraient que les manifestations pouvant justifier un arrêt de la vaccination.

Conclusions

Bien que l'analyse globale des cas de pharmacovigilance n'ait pas mis en évidence de signal particulier, le CRPV de Tours a suggéré une réactualisation du RCP actuel par l'ajout de certains effets indésirables inattendus (graves ou non) tels que : abcès et cellulite au site d'injection, purpura vasculaire et effets neurologiques à type de cris anormaux, hypertonie. Prevenar® étant enregistré selon une procédure centralisée, le Groupe de Travail de Pharmacovigilance Européen analysera cette proposition dès la mise à disposition par la firme de l'ensemble des cas similaires rapportés dans le monde jusqu'à ce jour.

Enfin, aux sept observations de maladie de Kawasaki post-vaccinales citées précédemment s'ajoutent les résultats préliminaires d'une étude post-marketing menée aux Etats-Unis sur 3 années à partir de mars 2000 avec la mise en évidence d'un risque relatif non ajusté de cette pathologie statistiquement significatif après administration du Prevenar® (RR=2.02 [$_{95\%}$CI : 1.16-3.63 ; p=0.012]) d'où la question posée par ce signal potentiel tant sur le plan national qu'européen.
Afin d'infirmer ou de confirmer ce signal dans les meilleurs délais, l'Afssaps a sollicité le concours de l'unité INSERM 149 et de la CNAM impliquées étroitement dans un suivi national d'une cohorte de 300 000 nourrissons exposés/non exposés au Prevenar®. Dans cette étude, commanditée par la Direction Générale de la Santé en 2002 pour l'évaluation à long terme de l'impact épidémiologique de la vaccination et du profil de sécurité d'emploi du Prevenar®, les sujets inclus sont identifiés à l'aide de la base de données ERASME de la CNAMTS.
Les représentants de l'Inserm récemment contactés, ont accepté d'analyser ce signal avec une mise à disposition de résultats préliminaires dans un délai de l'ordre de 2 à 3 mois, sous réserve de disposer de l'ensemble des données d'identification issues de la base de données ERASME.

IV - ENQUETE OFFICIELLE RELATIVE AUX ATTEINTES HEPATIQUES SOUS CHLOROQUINE ET/OU PROGUANIL

Objectifs de l'enquête

Le Centre Régional de Pharmacovigilance (CRPV) d'Angers a présenté les résultats de l'enquête concernant la survenue d'atteintes hépatiques sous chloroquine et proguanil.
Cette enquête fait suite à une notification d'atteinte hépatique mixte chez une patiente traitée par une association chloroquine-proguanil dans le cadre d'une prophylaxie antipalustre et à l'existence d'autres cas d'atteintes hépatiques enregistrées dans la Base Nationale de Pharmacovigilance alors que cet effet indésirable ne figure pas dans le résumé des caractéristiques du produit (RCP) des différents médicaments concernés.

La période de recueil remonte à 1985 pour la chloroquine, molécule la plus ancienne, et à la date de commercialisation pour les autres médicaments. La fin de la période de recueil a été fixée au 30/06/2004.

Une analyse a été faite de toutes les notifications spontanées d'atteinte hépatique associée à un traitement par chloroquine et/ou proguanil faites aux CRPV et aux firmes, et enregistrées au 30/06/2004.
L'incidence des notifications a été estimée par mois de traitement prophylactique.
Une analyse des données de la littérature a également été réalisée.

Cinq spécialités contiennent l'un ou l'autre des principes actifs : NIVAQUINE® (Sanofi-Aventis) - chloroquine, PALUDRINE® (Astra Zénéca) - proguanil, SAVARINE® (Astra Zénéca) - associant chloroquine et proguanil, MALARONE® (GSK) - associant atovaquone et proguanil, et NOPALU® (Pharmacie Centrale des Armées) - associant chloroquine et proguanil.
Toutes ont l'indication de prophylaxie antipalustre. NIVAQUINE® et MALARONE® sont également indiquées dans le traitement curatif de l'accès palustre.

Résultats

Au total, 69 observations françaises ont été analysées. Elles se répartissent selon le tableau suivant:

	Atteintes cytolytiques	Atteintes mixtes	Atteintes cholestatiques	Anomalies isolées du BBH	Total
Chloroquine seule	12	4	2	10	28
Proguanil seul	0	0	0	0	0
Chloroquine + proguanil	17	7	4	2	30
Proguanil + atovaquone	7	1	1	2	11
Total	36	12	7	14	69

BBH : Bilan Biologique Hépatique

Atteintes cytolytiques sous chloroquine seule :
Un seul cas plausible C_2S_2 pour lequel la chloroquine est le seul médicament suspect a été notifié. Il s'agit d'une femme de 21 ans traitée pour un accès palustre. L'évolution a été très rapidement favorable.
Atteintes mixtes sous chloroquine seule :
Un seul cas plausible C_2S_2 pour lequel la chloroquine est le seul médicament suspect a été notifié : il s'agit d'un homme de 48 ans traité pour un lupus, ayant eu une évolution favorable en moins d'un mois.
Atteintes cytolytiques sous chloroquine + proguanil :
Deux cas plausibles C_2S_2 pour lesquels l'association chloroquine-proguanil est le seul médicament suspect ont été notifiés. Il s'agit d'une femme de 23 ans ayant présenté un syndrome d'hypersensibilité à J8 d'un traitement prophylactique et d'une femme de 39 ans ayant présenté une cytolyse modérée à J28 du traitement avec récidive à la reprise.
Atteintes mixtes sous chloroquine + proguanil :
Trois cas plausibles C_2S_2 ont été notifiés où l'association chloroquine-proguanil est le seul médicament suspect. Dans ces 3 cas, un mécanisme immunoallergique est suspecté, soit du fait des signes cliniques associés, soit du fait d'éléments chronologiques.
Atteintes hépatiques sous proguanil + atovaquone :
Aucun cas plausible C_2S_2 n'a été notifié avec l'association atovaquone/proguanil comme seul médicament suspect.

Neuf cas, survenus hors France et issus des base des données des industriels, ont également été analysés. Parmi eux 3 cas sont survenus sous proguanil seul et 3 cas, survenus sous l'association chloroquine-proguanil, sont associés à des symptômes d'hypersensibilité.

L'analyse de la bibliographie fait apparaître qu'il existe une toxicité hépatique dose-dépendante de la chloroquine chez le patient atteint de porphyrie cutanée tardive (PCT), maladie dont la chloroquine à dose faible constitue par ailleurs un des traitements possibles (utilisation hors AMM). Dans les cas analysés pour l'enquête, cette pathologie sous-jacente n'est confirmée que chez un seul patient traité par chloroquine et suspectée chez un autre. Le proguanil, dont certains effets de nature immunoallergique sont déjà validés, semble être capable d'induire une atteinte hépatique dans un contexte d'hypersensibilité.

Discussion

Les observations où le médicament antipaludéen est le seul médicament suspect avec une imputabilité au moins plausible sont au nombre de 7 (2 sous chloroquine utilisée seule et 5 sous l'association chloroquine-proguanil). Il s'agit soit d'hépatites cytolytiques (3 cas), soit d'hépatites mixtes (4 cas). L'évolution, quand elle est connue, est favorable. Aucun cas d'hépatite fulminante n'a été rapporté en France.
L'analyse des observations fait souvent apparaître, lorsque le proguanil est présent, des manifestations évoquant une réaction d'hypersensibilité (fièvre, éruption, hyperéosinophilie...). Ces effets indésirables sont très rarement notifiés eu égard aux chiffres de vente des différentes spécialités étudiées.
La littérature fait état d'une toxicité hépatique dose-dépendante de la chloroquine en cas de PCT sous-jacente.
La chloroquine et le proguanil peuvent donc être responsables d'atteintes hépatiques de survenue exceptionnelle selon un mécanisme vraisemblablement différent.

Proposition et Conclusion

La rareté des effets indésirables hépatiques notifiés et l'absence de cas particulièrement sévères incitent à délivrer auprès des professionnels de santé une simple information sur la survenue possible de ce type d'effet indésirable.

Les modifications des rubriques « effets indésirables » et «mises en garde et précautions d'emploi » proposées consistent en :

- Rubrique « effets indésirables » du RCP des spécialités contenant de la chloroquine :

« très rares cas d'élévation des enzymes hépatiques ou d'hépatite survenant notamment chez les patients porteurs d'une porphyrie cutanée tardive (cf. mises en garde et précautions d'emploi) ».

- Rubrique « effets indésirables » du RCP des spécialités contenant du proguanil :

« très rares cas d'élévation des enzymes hépatiques ou d'hépatite survenant principalement dans un contexte d'hypersensibilité (fièvre, éruption cutanée, éosinophilie...) ».

- Rubrique « mises en garde et précautions d'emploi » du RCP des spécialités contenant de la chloroquine :

« Chez les sujets atteints de porphyrie cutanée tardive, la prise de chloroquine peut favoriser la survenue d'une atteinte hépatique et ce de façon dose-dépendante (cf. effets indésirables). »

Les membres de la Commission Nationale ont voté à l'unanimité pour l'adoption de ces modifications de RCP.

V - ENQUETE OFFICIELLE RELATIVE AUX EFFETS INDESIRABLES NEUROLOGIQUES OBSERVES AVEC LA SPECIALITE VESADOL® (HALOPERIDOL, BUZEPIDE METIODURE)

Le Centre Régional de Pharmacovigilance de Toulouse a présenté les résultats de l'enquête sur les effets indésirables neurologiques observés avec la spécialité VESADOL® (halopéridol, buzépide métiodure). Cette enquête a été mise en place à la suite du courrier d'un neurologue qui s'interrogeait sur le bien-fondé de l'utilisation de ce produit, pourvoyeur de mouvements iatrogènes anormaux, dans les troubles fonctionnels digestifs.
En accord avec l'Unité de Pharmacovigilance de l'AFSSAPS, il a été décidé que l'enquête porterait exclusivement sur les effets indésirables extrapyramidaux de ce médicament.

La spécialité VESADOL®, commercialisée en France et dans certains pays d'Afrique Noire par les Laboratoires JANSSEN-CILAG depuis 1970, est une association de buzépide métiodure et d'halopéridol. L'halopéridol est un neuroleptique, chef de file des butyrophénones, exerçant des effets extrapyramidaux puissants, des effets sédatifs et hypotenseurs faibles. Le buzépide est un ammonium quaternaire ayant des propriétés antimuscariniques. Ses effets sont similaires à ceux de l'atropine.
L'association d'un atropinique à un neuroleptique a, dans la spécialité VESADOL®, été proposée d'une part pour ses propriétés antispasmodiques digestives et d'autre part pour obtenir une réduction des effets extrapyramidaux du neuroleptique.

L'association halopéridol + buzépide est indiquée dans les «manifestations de l'anxiété associées à des troubles fonctionnels digestifs à composante spasmodique». L'AMM française indique que «cette spécialité contient un neuroleptique et doit être réservée aux cas d'inefficacité ou de mauvaise tolérance des thérapeutiques usuelles de l'anxiété». Dans cette indication, la posologie d'halopéridol est de 3 à 4 comprimés par jour, soit 0,9 ou 1,2 mg par jour d'halopéridol.

Bilan de l'enquête

Au total, 17 observations d'effets indésirables neurologiques extrapyramidaux ont été rapportés avec VESADOL® (14 observations étaient enregistrées dans la Base Nationale de Pharmacovigilance en date du mois d'avril 2005 et 3 observations supplémentaires ont été fournies par les Laboratoires JANSSEN-CILAG). Ces observations se répartissent comme suit :

- 12 observations, dont 6 graves, de syndrome parkinsonien survenant dans un délai de 24 heures à plusieurs années chez des patients d'âge moyen 73 ans traités à la dose de 0,3 mg/j le plus souvent. Dans tous les cas, VESADOL® est le seul médicament suspect. L'imputabilité est possible dans 9 cas et probable dans 1 cas.
- 3 observations de dyskinésies tardives survenant dans un délai de 9 semaines dans un cas et plusieurs années dans l'autre (donnée non documentée dans le dernier cas). Elles concernent des patients âgés de 49 et 80 ans (1 cas d'âge inconnu) traités à des posologies de 0,3 et 0,9 mg/j (donnée non documentée dans un cas). VESADOL® est le seul médicament suspect dans 1 cas et l'imputabilité est douteuse dans les 3 cas. Dans 2 cas, une interaction médicamenteuse est suspectée (avec un inhibiteur sélectif de la recapture de la sérotonine dans 1 cas, un autre neuroleptique dans l'autre cas).
- 1 observation grave de dyskinésies aiguës et 1 observation grave de dystonie aiguë survenant dans un délai de 48 heures chez des sujets jeunes (14 et 22 ans) traités dans les deux cas à la dose de 0,3 mg/j. Dans ces 2 cas, VESADOL® est le seul médicament suspect et l'imputabilité est possible.

A partir des chiffres de vente fournis par le laboratoire, le taux de notification des effets indésirables extra-pyramidaux peut être estimé à 1 pour 1.200.000 boîtes vendues. Ce chiffre doit bien sûr tenir compte d'une sous-notification notable, puisqu'il s'agit d'un effet indésirable « attendu ».

Discussion

Cette enquête montre que l'on retrouve, avec VESADOL®, les effets indésirables neurologiques habituellement décrits avec les neuroleptiques, c'est à dire des syndromes parkinsoniens, des dyskinésies tardives et enfin des dystonies-dyskinésies aiguës. Ces effets indésirables s'observent aux posologies usuelles malgré le faible dosage d'halopéridol présent dans VESADOL®. Comme attendu, les dyskinésies-dystonies aiguës se retrouvent plutôt chez les sujets jeunes et les syndromes parkinsoniens plutôt chez des sujets âgés. On constate que l'association d'un anticholinergique, le buzépide métiodure, à l'halopéridol n'empêche en rien la survenue du

syndrome parkinsonien induit par l'halopéridol. Enfin, la gravité de ces effets indésirables doit être soulignée: c'est en particulier le cas des dyskinésies tardives, dont on sait qu'il s'agit d'un tableau qui n'est jamais régressif à l'arrêt du médicament.
Le Résumé des Caractéristiques du Produit de VESADOL® semble suffisamment informatif puisqu'il précise très clairement la possibilité de survenue d'effets indésirables neurologiques dès les plus faibles doses, à type de syndrome extrapyramidal, de dyskinésies tardives ou encore précoces. On pourrait cependant ajouter le fait qu'en cas de survenue de syndrome parkinsonien, il convient d'arrêter le médicament. De même, la conduite à tenir devant les dyskinésies précoces (traitement par les médicaments anticholinergiques) devrait être précisée.
Par ailleurs, il a été rappelé que ce médicament qui contient de l'iode à raison de 0,8mg par comprimé expose les patients traités au long cours à un risque de surcharge iodé.

Au final, cette enquête a permis de rediscuter le rapport bénéfice / risque de ce médicament à la lumière des données actualisées. Le risque d'effets indésirables neurologiques graves et parfois irréversibles n'est plus acceptable au vu des alternatives thérapeutiques.

En date du 23 juin 2005, les laboratoires JANSSEN-CILAG ont informé le CRPV de Toulouse et l'Afssaps de leur décision d'arrêter la commercialisation de VESADOL®. Il convient de rappeler que cette spécialité s'est vue octroyer un Service Médical Rendu insuffisant en 2001 et que depuis janvier 2004, le médicament est déremboursé et que de ce fait le nombre de boîtes vendues continue à régresser significativement.

Dans le cadre de la décision de la cessation de la commercialisation de VESADOL®, les laboratoires JANSSEN-CILAG ont présenté le plan d'action suivant :
- information et arrêt de la distribution de VESADOL® aux grossistes : début décembre 2005
- information des professionnels de santé par un communiqué dans la presse médicale et pharmaceutique : courant décembre 2005
- arrêt de la commercialisation par les grossistes aux officines : 31 décembre 2005
- reprise des stocks existant chez les grossistes : janvier 2006
- écoulement des produits disponibles en officine au plus tard jusqu'au 30 septembre 2006 (l'écoulement des stocks ne devrait durer que 2 à 3 mois mais il sera possible jusqu'à la péremption du dernier lot produit).
- Radiation de l'AMM en septembre ou octobre 2006 lorsque la péremption du produit sera atteinte.

Conclusion de la Commission Nationale de Pharmacovigilance

Compte tenu de la cessation de commercialisation de VESADOL® par les laboratoires JANSSEN-CILAG avant la fin de l'année 2006, décision indépendante de l'enquête en cours, il n'apparaît pas nécessaire de ré-évaluer le bénéfice-risque de ce médicament. La Commission Nationale de Pharmacovigilance a pris acte du plan d'action proposé par les laboratoires JANSSEN-CILAG sous réserve que le communiqué destiné aux professionnels de santé rappelle le risque de survenue d'effets indésirables extrapyramidaux sous VESADOL®. Le document final devra être validé par l'Afssaps et le Centre Régional de Pharmacovigilance de Toulouse en charge de l'enquête avant sa diffusion.

Depuis la Commission nationale de pharmacovigilance, le laboratoire a cessé les ventes auprès des grossistes et effectué une reprise des stocks existants chez ceux-ci.
Enfin, l'Afssaps et le laboratoire JANSSEN-CILAG ont convenu d'une abrogation de l'AMM le 15 avril 2006.

VI – RESURGENCES DE DELIRES / ECHECS THERAPEUTIQUES SOUS RISPERDAL CONSTA®

Risperdal Consta® LP (rispéridone) est un antipsychotique atypique à action retard, bénéficiant d'une AMM nationale depuis octobre 2003, et commercialisé en France depuis mars 2005. Il est indiqué chez l'adulte dans le traitement des psychoses, en particulier des psychoses schizophréniques, en relais d'un traitement antipsychotique par rispéridone par voie orale. Le Risperdal Consta® LP doit être administré toutes les 2 semaines en injection intramusculaire profonde dans le muscle fessier. La posologie initiale de Risperdal Consta® LP doit être établie en tenant compte de la dose de rispéridone orale. La posologie habituelle est de 25 mg par voie intramusculaire toutes les 2 semaines. La posologie maximale ne doit pas dépasser 50 mg toutes les 2 semaines. L'administration de rispéridone par voie orale à posologie efficace doit être poursuivie pendant les 3 premières semaines de traitement par Risperdal Consta® LP, compte tenu de l'existence d'une période de latence de 3 semaines avant l'apparition de l'effet thérapeutique après la première injection de Risperdal Consta® LP.
La rispéridone est métabolisée par le cytochrome P450 2D6 en 9-hydroxy-rispéridone. L'ensemble rispéridone plus 9-hydroxy-rispéridone constitue la fraction active.

Un premier point relatif à Risperdal Consta® et résurgences des délires a été présenté en Comité Technique de Pharmacovigilance le 7 juin 2005.

Depuis mars 2004, 25 cas de résurgences de délires/hallucinations et d'échecs thérapeutiques ont été rapportés par notification spontanée en France chez des patients traités par Risperdal Consta® LP en relais d'un traitement oral par rispéridone. Dans 9 cas, aucun facteur de risque ni d'explication alternative à cette décompensation n'ont été retrouvés. Dans les autres cas, ont été notés un défaut d'observance, ou une absence de rispéridone orale en début de traitement par Risperdal Consta® LP, ou enfin un non-respect des recommandations concernant les doses de rispéridone orale/Risperdal Consta®.

Par ailleurs, le CRPV a analysé les observations notifiées dans le cadre de l'étude de phase IV DEPIST (Diagramme de l'Etat Psychotique utilisable par l'Infirmier dans la Schizophrénie Traitée au long cours). Sur 932 patients inclus, 3, 65% (34 observations) ont présenté des résurgences de délire/rechutes.

Plusieurs questions ont été soulevées par le CRPV pour expliquer ces observations : variabilité inter-individuelle ? Polymorphisme génétique au niveau de la métabolisation ? Modification de l'occupation des récepteurs ? Traitement de 3 semaines par rispéridone insuffisant en terme de durée ? Positionnement du Risperdal Consta® par rapport aux patients nécessitant de fortes doses de rispéridone orale ? Dosage plasmatique de rispéridone et de 9-hydroxy-rispéridone après l'arrêt de la rispéridone orale utile ?

Lors de la présentation, il a été décidé de transformer le point en enquête officielle de pharmacovigilance, et l'enquête a été officiellement mise en place sous la responsabilité du Centre Régional de Pharmacovigilance de Montpellier. Ce dossier doit être à nouveau présenté à la Commission nationale de Pharmacovigilance du 31 Janvier 2006.

ANNEXES

SUJETS ABORDES LORS DES SEANCES DU COMITE TECHNIQUE DE PHARMACOVIGILANCE DU 14 OCTOBRE 2005 ET 8 NOVEMBRE 2005 ET NON PRESENTES EN COMMISSION NATIONALE

1/ Comité technique du 14 octobre 2005

- Etude sur les conditions d'utilisation du misoprostol dans l'interruption de grossesse

A la suite de 4 cas mortels de septicémie aux Etats-Unis lors d'IVG utilisant 200 mg de mifépristone par voie orale et 800 µg de misoprostol par voie intravaginale, une lettre a été adressée par l'Afssaps aux gynécologues, obstétriciens et pharmaciens hospitaliers afin de rappeler les conditions d'utilisation de la mifépristone : 600 mg de mifépristone par voie orale, suivis 36 à 48 heures après de l'administration d'un analogue d'une prostaglandine, 400µg de misoprostol par voie orale ou 1 mg de géméprost par voie vaginale.
Cette lettre et le communiqué de presse sont accessibles sur le site internet de l'Afssaps depuis le 18 octobre 2005. Par ailleurs, un arbitrage européen a été déclenché en décembre 2005, où la question des doses et des voies d'administration de la mifépristone et du misoprostol à recommander lors d'une interruption de grossesse a été posée.

- Point sur les tendinopathies observées durant les traitements corticoïdes administrés par voie générale

Au cours du Comité technique de pharmacovigilance du 10 mai 2005, le centre régional de pharmacovigilance (CRPV) de Caen a présenté le cas d'un patient de 57 ans décrivant des douleurs bilatérales des tendons d'Achille au cours d'une corticothérapie par voie orale de 9 jours, suivies d'une rupture du tendon d'Achille droit 8 jours après le début d'un traitement par une fluoroquinolone administrée en solution auriculaire. Alors que ce type d'effet semblait connu, le CRPV de Caen a souligné qu'il ne figurait pas dans les différents Résumés des Caractéristiques du Produit (RCP) des corticoïdes administrés par voie générale.
A l'issue de la présentation de ce cas, un point portant sur les tendinopathies observées sous corticothérapie par voie générale a été demandé par le comité technique.
Ce point s'est appuyé sur une analyse de la base nationale de pharmacovigilance ainsi que sur l'analyse de la littérature.
Il apparaît que les corticoïdes systémiques peuvent favoriser la survenue de tendinopathies, en présence de facteurs de risque médicamenteux (fluoroquinolones) ou pathologiques (lupus érythémateux systémique, dialysés et greffés rénaux, maladies rhumatismales). Parallèlement, la vingtaine de cas recensée dans la littérature chez des patients sous corticothérapie le plus souvent prolongée pour une affection broncho-pulmonaire chronique ne semble pas expliquée par la pathologie traitée ayant justifié l'utilisation de corticoïdes.
Le risque de rupture tendineuse, au niveau de lésions préexistantes, trouve des explications pharmacologiques qui s'appuient sur des travaux expérimentaux. Les effets d'une corticothérapie locale sont ainsi mieux compris. Cependant, aucune étude expérimentale effectuée après corticothérapie systémique n'a été identifiée par la recherche bibliographique.
La présence dans la base nationale de pharmacovigilance de plusieurs cas de tendinites, éventuellement suivies de ruptures, dans des indications non réputées en relation avec ces complications, en particulier dans 1 cas d'otite, est un argument à souligner en faveur du rôle propre de cette classe de médicament dans le cadre d'une administration par voie générale.

Au total, le Comité technique a proposé les modifications suivantes dans les RCPs des corticoïdes systémiques :

- Rubrique Effets indésirables : « possibilité de ruptures tendineuses (et douleurs ?) »
- Rubrique Mises en garde et précautions particulières d'emploi : « préconiser la surveillance de l'apparition de signes tendineux pour mettre au repos les tendons et réévaluer la nécessité du traitement à un stade précoce »
- Rubrique Interactions : « à prendre en compte avec les fluoroquinolones »

La question reste en suspens pour les corticoïdes inhalés, les dermocorticoïdes et les autres formes locales (ophtalmiques, auriculaires).

2/ Comité technique du 8 novembre 2005

- Point sur les effets indésirables extrapyramidaux de la trimétazidine (Vastarel®, Centrophène® Gé)

A la suite de la notification spontanée d'un cas de syndrome parkinsonien au CRPV de Toulouse et de la publication dans la littérature de plusieurs observations, le CRPV de Toulouse a présenté à la demande de l'Afssaps un point sur les effets extrapyramidaux de la trimétazidine.

La trimétazidine est un dérivé pipérazinique dont le mécanisme d'action reste mal connu. Elle est indiquée dans :
- la prophylaxie de la crise d'angor (Service Médical Rendu « modéré »)
- le traitement symptomatique d'appoint des vertiges et des acouphènes (Service Médical Rendu « modéré »)
- le traitement d'appoint des baisses d'acuité et des troubles du champ visuel d'origine vasculaire (Service Médical Rendu « insuffisant »).

L'analyse des données de la littérature et des notifications spontanées, permet de mettre en évidence un signal, certes faible mais certain de survenue de syndrome parkinsonien sous trimétazidine. Le mécanisme reste inconnu mais une action sur les neurones dopaminergiques n'est pas exclue du fait de la structure chimique pipérazinique de la trimétazidine.

Le Comité Technique propose que la survenue exceptionnelle de syndrome parkinsonien soit ajoutée dans la monographie de la trimétazidine dans la rubrique « effets indésirables ». Une demande de modification de l'information a été envoyée par l'unité pharmacovigilance aux laboratoires concernés.

Annexe 3-70

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Saint-Jacques – 25030 BESANCON Cedex

MEDIATOR® (benfluorex)

ENQUETE OFFICIELLE

Troubles neuropsychiatriques

Hypertensions artérielles pulmonaires

Commission Nationale du 29 novembre 2005

Confidentiel

M. DAVID-LAROCHE
J.P. KANTELIP

Annexe 3-70

Lors du Comité Technique de Pharmacovigilance du 7 décembre 2004 plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique ayant été rapportés, il a été décidé d'analyser les données relatives aux troubles neuro-psychiatriques avec MEDIATOR®

Suite à une notification d'hypertension artérielle pulmonaire rapportée lors du Comité Technique du 8 mars 2005, l'enquête a été étendue aux hypertensions artérielles pulmonaires.

Le MEDIATOR® (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés, dosés à 150 mg.

Ses indications sont :
- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité Technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène. (Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Historique :
Une première mise au point des effets indésirables du benfluorex a été présentée lors du Comité Technique du 11 juillet 1995, suivie d'une enquête officieuse dont les rapports ont été présentés aux Comités Techniques:
- du 30 avril 1998 sur les effets indésirables du benfluorex, rapportés aux CRPV
- du 10 septembre 1998 sur le métabolisme et les chiffres de ventes du benfluorex

et de l'enquête officielle présentée aux Comités Techniques des 17 décembre 1998 et 20 juillet 1999.

Le Résumé des Caractéristiques du Produit a été modifié suite à une Demande de Modification de l'Information Médicale expertisée par le CRPV de Besançon en juin 2000 d'une part, et une réunion de Pharmacovigilance à l'EMEA le 30 novembre 2000 d'autre part (pour choc et effets hépatiques).
(Les modifications sont inscrites en gras dans le paragraphe ci-dessous)

Les effets indésirables sont :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, **confusion**, somnolence, état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles
- **très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke**
- **élévation des enzymes hépatiques, hépatite (très rare)**

Métabolisme :

➢ In vivo : Chez l'homme, le MEDIATOR® est hydrolysé très rapidement au niveau plasmatique et hépatique par des estérases en S422 (dérivé alcool), puis transformé en 8 métabolites majeurs identifiés parmi lesquels, par oxydation (S1475, dérivé acide) ou désalkylation (S585, norfenfluramine).
Le métabolite majoritaire est le dérivé carboxylique : S1475.
Le métabolite primaire S422 et la norfenfluramine sont retrouvés à des taux très inférieurs.

Après administration de benfluorex radioactif, on retrouve 87 à 99% de la radioactivité après 72 heures dans les urines. L'absence de quantité significative dans les fécès montre que le produit est bien absorbé.
Il n'existe pas de phénomène d'accumulation.

L'élimination se fait en 2 phases :
- une première phase rapide (60% en 3 ou 4 heures)
- une seconde phase lente de 36 heures environ.

➢ In vitro : Les travaux faits in vitro après incubation d'hépatocytes frais humains montrent que les principaux cytochromes P450 jouent un rôle très minoritaire dans le métabolisme du benfluorex.

Annexe 3-70

TROUBLES NEURO-PSYCHIATRIQUES

A. Asthénie, somnolence ou états vertigineux sont mentionnés dans les RCP

B. Troubles psychiatriques lors du traitement

35 cas ont été rapportés dont 10 déclarés depuis l'enquête présentée en juillet 1999.
Remarque : Les nouveaux cas (10) notifiés depuis le rapport de juillet 1999 sont inscrits ***en gras.***
Elles concernent 18 hommes (âge moyen : 58,5 ans) et 17 femmes (âge moyen : 60 ans).

Les troubles psychiatriques sont divers :
- agressivité (4), nervosité (3), irritabilité
- cauchemars (2), angoisse, stupeur, dépression
- désorientation (7), *confusion* (5),* aggravation des troubles cognitifs
- agitation (3), trouble du comportement (3)
- délire (2), bouffée délirante aiguë

(*)confusion est inclus dans le dernier RCP

Remarque : La responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue, dans la plupart des notifications.

1. Imputabilité :

4 cas sont imputés « vraisemblable » :

- NC9500171 : nervosité et nausées chez une femme de 50 ans, 1 à 2 h après la prise de 1 comprimé de MEDIATOR®.

- **128E22** : chez un homme de 72 ans , traité pour démence, prenant pendant plusieurs années MEDIATOR® pour troubles métaboliques et MODOPAR® pour maladie de Parkinson, est observée une amélioration de ses troubles cognitifs lors d'un arrêt fortuit du MEDIATOR® et une aggravation lors de la reprise du MEDIATOR®.

- S10010345 : désorientation et obnubilation, chez une femme de 80 ans. Le traitement a été arrêté après 13 jours. Une réadministration ultérieure a été positive (traitement associé : KERLONE® et MOGADON®).

- **CN0000093** : désorientation temporo-spatiale et agitation chez un homme de 76 ans. Le délai d'apparition des troubles est inconnu, mais les signes cliniques se sont améliorés à l'arrêt du MEDIATOR® et la réadministration est positive. Les autres médicaments ne sont pas arrêtés (DAONIL®, LASILIX®, SINTROM®, MONICOR L.P®. et FOZIRETIC®). *(cas décrit également paragraphe suivant « gravité »)*

5 cas sont imputés « plausible »

- NC9700094 : accès d'agitation et agressivité, chez une femme de 74 ans, pendant la prise de MEDIATOR®, pendant 6 jours. Disparition des symptômes 12 heures après l'arrêt du MEDIATOR®.
- NC9300347 : irritabilité chez un homme de 39 ans, traité pendant 11 mois par MEDIATOR®. L'évolution est favorable à l'arrêt du médicament.
- MA9100069 : angoisse et palpitation, chez un homme de 40 ans, 2 heures après avoir ingéré 4 comprimés de MEDIATOR®.
- NC9300349 : dépression, chez un homme de 50 ans, traité pendant 9 mois par MEDIATOR®. L'évolution est favorable à l'arrêt du médicament.
- CF9000137 : désorientation chez une femme de 79 ans, traitée par MEDIATOR®, HALDOL®, SERESTA®, ZESTRIL®, CATAPRESSAN®, PRAXILENE®, SERMION®. L'évolution est favorable à l'arrêt de tous les médicaments.

26 cas ont été imputés « douteux » dont 13 (C2, S1).

2. Gravité :

Les effets indésirables ont nécessité une hospitalisation dans 9 cas.

a) Confusion : 4 cas

SE9500017 : Un **état confusionnel** ayant duré 12 h est survenu chez une femme de 41 ans après 83 jours de traitement par MEDIATOR® (1cp/j) et INCITAL®, et 2 ans par LEXOMIL®. Elle avait été retrouvée errante sur la voie publique après une dispute avec son mari. (Imputabilité : C1,S1)

010326 : Un homme de 61 ans, traité par MEDIATOR® (dose et durée inconnues), FONZYLANE® et SINTROM®, est hospitalisé pour déshydratation avec fièvre et **confusion**. L'évolution est favorable après réhydratation et arrêt du MEDIATOR®.

120M85 : Un homme de 69 ans, traité par MEDIATOR®, 2 cp/j pendant 11 jours pour désordre métabolique est admis à l'hôpital pour malaises avec **confusion** et amnésie. Le MEDIATOR® est arrêté, mais les troubles de mémoire continuent. Le scanner cérébral montre une atrophie cortico-souscorticale.
Le traitement associé est PREVISCAN® et CORDARONE®.

S01000031 : Un homme de 63 ans a été hospitalisé à plusieurs reprises pour confusion mentale inexpliquée. Une recherche des médicaments sur l'urine par technique de polarisation de fluorescence révèle une réponse positive pour les dérivés amphétaminiques et une chromatographie gazeuse couplée à une spectrométrie de masse ne confirme pas l'abus d'amphétamines usuels (incluant l'ecstasy).
Cependant, la norfenfluramine est retrouvée à des concentrations de 687 ng/ml dans l'urine et 8.4 ng/mg dans les cheveux.
La présence de norfenfluramine et l'absence de fenfluramine sont en faveur d'un abus illicite de MEDIATOR® (dose inconnue). L'évolution est inconnue. (Imputabilité : C1,S1)
(Cas publié :Norfenfluramine : usage thérapeutique ou toxicomanie ? V.CIRIMELE et coll. Journal de Médecine Légale Droit Médical, 2001, Vol.44, N°1, 23-26.

b) Désorientation temporo-spatiale : 3 cas

10345 : Une femme de 80 ans, avec des séquelles d'accident vasculaire cérébral, traitée pour hypercholestérolémie par MEDIATOR® 3cp/j pendant 13 jours est hospitalisée pour **désorientation temporo-spatiale et obnubilation** avec hypotension artérielle. L'évolution est favorable à l'arrêt du MEDIATOR®. Le rechallenge est positif.
Le traitement associé est: KERLONE®, MOGADON®.

RE037148 : Une patiente de 66 ans, obèse et grabataire, est amenée à l'hôpital en raison de l'apparition d'un syndrome confusionnel avec état stuporeux et une hyperthermie à 40°. Ses antécédents sont assez chargés avec entre autres, un état dépressif, un asthme et une cardiopathie hypertensive. Le traitement par MEDIATOR® (3cp/j) avait débuté 10 à 12 jours avant son hospitalisation à raison de 3 cp/j. Après l'arrêt du MEDIATOR®, on note une amélioration en quelques jours de la **désorientation temporo-spatiale**. Le traitement habituel de la patiente est : ASPEGIC®, COAPROVEL®, CORVASAL®, DIFFU K®, MONOTILDIEM®, MOVICOL®, SEROPRAM®, TRINIPATCH®, MEDIATENSYL®, VASTEN®, SERETIDE® et VENTOLINE®. (Imputabilité : C2,S1)

CN0000093 : Chez un homme de 76 ans, traité depuis 2 ans par MEDIATOR®, 3 cp/j, est apparu une **désorientation temporo-spatiale** et agitation, dont le délai d'apparition des troubles est inconnu, mais les signes cliniques se sont améliorés à l'arrêt du MEDIATOR® et la réadministration a été positive. Les autres médicaments ne sont pas arrêtés (DAONIL®, LASILIX®, SINTROM®, MONICOR L.P.® et FOZIRETIC®) *(dossier imputé «C3,S1 » décrit paragraphe précédent).*

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RN9500096 : Une patiente de 59 ans, sans antécédent psychiatrique, en cure d'amaigrissement (perte de 10 kg) depuis 3 mois avec MEDIATOR® (3cp depuis 73j), LIPANTHYL®, Amfépramone®, Craetegus 100mg, PILOSURYL®, CANOL®, STRESAM®, OLIVIASE®, RELVENE® et TOP MAG® est hospitalisée pour **bouffée délirante aiguë** avec confusion, désorientation temporo-spatiale et agitation. L'évolution est favorable 8 jours après l'arrêt de tout le traitement et la mise sous neuroleptiques. (Imputabilité : C1,S2)

TO041306 : Une **bouffée délirante aiguë** à thème de persécution et de complot avec agitation extrême et opposition des soins a nécessité une hospitalisation sous contrainte chez un homme de 50 ans qui était traité par MEDIATOR® (1cp/j) depuis 29 mois, associé à COTAREG® et ZYLORIC®. Les troubles ont disparu en 24h sous SOLIAN IM®, TERCIAN IM® ET RIVOTRIL®. Le patient est sorti de l'hôpital avec SOLIAN® 400mg, 2 fois par jour. (Imputabilité : C1,S2)

3. Tableau récapitulatif des observations : (voir pages suivantes)

Les nouveaux cas (10) notifiés depuis le rapport de juillet 1999 sont inscrits **en gras**.

Troubles psychiatriques lors du traitement (1)

N°	S/Age	Durée TTT	Posologie/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables
S01001236	**M ,54**	**17 jours**	**450 mg**	**C2,S1**	**TRANDATE, C1,S1**		**A**	**N**	**Agressivité,irritabilité insomnie**
LY9600963	M,45	1 mois	450 mg	C1,S1	LEXOMIL, C2,S1		A	N	agressivité
NC9700094	F,74	6 j	225 mg	C2,S2			A	N	agressivité
541173	F,45	8j	300 mg	C2,S1	CORENITEC,C1,S1 LYSANXIA		A		Agressivité + hallucination
NC9300347	M,39	11 mois	150 mg	C2,S2			A	N	Irritabilité
NC9500171	F,50	1 cp	150mg	C3,S2			A	N	Nervosité
MP9800179	F,47	11j	300 mg	C2,S1	LIPANOR, C1,S1		A	N	Nervosité
124G84	F,35	20 j	300 mg	C2,S1	MAXEPA LEVOTHYROX HYDROCORTISONE	Hypothyroïdie Insuffisance surrénale	A	N	Nervosité +excitation
MA9100069	M,40	1 j	600 mg	C2,S2			A	N	Angoisse
TS9500338	F,69	8 j	150 mg	C2,S1	DAONIL, C1,S1 ALPRESS BITILDIEM DIAMICRON...		A	N	Stupeur
LY8900392	M,52	20 j	450 mg	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1		A	N	Cauchemars
10540O46	M, ?	qq semaines	450 mg	C1,S1	ZOCOR, C1,S1 PERSANTINE MAXEPA TILDIEM DAONIL		A	N	Cauchemars
NC9300349	M,50	9 mois	450 mg	C2,S2	LOPRIL, C1,S1		A	N	Dépression Paresthésie, asthénie
SE9500017	F,41	84 j	150 mg	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1		A	O	confusion
010326	M,61	?	?	C1,S1	FONZYLANE, C1,S1 SINTROM, C1,S1		A	O	Confusion Autre cause !
120M85	M,70	11j	300 mg	C2,S1	PREVISCAN , C1,S1 CORDARONE, C1,S1	Scanner cérébral : atrophie cortico-souscorticale	A	O	Confusion Troubles de la mémoire
S01000031	**M ,63**	**?**	**?**		**Drogue ?**		**U**	**O**	**Confusion**
127V18	**M,70**	**1 jour !**	**150 mg**	**C2,S1**	**TERALITHE LEXOMIL NOCTRAN**	**Syndrome dépressif**	**A**	**N**	**Confusion Somnolence**
128E22	**M,72**	**+ années**	**?**	**C3,S1**	**MODOPAR**	**Démence**	**A**	**N**	**Aggravation des troubles cognitifs**

Troubles psychiatriques lors du traitement (2)

N°	S/Age	Durée TTT	Posologie/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables
CF9000137	F,79		450 mg	C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2 SERMION, C2,S2		A	N	désorientation
010345	F,80	13 j	450 mg	C3,S1	MOGADON, C1,S1 KERLONE, C1,S1		A	O	Désorientation Obnubilation
060J96	F,80	?	?	C1,S1	RENITEC ADALATE HEMIDAONIL TILDIEM		A	N	Désorientation
060J13	F,82	1 mois	450 mg	C2,S1	DAONIL		A	N	Désorientation
120M52	M,60	2 j	150 mg	C2,S1	LIPANTHYL, C1,S1 ASPEGIC, C1,S1		A	N	Désorientation Somnolence
RE037148	**F,66**	**13 j**	**450 mg**	**C2,S1**		**Syndrome dépressif**	**A**	**O**	**Désorientation temporospatiale Etat stuporeux**
CN0000093	**M,76**	**2 ans**	**450 mg**	**C3,S1**	**DAONIL, C1,S1 SINTROM, C1,S1 LASILIX, C1,S1 MONICOR L.P., C1,S1 FOZIRETIC, C1,S1**		**A**	**O**	**Désorientation temporospatiale Agitation**
MA8900523	F,40		150 mg	C1,S1	ISOMERIDE, 1j, C2,S1		A	N	Agitation
DJ9800349	M,74	3 mois	450 mg	C2,S1			A	N	Agitation
PA0200221	**F,70**	**1 j**	**3 cp en 1 prise**	**C1,S1**			**A**	**N**	**Agitation, paresthésie**
10060560	M,75	Plusieurs mois	450 mg	C2,S1	DAONIL		A	N	Trouble du comportement
GR0100547	**F,44**	**4 mois**	**450 mg**	**C2,S1**	**OLIGOSOL, C2,S1**	**Syndrome dépressif**	**F**	**N**	**Trouble du comportement Hallucination, vertige**
GR0100594	**F, ?**	**9 mois**	**450 mg**	**C1,S1**			**U**	**N**	**Trouble du comportement**
RN9500096	F,59	73 j	450 mg	C1,S2	LIPANTHYL, C1,S2 PILOSURYL, C1,S2 CANOL, C1,S2 OLIVIASE, C1,S2 Amfépramone, C1,S2		A	O	Bouffée délirante aiguë
GR8700216	M,45	16 j	450 mg	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1		A	N	délire
TO041306	**M,50**	**29 mois**	**150 mg**	**C1,S2**	**COTAREG, C1,S1 ZYLORIC, C1,S1**		**B**	**O**	**Bouffée délirante aiguë**

3. Troubles psychiatriques apparaissant lors du sevrage

10 notifications de troubles psychiatriques apparaissant lors du sevrage ont été rapportés, 6 par les CRPV, 4 par le laboratoire.

Ils concernent 2 hommes et 8 femmes, dont la moyenne d'âge est respectivement 30,5 ans (27-34) et 45,25 ans (30-65).

Le délai d'apparition des troubles après l'arrêt du MEDIATOR® est très variable : de 1 jour (après un traitement de 8 ans) à 3 semaines (après un traitement de 4 à 15 mois).

La durée de traitement par MEDIATOR® est de 1 mois à 8 ans.

Dans les 3 observations qui ont nécessité une hospitalisation (gravité = O dans le tableau page 10), il existe un terrain ou des antécédents prédisposants :

- **LY0200303** : une femme de 36 ans, traitée par MEDIATOR® pendant 6 mois pour obésité avec hypercholestérolémie et PROZAC pendant 6 semaines pour syndrome dépressif, est hospitalisée en psychiatrie pour **état anxiodépressif aigu** avec crise de panique, 2 à 3 semaines après l'arrêt des 2 médicaments.
L'état de la patiente s'améliore rapidement sous SOLIAN® et STABLON®. (Imputabilité : C1,S1)

- **LY0200036** : chez une femme de 34 ans, avec des troubles dysthymiques, suivie pour difficultés psychologiques de type border line, en rupture de traitement neuroleptique depuis plusieurs mois, apparaît une **décompensation avec délire persécutif et anxiété**, environ 3 semaines après un traitement de 4 mois par MEDIATOR®.
La patiente sera traitée pour troubles psychotiques, l'évolution est inconnue. (Imputabilité : C1,S1)

- **LY0200037** : une femme de 53 ans, diabétique non insulino-dépendante, ayant fait 2 épisodes maniaques en 1985 et 1996 (ce deuxième épisode étant survenu à la suite d'un régime amaigrissant accompagné peut-être du benfluorex) est hospitalisée pour **accès maniaque atypique** environ 3 semaines après l'arrêt d'un traitement de 15 mois par MEDIATOR®. Il est a noté un amaigrissement de 20 kg en 1 an.
La patiente sera traitée pour troubles psychotiques, l'évolution est inconnue. (Imputabilité : C1,S1)

Les autres troubles sont identiques à ceux décrits pendant le traitement par MEDIATOR® :

- vertige (4), somnolence (2)
- cauchemar, angoisse (2)

Dans 1 cas, l'imputabilité de MEDIATOR® est « vraisemblable » :

- PA97355052 : il s'agit d'un syndrome de sevrage avec **excitation** chez un homme de 27 ans, sportif, qui consomme (sur prescription médicale) à doses croissantes (1cp/semaine au début jusqu'à 9 cp/j) du MEDIATOR® comme "dopant ».
Ce patient avait eu un épisode similaire quelques mois plus tôt. (Imputabilité : C3,S1)

Troubles psychiatriques apparaissant lors du sevrage

Les nouveaux cas (8) notifiés depuis le rapport de juillet 1999 sont inscrits **en gras.**

N°	S/Age	Durée TTT	Poso/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables	sevrage
MP0300791	**F,58**	**8 ans**	**450 mg**	**C2,S2**	**LIPANTHYL ,C2,S1 LEVOTHYROX, C1,S1 EUPRESSYL, C1,S11**		**A**	**N**	**Vertige, somnolence**	24h
060141	**M,34**	**2 mois**	**300 mg**	**C2,S1**			**A**	**N**	**Vertige, sueur**	2 jours
TO001223	**F,30**	**3 mois**	**450 mg**	**C1,S1**	**SURGAM CLAMOXYL**		**A**	**N**	**Céphalalgie, malaise, somnolence**	9 jours
2000276	**F,34**	**1 mois**	**450 mg**	**C2,S1**	**XENICAL ESBERIVEN**		**A**	**N**	**Nausée, vertige , fatigue, cauchemar, tremblement**	
LY0200303	**F,36**	**6 mois**	**300 mg**	**C1,S1**	**PROZAC, C1,S1**	**Syndrome dépressif**	**B**	**O**	**Etat anxiodépressif**	2 à 3 semaines
S03000265	**F,52**	**+ années**	**450 mg**	**C1,S1**	**LEVOTHYROX LIPANTHYL**		**U**	**N**	**Angoisse, nervosité, vertiges**	Quelques jours
10060219	F,65	2 ans		C1,S1			A	N	Bouffées d'angoisse	
PA9735052	M,27	6 mois		C3,S1	« 9 cp/j (dopant) »		U	N	Excitation	
LY0200036	**F,34**	**4 mois**		**C1,S1**		**Troubles dysthymiques sur personnalité pathologique**	**U**	**O**	**Bouffées délirantes**	3 semaines
LY0200037	**F,53**	**15 mois**		**C1,S1**	**GLUCOR, C1,S1 STAGID, C1,S1 LEVOTHYROX, C1,S1**	**Troubles dysthymiques**	**U**	**O**	**Exaltation maniaque atypique**	3 semaines

Annexe 3-70

4. Troubles neurologiques

Les nouveaux cas (4) notifiés depuis le rapport de juillet 1999 sont inscrits **en gras**.

12 notifications ont été rapportées, 9 par les CRPV, 3 par le laboratoire :
Elles concernent 8 hommes et 4 femmes :

- Convulsions : 2 cas

PA9223988 : Chez un homme de 60 ans, survient une **crise convulsive généralisée**, alors qu'il est traité par MEDIATOR® 1cp/j (durée inconnue), TENSIONORME® depuis 10 ans et DIFFU K®. L'évolution est favorable à l'arrêt des 3 médicaments.

10060J47 : Une femme de 36 ans traitée par MEDIATOR® depuis 2 mois et DAONIL®, fait une **crise comitiale**, dont l'évolution est favorable.

- Neuropathies : 2 cas

MA8700716 : Chez un homme de 73 ans, traité pour un diabète léger par MEDIATOR® pendant 9 ans apparaît une **neuropathie sensitivomotrice** des membres inférieurs. Une autre étiologie peut être envisagée. L'évolution est inconnue.

TS9300183 : Une **neuropathie** est rapportée chez un homme de 68 ans traité depuis 3 mois par MEDIATOR® et GLUCOPHAGE®, et 5 mois par AZANTAC®. Le traitement habituel est DIAMICRON®, SURBRONC® et CYCLOSPASMOL®.

- Paresthésies : 7 cas

Dans 3 cas (**PA0200221,** NC9300349, **MA03P0355**), il existe des symptômes associés cités ci-dessus agitation, dépression, vertige et asthénie.

Le délai d'apparition est très court : de 1 à 8 jours dans la majorité des cas. Dans 1 cas, où la neuropathie est associée à une dépression et asthénie, le délai est de 9 mois (NC9300349).

L'évolution, quand elle est connue, est favorable rapidement en quelques heures.

A noter que dans 2 cas, il s'agit de mésusage :

- **MA03P0355 :** prise de 6 comprimés en 1 fois, par une femme de 26 ans, qui a présenté des douleurs abdominales, des vertiges, une asthénie et des paresthésies au niveau des membres inférieurs.
- MA9700170 : automédication chez une femme de 42 ans, qui après le deuxième comprimé de MEDIATOR® est survenue une sensation de chaleur accompagnée de picotements des extrémités et des palpitations. L'évolution est inconnue.

- Tremblements des mains

128F60 : un patient de 72 ans ayant débuté depuis 5 jours un traitement par MEDIATOR®, LIPANTHYL® MONO-TILDIEM® et HYPERIUM® développe un **tremblement des mains.**
HYPERIUM® est remplacé par diltiazem puis trandolapril, LIPANTHYL® remplacé par atorvastatine et les doses de MEDIATOR® de 300 mg/j sont diminuées de moitié. Les tremblements régressent.
Le MEDIATOR® est arrêté ensuite.

Troubles neurologiques

N°	S/Age	Durée TTT	Poso/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Commentaires
CONVULSION									
PA9223988	M,60	?	150 mg	C2,S1	TENSIONORME, C2,S1 DIFFU K		A	N	Tensionorme : B3
10060J47	F,36	2 mois		C1,S1	DAONIL		A		Crise comitiale
NEUROPATHIE									
MA8700716	M,73	9 ans	?	C1,S1	HEMOCLAR TORENTAL		U	N	Autre étiologie
TS9300183	**M,68**	**3 mois**	**?**	**C2,S1**	**AZANTAC, 1j, C2,S1** **GLUCOPHAGE, C2,S1**		**A**	**N**	**Imputabilité Azantac : B2**
PARESTHESIE									
BX8800193	M,36	8 j	300 mg	C1,S1	PRAXINOR, 8j, C1,S1		F	N	
LM9500090	M,61	4 j	150 mg	C2,S1	Traitement associé inconnu		A	N	
10051683	M,65		450 mg	C2,S1	DAONIL GLUCOPHAGE LIPANOR ANGIOXINE		A	N	
MA9700170	F,42	1 j	150 mg	C2,S2	TAMIK, C1,S1		U	N	Mésusage
MA03P0355	**F,26**	**6 cp en 1 j**	**900mg**	**C2,S2**			**A**	**N**	**Mésusage Vertige, asthénie**
PA0200221	**F,70**	**1 j**	**3 cp en 1 prise**	**C1,S1**			**A**	**N**	**Agitation, paresthésie**
NC9300349	M,50	9 mois	450 mg	C2,S2	LOPRIL, C1,S1		A	N	Dépression Paresthésie, asthénie
128F60	**M,72**	**5 j**	**450 mg**	**C2,S1**	**LIPANTHYL, C2,S1** **HYPERIUM, C1,S1** **MONOTILDIEM, C1,S1**		**A**	**N**	**Tremblements des mains**

Annexe 3-70

5. Abus

2 cas d'abus ont été rapportés :

- 1 cas rapporté par le laboratoire sans effet indésirable :
  - S01001135 : Un homme de 42 ans, traité par MEDIATOR® 150 mg 2 fois par jour pour hypertriglycéridémie depuis décembre 1999, augmente les doses à 10 comprimés par jour de janvier à novembre 2001, puis retourne à une dose normale à 2 comprimés par jour ensuite.
  Le traitement associé était TERCIAN® et LEPTICUR®.
  Aucun effet indésirable n'est rapporté.

- 1 cas rapporté par un CRPV avec effet indésirable : (déjà cité page 9, paragraphe sevrage)
  - PA97355052 : il s'agit d'un syndrome de sevrage avec **excitation** chez un homme de 27 ans, sportif, qui consomme (sur prescription médicale) à doses croissantes (1cp/semaine au début jusqu'à 9 cp/j) du MEDIATOR® comme « dopant ».
  Ce patient avait eu un épisode similaire quelques mois plus tôt. (Imputabilité : C3,S1)

II – HYPERTENSIONS PULMONAIRES :

Suite à une notification d'hypertension artérielle pulmonaire (HTAP) rapportée par le CRPV de Montpellier (MP0300189) lors du Comité Technique du 8 mars 2005, l'enquête sur MEDIATOR® a été étendue aux hypertensions artérielles pulmonaires.

17 notifications (6 CRPV et 13 laboratoire) dont 2 doublons, ont été rapportées :

1. Notifications où MEDIATOR® est associé à un anorexigène :

Lors de la présentation du rapport MEDIATOR® en décembre 1998, 11 notifications d'«Hypertension artérielle pulmonaire » avaient été rapportées.
(9 d'entre elles faisaient partie de l'enquête « Anorexigènes et hypertensions artérielles pulmonaires » présentée au Comité technique du 28 avril 1995)
Elles ont été expertisées par le Professeur WEITZENBLUM (Strasbourg) :
- 7 ont été classées en HTAP d'allure idiopathique
- 3 en HTAP post-capillaire
- 1 en HTAP post-embolique

Le MEDIATOR® n'était jamais prescrit seul : il était présent en association à un ou plusieurs anorexigènes :
- ISOMERIDE® : 7 fois
- ISOMERIDE® + PONDERAL® : 2 fois
- ISOMERIDE ®+ FENPROPOREX® : 1 fois
- DININTEL® + TENUATE DOSPAN® + FRINGANOR® : 1 fois

La durée de traitement par MEDIATOR® est précisée dans 7 cas sur 11 : elle est de plusieurs mois à 5 ans.

Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® est :
- concomitante dans 5 cas,
- antérieure dans 2 cas,
- imprécise dans 1 cas.
- **postérieure dans 3 cas** *(voir détail page suivante) :*

➢ 840425 :
Une femme, 57 ans, obèse depuis longtemps, ayant pris PONDERAL® pendant 2 mois en 1978 et ISOMERIDE® en 1986 (durée inconnue) est hospitalisée en janvier 1993 pour suspicion d'embolie pulmonaire. La scintigraphie pulmonaire est normale.
Le traitement habituel est VOLTARENE®, FELDENE® et DOLIPRANE® pour lombalgies.

En septembre 1993, lors d'une consultation cardiologique, on note une dyspnée stade 3 et un souffle systolique d'insuffisance tricuspidienne. Des signes d'hypertrophie ventriculaire droite sont retrouvées à l'électrocardiogramme.
La dyspnée s'aggravant progressivement, la patiente est hospitalisée en novembre 1993.
A noter que la patiente aurait pris MEDIATOR® , VEINOBIASE®, STILNOX® et XANAX® au cours du mois de septembre 1993.
A l'échodoppler cardiaque, la PAP systolique (PAPs) est estimée à 73 mmHg.
Le cathétérisme cardiaque confirme l'HTAP précapillaire.

En février 1994, l'échodoppler montre une aggravation de la PAPs à 95 mmHg, mais l'état clinique de la patiente est légèrement amélioré début juin 1994.

→ *Avis de l'expert : « HTAP d'allure idiopathique »*

➢ 840663 :
Chez un homme de 48 ans, dont les antécédents sont une hypertension artérielle traitée par FLUDEX®, des glycémie, cholestérolémie et uricémie aux limites supérieures de la normale, un syndrome restrictif post-traumatique, un tabagisme interrompu depuis 1987 et une obésité traitée par ISOMERIDE® de septembre 1990 à avril 1991, est hospitalisé en février 1992 pour syndrome obstructif post-tabagique sévère et aggravation du syndrome restrictif. Une dyspnée d'effort est cotée stade 3-4.
Le traitement de sortie est : MEDIATOR®, VECTARION®, BRONCHODUAL® et BRONILIDE®. FLUDEX® est remplacé par ECAZIDE®, puis LUMITENS®.

Après une amélioration, la dyspnée s'est aggravée et le patient est hospitalisé à nouveau en mai 1993 pour bilan de l'hypoxémie.
A l'échocardiographie, les cavités droites sont très dilatées, comprimant les cavités gauches. La PAPs est estimée à 50 mmHg.
Le cathétérisme droit effectué en juin 1993 pose le diagnostic d'HTAP précapillaire avec une PAP systolique à 90 mmHg. Le patient décède 24 mois plus tard.

→ *Avis de l'expert : « HTAP d'allure idiopathique »*

➢ 840B19 :
Une femme de 51 ans, ayant une HTA, une obésité après une première grossesse en 1966, traitée par PONDINIL® en 1974, puis par ISOMERIDE® de 1985 à 1989 (2 fois 3 mois), une hyperlipidémie traitée par MEDIATOR® de 1989 à janvier 1995, est hospitalisée en août 1994 pour bilan d'un syndrome sec.

Une échocardiographie met en évidence une double atteinte aortique et mitrale et une HTAP. Le traitement antérieur comporte : LIPUR®, SECTRAL®, DEBRIDAT®, PRAGMAREL®, ENDOTELON®.

En décembre 1994, lors d'une échocardiographie de contrôle, la PAPs est estimée à 60-65 mmHg.
Le traitement de la patiente est alors : SECTRAL®, MODURETIC®, KALEORID®, RANIPLEX®, PREPULSID®.

En janvier 1995, l'état de la patiente est stable avec une PAPs évaluée à 55 mmHg.

→*Avis de l'expert : « probable HTAP secondaire à une cardiopathie gauche ».*

Annexe 3-70

2. Notification où MEDIATOR® n'est pas associé à un anorexigène : 5 notifications

Les nouveaux cas (5) notifiés depuis le rapport de juillet 1999 sont inscrits ***en gras***

4 dossiers ont été expertisés par le Professeur WEITZENBLUM, le cinquième étant trop succinct, le sixième nous étant parvenu récemment.

➢ **TO040278 :**

Une femme de 36 ans, traitée pendant 2 ans par MEDIATOR®, 3cp/j, LEVOTHYROX®, GINKOR Fort®, PRAXINOR®, PROZAC®, HEPTAMYL® et CANOL® est hospitalisée le 25 novembre 2003 suite à une détresse respiratoire aiguë. Le diagnostic est un syndrome alvéolo-interstitiel bilatéral. Il n'y a pas de syndrome inflammatoire.
Les antécédents sont une hypothyroïdie, un tabagisme, un surpoids et une insuffisance aortique de grade 2 découverte un an auparavant.
L'échographie montre une fonction systolique ventriculaire gauche à 65%, avec un ventricule gauche dilaté, une insuffisance mitrale de grade 2 et une insuffisance aortique de grade 2.
Le doppler veineux ne montre pas de thrombose veineuse des membres inférieurs.
L'état de la patiente s'améliore sous ALDACTONE®, LASILIX® et RENITEC®. Le traitement associé est LEVOTHYROX®, PROZAC® et CANOL®.
Une échographie de contrôle réalisée après normalisation clinique et radiologique montre une oreillette gauche dilaté et des cavités droites non dilatées sans HTAP.
Conclusion du cardiologue: *« Décompensation cardiaque associée à une probable infection virale broncho-pulmonaire ».*
Le 5 janvier, la patiente est hospitalisée à nouveau pour récidive d'un subOAP sur valvulopathies aortique et mitrale à la faveur d'une virose.
La valvulopathie est recontrôlée par échographie par voie transthoracique : il existe alors une élévation des pressions artérielles pulmonaires avec une PAPs estimée à 50mmHg (N :15 mmHg), le ventricule et l'oreillette gauches sont dilatées.
Le 23 janvier 2004, le remplacement des valves est effectué. On ne note aucun problème dans les suites de l'opération.
L'anatomopathologie des valves montre une lésion dégénérative aspécifique.

Le diagnostic différentiel élimine :
- une maladie rhumatismale : l'aspect échographique n'est pas en faveur
- une endocardite : la recherche est négative
- une maladie auto-immune : les autoanticorps et la recherche des phospholipides sont négatifs.

Il est à noter que la soeur de la patiente est suivie pour valvulopathie.
Le traitement de sortie est PREVISCAN®, RENITEC®, PROZAC®, LEVOTHYROX®.

→*Avis de l'expert* : *« cardiopathie valvulaire sévère, l'OAP ayant entrainé une HTAP post-capillaire. »*

➢ **MP0500189 :**

Une femme de 55 ans, traitée par MEDIATOR®, 1cp/j, depuis 31 mois est hospitalisée en janvier 2005 pour suspicion d'embolie pulmonaire, avec dyspnée d'effort importante, progressivement croissante depuis plusieurs mois.
A l'échographie cardiaque, la PAPs oscille entre 75 et 80 mmHg.
L'angioscanner thoracique ne met pas en évidence de signe d'embolie pulmonaire, mais il semble exister un caillot dans l'artère sous segmentaire gauche.
Les D Dimères sont élevés à 12000.
La scintigraphie pulmonaire de ventilation perfusion montre des troubles perfusionnels avec vraisemblablement un petit épanchement pleural gauche, faisant suspecter des épisodes emboliques multiples partiellement reperfusés
Conclusion du cardiologue : « *Possible embolie pulmonaire compliquée d'HTA pulmonaire importante avec à la scintigraphie des défects périphériques disséminés. Il s'agit possiblement de micro-embols d'installation progressive mais on ne peut exclure formellement une HTAP primitive de type veino-occlusif.* »

Dans [illegible] la patiente [illegible] embolie pulmonaire [illegible] publique, compliquée d'une phlébite, traitée par antivitamines K pendant un an, une HTA ancienne traitée par COTAREG® et un tabagisme modéré.
Le 31 janvier, l'échographie cardiaque de contrôle met en évidence une diminution de la PAPs à 65 mmHg, le ventricule droit est dilaté, l'insuffisance tricuspide est relativement importante.

Le 1 février 2005, la patiente est sortie avec une PAPs à 65 mmHg, le traitement de sortie étant PREVISCAN® (en prévention d'une embolie pulmonaire), COTAREG® et MOPRAL®.
Le 22 février 2005, elle est hospitalisée à nouveau avec altération de l'état général, des douleurs thoraciques, des vomissements et une dyspnée.
La pression artérielle pulmonaire est à 80-85 mmHG, Sa tension artérielle est à 120/90, mais elle chute dans la nuit suivante à 8/5.
La patiente fait une asystolie et décède le lendemain par arrêt cardio-circulatoire.

→*Avis de l'expert* : *« Vraisemblable HTAP post-embolique »*

➢ PS9900385 :
Chez une femme de 50 ans, ayant comme antécédent une hypertension artérielle traitée par LOGIRENE®, 0,5 cp/j et TRIATEC® 2,5 cp/j et une hypercholestérolémie traitée par LIPANTHYL® 1 cp/j et MEDIATOR®, 1 cp/j, est découvert une hypertension artérielle pulmonaire.
Le début des symptômes remontent à décembre 1998 avec l'installation d'une dyspnée d'effort, qui s'est majorée après un an d'évolution.
Lors d'un bilan en mai 1999, la pression artérielle pulmonaire systolique (PAPs) est estimée à 91 mmHg à l'échographie cardiaque.
Un bilan en juin 1999 confirme une HTAP avec une coronarographie, une angiographie et une scintigraphie pulmonaire normales.
Au cathétérisme droit, la pression artérielle pulmonaire moyenne (PAPm) est à 51 mmHg.
Un traitement par FLOLAN® est instauré (21 juin 1999).

Un bilan réalisé à trois mois montre une réelle amélioration et la patiente reste stable cliniquement jusqu'en septembre 2001, où elle constate une réaggravation de la dyspnée d'effort mais la PAPm est alors stable à 55mmHg.

→ *Avis de l'expert : « HTAP d'allure idiopathique »*

➢ **S02001877** :
Une patiente de 55 ans est traitée pendant un an (juillet 2001-septembre 2002) par MEDIATOR® pour un diabète non insulino-dépendant et une dyslipidémie, associé à ALDACTONE®, LASILIX® et TERALITHE®.
En juin 2002, un cathétérisme cardiaque droit montre une hypertension précapillaire avec une PAP à 51 mmHg. L'échographie montre des cavités droites dilatées.
L'échodoppler des membres inférieurs et la scintigraphie pulmonaire sont normaux.

En octobre 2002, la patiente est hospitalisée avec une dyspnée de grade 3. Au cathétérisme cardiaque droit, la PAPm est à 40 mmHg.
Les différents traitements pris par la patiente sont :
PREVISCAN®, LESCOL®, AMAREL®, STABLON®, ATARAX®, TEMESTA®, LIPANTHYL®, LIPUR®, TOCO®, GLUCOPHAGE®.
L'évolution est inconnue.

➢ **S02001046** :
Une femme de 59 ans traitée par MEDIATOR® , 3 cp/j pour un désordre métabolique lipidique depuis novembre 1992 associé à de nombreux médicaments est hospitalisée en mars ou avril 2002 pour dyspnée et malaise.
Une hypertension pulmonaire est diagnostiquée. Le MEDIATOR® est alors arrêté.
Les différents traitements associés sont : CAPTEA®, LOPRIL®, PROGYNOVA®, UTROGESTAN®, HUMORYL® et PRAXINOR®
L'évolution est inconnue et le dossier succinct. *(dossier non expertisé)*

Un homme de 74 ans, avec un BMI = 31, a comme antécédents : une cardiopathie hypertensive diagnostiquée en 1982 avec des épisodes de tachycardie paroxystique depuis 1977, une arythmie par fibrillation auriculaire et un souffle systolique mitral et aortique depuis 1982. Il est traité par MODURETIC® ET SELOKEN® depuis 1982, puis par KERLONE®, HYTACAND®, CHRONO-ADALATE® depuis plusieurs années (au moins 2003) et PREVISCAN® depuis 2001. D'autre part, ce patient prend du MEDIATOR®, 3cp/j pour dyslipidémie depuis 1996.
En 1982, il existe un souffle systolique avec foyers mitral, aortique et aux 2 carotides.

En 2004, lors d'une consultation cardiologique pour dyspnée d'effort et toux sèche persistante signalée depuis février 2003, et apparition récente d'œdèmes des membres inférieurs, la PAPs est estimée à 52 mmHg à l'échocardiographie. L'insuffisance mitrale est de grade I, les cavités droites sont dilatées avec une insuffisance tricuspidienne de grade II.

En juin 2005, la dyspnée s'est aggravée. L'échocardiographie est stable par rapport à 2004, l'insuffisance mitrale est peu importante, l'insuffisance tricuspidienne est importante, la PAPs est estimée à 55 mmHg.
Le 4 août 2005, le patient consulte un pneumologue, car il se plaint de toux survenant dans le primo-décubitus, qui ne semble qu'en partie liée à la cardiopathie, pour discuter du maintien des antihypertenseurs, notamment béta-bloquants et antagoniste de l'angiotensine II. On évoque la possibilité d'un reflux gastro-oesophagien, qui sera traité par OGAST® pendant 1 mois.

Le 30 août 2005, le MEDIATOR® est arrêté. L'état du patient s'améliore très rapidement avec disparition de la toux et de l'essoufflement.(le lendemain de l'arrêt du MEDIATOR®, selon le patient). *(dossier non expertisé)*

3. Fréquence :

Depuis le début de la commercialisation de MEDIATOR®, le nombre de boites de 30 comprimés vendues est de : 110 693 331, correspondant à 45 515 349 mois de traitement*.
(Le nombre de patients traités est évalué à 3 390 459 patients).

Après élimination des HTAP post-emboliques (2) et post-capillaires (5), il reste 10 cas HTAP d'allure idiopathique soit :
- 1 cas pour 11 069 333 boites vendues
- ou 1 cas pour 4 551 534 mois de traitement.

(*) mois de traitement : estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés (1 mois = 30,4 jours).

Après élimination des HTAP d'allure idiopathique (7) survenues lors de traitement par MEDIATOR associé à un anorexigène et un dossier trop succinct (S02001046), il reste 2 cas d'HTAP d'allure idiopathique soit :
- 1 cas pour 55 346 666 boites vendues
- ou 1 cas pour 22 757 674 mois de traitement.

III – CONCLUSIONS :

- Troubles neuropsychiatriques :
Cette enquête de Pharmacovigilance permet de confirmer la réalité des *confusions* qui peuvent apparaître sous MEDIATOR. Cet effet est déjà présent dans le RCP, mais il paraît judicieux de développer le terme *« confusion »* en détaillant les symptômes tels que : Troubles des fonctions cognitives : *désorientation temporo-spatiale,* troubles du comportement *: agitation, délire,* troubles de la perception : *hallucinations*

-Hypertensions artérielles pulmonaires :

Compte tenu de l'incidence des HTAP d'aooure idiopathique (1 à 2 cas par millions et par an), le nombre de cas d'HTAP d'allure idiopathique rapporté dans l'enquête ne constitue pas un signal significatif de toxicité du MEDIATOR dans la classe organe cardiovasculaire.

Hypertensions artérielles pulmonaires (1)

N°	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
PP890081	F,42	1 an	DININTEL TENUATE DOSPAN FRINGANOR	5 ans 5 ans 5 ans	Concomitant	U	
NC9300007 = 052454	M,48	4 ans	ISOMERIDE ZYLORIC LIPANTHYL	3 ans 6 ans	Concomitant	D	
10052455	F,46	25 mois	ISOMERIDE CORGARD BUSPAR VELITEN ALDACTONE	580 jours	Concomitant	F	
10052733	F,71	60 mois	ISOMERIDE	45 jours	Antérieur	F	HTA post-capil
10840193	F,47	?	ISOMERIDE COVERSYL LASILIX GLUCOPHAGE	730 jours	Concomitant	F	
10840255	F,57	?	ISOMERIDE PONDERAL STILNOX XANAX VEINOBIASE	? 2 mois	Postérieur	F	
10840663	M,48	+ mois	ISOMERIDE FLUDEX	210 jours	Postérieur	F	
10840770	F,66		ISOMERIDE FENPROPOREX	1 mois	Antérieur	F	HTAP post-embo
10840954	F,54		ISOMERIDE STAGID DIAMICRON	1-2 semaines	Inconnu	A	HTA post-capil
10840B19	F,51	5 ans ?	ISOMERIDE SECTRAL MODURETIC KALEORID LEXOMIL RANIPLEX PREPULSID	6 mois	Postérieur	F	HTA post-cap
10840D01	F,59	4 ans	ISOMERIDE PONDERAL ZOCOR PROGESTOGEL SPIROCTAN	Environ 12 mois Environ 6 mois	Concomitant	D	

Hypertensions artérielles pulmonaires (2)

N°	S/Age	Durée TTT	TTT associé	Evolution	Commentaires
TO040278	**F,36**	**2 ans**		**B**	**HTAP post-capillaire**
MP0500189	**F,55**	**31 mois**	**MOPRAL PREVISCAN COTAREG VIOXX**	**D**	**HTAP post-embolique**
PS9900385	F,50	4 à 5 ans	LOGIRENE TRIATEC Fenofibrate	U	
S02001877	**F,55**	**1 an**	**TERALITHE ALDACTONE LASILIX LESCOL PREVISCAN LIPANTHYL, LIPUR GLUCOPHAGE...**	**U**	
S02001046	**F,59**	**9.5 ans**	**CAPTEA LOPRIL HUMORYL PRAXINOR PROGYNOVA UTROGESTAN**	**U**	
NT0500397 = S05001666	**M, 74**	**9 ans**	**HYTACAND CHRONO-ADALATE KERLONE PREVISCAN**	**B**	**HTAP Post-capillaire**

Les nouveaux cas (5) notifiés depuis le rapport de juillet 1999 sont inscrits ***en gras***

Annexe 3-71

COMPTE-RENDU REUNION MEDIATOR /AFSSAPS 13.10.06

Objectif :

Examen des modalités pratiques de mise en œuvre des études demandées (courrier AFSSAPS du 16.03.06, suite au rapport de la Commission Nationale de Pharmacovigilance du 29.11.05) :

- étude d'utilisation-prescription
- étude expérimentale sur modèle animal d'HTAP

N.B. : Etude au niveau des Centres d'Evaluation et d'Information sur la Pharmaco-dépendance (CEIP) : à mettre en œuvre par l'AFSSAPS.

Représentants AFSSAPS :

- Mme CASTOT (Surveillance des risques, du Bon Usage et de l'Information sur les Médicaments)
- Mme KREFT-JAIS (Pharmacovigilance)
- Professeur CARON (Président Commission Pharmacovigilance)
- Mme POROKHOV (Pharmacovigilance, Gamme métabolisme)
- Mme REY-QUINIO (Evaluation thérapeutique, Pharmaco-toxico-clinique 2)
- Mme DAVID (Rapporteur Centre régional Pharmacovigilance Besançon)

Délégation Servier :

- Francis WAGNIART (Pharmacovigilance)
- Marie FRANCILLARD (Division thérapeutique métabolisme)
- Marie PARAIRE (Division thérapeutique métabolisme)
- Guyslaine CLEMENT-BAUDENA (Etudes utilisation-prescription)
- Pierre MONTES (Affaires pharmaceutiques France)

Rappel du contexte :

Evaluation du rapport bénéfice/risque rejoignant la demande en cours de la HAS en vue de la réévaluation du SMR de la spécialité.

Présentation des résultats d'étude d'utilisaton-prescription :

Etude menée par l'Institut Thalès sur la période mai 2004 / avril 2005 et mai 2005 / avril 2006, montrant qu'environ 80 % des prescriptions de Médiator sont réalisées chez des patients dyslipidémiques et/ou diabétiques, 11,5 % chez des patients obèses et 8,5 % pour d'autres diagnostics. Ces chiffres restent stables. L'AFSSAPS demande de préciser les caractéristiques de la population obèse.

Présentation du synopsis de l'étude modèle animal envisagée :

- Grandes classes de modèles animaux utilisés
- Rationnel du choix du rat Fawn Hooded
- Schéma de l'étude : les représentants de l'AFSSAPS envisagent de soumettre cette proposition au Groupe de travail pré-clinique de la Commission d'AMM.

Prochaines étapes :

- Réévaluation du bénéfice/risque envisagée le 23 novembre par le Groupe de travail interne / diabète
- Proposition d'étude modèle animal à soumettre au Groupe de travail pré-clinique si possible en novembre ou décembre, puis à la Commission de pharmacovigilance.

Modèle animal
Hypertension artérielle pulmonaire (HTAP)

- Rappel caractéristiques HTAP
- Modèles animaux HTAP - Choix du modèle
- Projet d'étude

1

Rappel caractéristiques HTAP

- Résistance vasculaire pulmonaire élevée et insuffisance ventriculaire droite
- « Remodeling » vasculaire des petites artères pulmonaires
  - prolifération anarchique des cellules endothéliales et musculaires lisses
  - muscularisation des artérioles et épaississement de la media

2

Modèles animaux d'HTAP

- Stimuli (patho)physiologiques :
  - ex. rat en hypoxie chronique
- Stimuli chimiques et toxiques :
  - ex. rat monocrotaline
- Modèles génétiques :
  - ex. rat Fawn-Hooded

3

Modèles animaux d'HTAP : choix du modèle

Rat Fawn-Hooded (FH) : modèle retenu

- Déficit de stockage de la sérotonine dans les plaquettes
- Susceptibilité de développer spontanément une HTAP
- HTAP accélérée si exposition en altitude (hypoxie légère)

4

Projet étude rat Fawn-Hooded (FH)

- Rats FH (n=80) : 8 groupes contrôles ou traités 6 mg/kg
- Normoxie ou hypoxie chronique
- Traitement par voie orale en chronique (3 semaines + réversibilité)
- Paramètres évalués :
  - Hémodynamiques : Pression artérielle pulmonaire
    Pression artérielle systémique
  - Index d'hypertrophie ventriculaire droite : poids VD/VG+septum
  - Histologie : prolifération cellulaire et degré de muscularisation des artérioles

5

Annexe 3-71

PROJET D'ETUDE MODELE ANIMAL HYPERTENSION ARTERIELLE PULMONAIRE

Introduction

L'hypertension artérielle pulmonaire (HTAP) est caractérisée par une résistance vasculaire pulmonaire élevée et une insuffisance ventriculaire droite. Elle est associée à des modifications vasculaires.
Le « remodeling » vasculaire consiste en des altérations structurales et fonctionnelles des cellules endothéliales et musculaires lisses dans les petites artères pulmonaires, le mécanisme pathogène précis de ce « remodeling » vasculaire pulmonaire n'étant pas encore complètement élucidé.
Histologiquement, la maladie est caractérisée par une prolifération anarchique des cellules endothéliales et musculaires lisses avec une muscularisation des artérioles non préalablement muscularisées et un épaississement de la media des artérioles normalement muscularisées.

Justification du modèle

Une grande variété de modèles animaux a été développée afin d'essayer de comprendre les mécanismes physiopathologiques de l'HTAP idiopathique et de pouvoir évaluer des stratégies thérapeutiques.
Trois grandes classes de modèles expérimentaux in vivo ont été utilisées :

- Les modèles utilisant des stimuli (patho)physiologiques comme l'hypoxie aiguë et chronique chez le rat et la souris principalement (1). En réponse à une hypoxie aiguë, il est observé une vasoconstriction des artères pulmonaires, à la différence des artères systémiques qui se dilatent, et une exposition chronique à l'hypoxie conduit à une HTAP.
- Les modèles utilisant des stimuli chimiques et toxiques comme la monocrotaline chez le rat (2). La monocrotaline est une phytotoxine qui induit une lésion endothéliale avec une toxicité sélective pour les vaisseaux pulmonaires, sans effet sur les vaisseaux systémiques.
- Les modèles dits génétiques comme le rat Fawn-Hooded (FH) (3). Le rat FH, qui présente un déficit de stockage de la sérotonine dans les plaquettes, a une susceptibilité génétique de développer une HTAP soit spontanément, soit de façon accélérée et plus sévère par une exposition en altitude donc à un facteur environnemental (ici l'hypoxie légère).

Tous ces modèles expérimentaux partagent à des degrés divers les caractéristiques de l'atteinte vasculaire observée dans l'HTAP, sachant qu' aucun modèle animal ne reproduit complètement l'ensemble des modifications observées sur les prélèvements de poumons de patients atteints d'HTAP idiopathique. De plus, il est à noter que tous ces modèles ont été développés dans le but d'étudier des thérapeutiques spécifiques de l'HTAP et non pour évaluer le potentiel toxique de médicaments.
Les modèles expérimentaux qui ont été les plus utilisés sont ceux cités précédemment, à savoir le rat en hypoxie, le rat monocrotaline et le rat Fawn-Hooded (FH).

Parmi ces trois modèles, le rat FH a été retenu. Chez l'Homme, le facteur sérotoninergique semble très important dans la prédisposition à développer une HTAP idiopathique.

Proposition d'étude

L'effet de benfluorex serait évalué sur différents groupes de rats FH en conditions de normoxie ou d'hypoxie. Cela permettrait d'étudier deux situations : développement d' une HTAP chez un animal présentant une susceptibilité génétique d'en développer ; potentialisation d'une HTAP induite par une exposition à une hypoxie chronique.
En pratique, benfluorex sera administré par voie orale en traitement chronique.

Différents paramètres seront évalués à l'issue de ce traitement chronique et après arrêt du traitement dans un groupe de réversibilité:

1. Paramètres hémodynamiques : après anesthésie, un cathéter sera inséré dans l'artère pulmonaire pour mesure de la pression artérielle pulmonaire (PAP) et dans l'artère carotide droite pour mesure de la pression artérielle systémique (PAS).

2. Index d'hypertrophie ventriculaire droite : après prélèvement du cœur le ratio du poids du ventricule droit sur le poids du ventricule gauche plus le septum sera évalué.

3. Remodeling vasculaire pulmonaire : après prélèvement et fixation, des coupes sont effectuées sur le poumon droit et examinées après coloration pour l'évaluation du degré de remodeling vasculaire (muscularisation des artérioles)

Références

(1) Van Suylen RJ et al. Pulmonary artery remodeling differs in hypoxia- and monocrotaline-induced pulmonary hypertension. Am J Respir Crit Care Med, 1988 ; 157:1423-1428.

(2) Schermuly RT et al. Chronic sildenafil treatment inhibits monocrotaline-induced pulmonary hypertension in rats. Am J Respir Crit Care Med, 2004;169:39-45.

(3) Le Cras TD et al. Early abnormalities of pulmonary vascular development in the Fawn-Hooded rat raised at Denver's altitude. Am. J. Physiol Lung Cell Mol Physiol, 2000 ; 279:L283-291.

Objectif de l'étude

Recherche d'un éventuel mésusage de MEDIATOR par l'analyse de son utilisation / prescription

Choix méthodologique : observatoire THALES

- L'observatoire épidémiologique permanent THALES :
  - est fondé sur l'activité régulière d'un échantillon national de médecins généralistes libéraux (1 200 MG) informatisés équipés du logiciel Doc'ware
  - permet de recueillir et d'analyser longitudinalement des données issues de dossiers patients en étudiant précisément le contexte de la prescription dans la pratique courante
  - la procédure permet de remonter en continu via le réseau informatique des données anonymes et codées

Choix méthodologique : observatoire THALES (suite)

- La représentativité de l'échantillon est établie sur 3 critères
  - répartition par région
  - répartition par sexe
  - répartition par tranche d'âge
- Cette garantie de représentativité sur les critères usuels considérés comme ayant un impact sur les pratiques de prescriptions, permet de procéder à des extrapolations nationales sur les paramètres mesurés.
- Par ailleurs, il est vérifié :
  - que l'observatoire recouvre des réalités proches des référentiels connus pour le secteur conventionnel (secteur 1 et secteur 2) et le potentiel T.V.F
  - que la population des patients suivis par les médecins THALES a les mêmes caractéristiques que la population des patients du régime général d'Assurance Maladie suivie en médecine de ville (âge, sexe, taux ALD)

Méthodologie de l'étude MEDIATOR

- Analyse de la prescription de MEDIATOR chez les médecins généralistes en fonction des indications pour lesquelles il a été prescrit.
- Période analysée :
  - mai 2004 – avril 2005
  - mai 2005 – avril 2006
- Nous avons distingué 5 groupes exclusifs de patients :

A : Patients diagnostiqués **dyslipidémiques** dans l'année (non diagnostiqués diabétiques)

B : Patients diagnostiqués **diabétiques** dans l'année (non diagnostiqués dyslipidémiques)

C : Patients diagnostiqués **diabétiques et dyslipidémiques** dans l'année

D : Patients **non diabétiques, non dyslipidémiques** ayant reçu un diagnostic « **obèses** », « **surcharge pondérale** », « **prise de poids** », associé à la prescription de MEDIATOR

E : **Autres patients non diabétiques, non dyslipidémiques** ayant reçu d'**autres diagnostics** associés à la prescription de MEDIATOR

Répartition du nombre de prescriptions et de patients traités par MEDIATOR en fonction du diagnostic

		de mai 2004 à fin avril 2005			de mai 2005 à fin avril 2006		
		Nombre de patients MEDIATOR	Nombre de prescriptions MEDIATOR générales	Nombre de prescriptions par patient	Nombre de patients MEDIATOR	Nombre de prescriptions MEDIATOR générales	Nombre de prescriptions par patient
A	Patients dyslipidémiques	270 302	609 998	2,3	286 909	668 490	2,3
		50,8%	44,8%		51,6%	45,5%	
B	Patients diabétiques	63 161	203 395	3,2	64 909	213 551	3,3
		11,9%	14,9%		11,7%	14,5%	
C	Patients dyslipidémiques et diabétiques	81 349	306 222	3,8	80 662	301 170	3,7
		15,3%	22,5%		14,5%	20,5%	
D	Patients avec diagnostic obésité / surcharge pondérale / prise de poids associé à la prescription	76 443	172 527	2,3	73 193	157 679	2,2
		14,3%	12,7%		13,2%	10,7%	
E	Patients avec d'autres diagnostics associés à la prescription du MEDIATOR	43 049	121 230	2,8	43 615	127 264	2,9
		8,1%	8,1%		7,8%	8,7%	
Total MEDIATOR		534 330	1 463 378	2,8	553 328	1 468 153	2,7
		100,0%	100,0%		100,0%	100,0%	

CONCLUSION

- Environ 80 % des prescriptions de MEDIATOR sont réalisées chez des patients dyslipidémiques et / ou diabétiques

  (mai 04 – avril 05 : 80,3 % / mai 05 – avril 06 : 80,5 %)

- 11,5 % chez des patients « obèses »

  (mai 04 – avril 05 : 11,5 % / mai 05 – avril 06 : 10,7 %)

- Ces taux restent stables au cours du temps

Annexe 3-71

Beatrice POROKHOV - SERVIER- Mediator- Compte-rendu de réunion de concertation du 13 mars/ Diaporamas

MARS 2007
MEDIATOR / Sunca

De :
Destinataire : ,
Date : Mar, Mars 20, 2007 20:48
Objet : SERVIER- Mediator- Compte-rendu de réunion de concertation du 13 mars/ Diaporamas
CC : , ,
Pièces jointes : , ,

Mesdames,

Comme convenu lors de notre réunion de concertation mardi dernier, au cours de laquelle nous avons fait le point sur Mediator, je vous prie de bien vouloir trouver ci-joint une proposition de compte-rendu des points discutés. Sont également jointes les présentations Powerpoint préparées en vue de la réunion de la Commission nationale de PV de mardi prochain, le 27 mars.

Afin de m'assurer de la bonne transmission du message, je vous serai reconnaissante de bien vouloir m'en confirmer réception. Je reste à votre disposition pour toute question ou information complémentaire.

Veuillez agréer, Mesdames, l'expression de mes sincères salutations.

Florence MAHLBERG-GAUDIN
Directeur adjoint- Affaires Pharmaceutiques France
AMM et Transparence

Laboratoires SERVIER- Science Union

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COMPTE-RENDU DE REUNION

Mardi 13 mars 2007, de 18h à 19h, à l'AFSSAPS- Saint-Denis

Objet : Réunion de concertation - Point sur MEDIATOR®

Ordre du jour : En prévision de la réunion de la Commission nationale de pharmacovigilance du mardi 27 mars 2007 :

- Mise à jour sur la pharmacovigilance
- Résultats de la réévaluation du B/R
- Résultats de l'étude d'utilisation

Participants :

Représentants AFSSAPS :

- Pr J. CARON (Président de la Commission nationale de pharmacovigilance)
- Dr JP. KANTELIP (Directeur du centre régional de pharmacovigilance de Besançon)
- Dr M. DAVID-LAROCHE (CRPV Besançon) *Présente au téléphone*
- Dr C. KREFT-JAIS (Chef de département délégué à la pharmacovigilance)
- Mme B. POROKHOV (Unité de pharmacovigilance, Gamme métabolisme)

Représentants SERVIER :

- Dr G. CLEMENT-BAUDENA (Directeur- Etudes d'utilisation/prescription)
- Dr M. FRANCILLARD (Directeur division thérapeutique métabolisme)
- Mme F. MAHLBERG-GAUDIN (Directeur adjoint affaires pharmaceutiques France)
- M. P. MONTES (Directeur affaires pharmaceutiques France)
- Mme M. PARAIRE (Chef de département préclinique- Division métabolisme)
- Dr F. WAGNIART (Directeur de la pharmacovigilance)

Déroulement de la réunion :

1. ***Rappel des conclusions de la Commission de pharmacovigilance de novembre 2005, par le Pr Caron,*** et la décision d'une réévaluation de la balance bénéfice/risque de MEDIATOR® (13 voix pour, 10 voix contre, 5 abstentions) et mise en œuvre des études suivantes :
   i. Etude d'utilisation/prescription
   ii. Réévaluation de l'efficacité de MEDIATOR® dans le diabète de type 2.
   iii. Etude expérimentale sur modèle animal permettant d'évaluer le potentiel de MEDIATOR® à engendrer des HTAP
   iv. Etude au niveau des CEIP par saisine de la Commission nationale des stupéfiants et psychotropes, afin d'évaluer un éventuel problème de pharmacodépendance.

2. ***Mise à jour de la pharmacovigilance (Dr DAVID-LAROCHE, téléphone)***

   a. HTAP

Trois nouveaux cas ont été discutés :

- Un cas provenant du CRPV de Toulouse : patiente de 50 ans, avec obésité (92 kg- 156 cm, IMC = 38 kg/m²), diabète et HTA. Traitée entre 2000 et 2003 à 3 cp/j. Présente une dyspnée, hypoxémie, sans apnée du sommeil. Cathétérisme en sept 2005. Instauration d'un antagoniste calcique. En 2006, découverte d'une communication inter-auriculaire.

- Deux cas très récents, provenant du CRPV de Brest :
  - 1 patiente de 51 ans, obèse (110 kg-163 cm ; IMC= 41 kg/m²)), avec diabète, phlébite, apnées du sommeil, BPCO tabagique, ayant pris Mediator pendant 3 mois il y a 10 ans. En décembre 2006 : PAPm= 60mmHg
  - 1 femme de 58 ans, obèse (127 kg - 161 cm ; IMC= 49 kg/m²) avec diabète et HTA, et traitement par Mediator pendant 10 ans. En décembre 2006 : PAPm=46 mmHg

Il a été proposé de faire évaluer ces cas par un expert, si possible avant la Commission nationale du 27 mars.

b. Troubles neuro-psychiatriques

- 2 cas de bouffées délirantes
- 1 cas de dépression chez une femme dépressive avant l'initiation du traitement.

Conclusion :

- Au total, 18 notifications d'HTAP, sans compter les 2 cas très récents de Brest (7 par CRPV, 13 par le laboratoire, 2 doublons), dont 11 avec prise associée d'anorexigène.
- La fréquence est donc de 1 cas/11 411 298 boîtes (*vs.* 1 cas/11 069 333 en 2005), soit 1 cas/ 4 692 145 mois de traitement (*vs.* 1/ 4 555 534 en 2005).

Pas de modification depuis la Commission nationale de 2005 : bilan comparable à 2005, pas d'éléments nouveaux.

3. Etude d'utilisation/ prescription

Présentation des résultats par G. Clément-Baudena (Servier).

- Rappel des résultats présentés en réunion de concertation du 13 octobre 2006 :
  - Méthodologie : observatoire Thalès
  - Résultats de prescriptions stables sur les périodes mai 2004-avril 2005 et mai 2005-avril 2006 : ~80% chez les patients ayant une dyslipidémie et/ou diabète, 10.7% chez des patients obèses ou avec surcharge pondérale, et 8.7 % pour autres diagnostics.
- Typologie des patients du groupe obésité (analyses demandées lors de la réunion de concertation du 13/10/2006) :
  - Le groupe de prescription pour obésité/surcharge pondérale (représentant 10.7% des prescriptions), inclut principalement des femmes (85%, *vs.* 66% du total de prescriptions),
  - L'analyse n'a pas montré de différence de saisonnalité entre le groupe « obésité » et le total patients MEDIATOR.

Conclusion : l'information apportée correspond à la demande. Données claires et précises.

4. Etude expérimentale

Le groupe de travail préclinique a été chargé d'évaluer le projet proposé par le laboratoire. Le groupe a conclu à l'absence de modèle animal validé permettant l'exploration d'un mécanisme potentiateur/déclencheur d'HTAP. La démarche active du laboratoire dans la recherche d'un modèle a été reconnue.

5. *Réévaluation bénéfice/risque*

L'étude Moulin a été évaluée par le groupe de travail DEUG. Dans l'attente du relevé d'avis définitif, les conclusions n'ont pas été discutées plus en détails.

6. *Enquête de pharmacodépendance au niveau des CEIP*

Enquête non réalisée.

CONCLUSION :

Pas d'éléments nouveaux en termes de pharmacovigilance depuis 2005 : bilan comparable.
Tous les éléments à préparer pour l'évaluation par la Commission nationale de pharmacovigilance sont disponibles.

Plan d'action :

- **Envoi par Servier (*semaine précédant la réunion de la Commission nationale de pharmacovigilance du 27 mars ; adresser à Mme Porokhov) :***
  - **Compte-rendu de la réunion de concertation du 13 mars ;**
  - **Présentation Powerpoint préparée pour le 27 mars, incluant :**
    - **Les résultats de l'étude de prescription**
    - **4-5 diapos résumant l'étude Moulin,**
    - **1-2 diapos sur le modèle animal**
- **Envoi par le département de Mme Rey-Quinio ou de Mme Kreft-Jays, d'ici la fin de semaine, du relevé d'avis du groupe de travail DEUG et du calendrier de passage en Commission d'AMM (*adresser au contact Servier : B. Dehesdin ou F. Mahlberg-Gaudin)***
- **Le résumé de la PV sera préparé par le rapporteur**

afssaps
Agence française de sécurité sanitaire des produits de santé
Direction de l'Evaluation des Médicaments et des Produits Biologiques
Unité de Pharmacovigilance

Saint-Denis, le 29 mai 2007

COMMISSION NATIONALE DE PHARMACOVIGILANCE

Compte rendu de la réunion du mardi 27 mars 2007

Etaient présents :

Membres de la Commission nationale de pharmacovigilance :

M. CARON (président)
M. ANDREJAK (vice-président)
M. BALLU (représentant de la Direction Générale de la Santé, membre de droit)
Mme BARBAUD
Mme BAVOUX suppléante de Mme LAINE-CESSAC
M. BLAYAC suppléant de M. MONTASTRUC (pour les dossiers ZYBAN® et ARIXTRA®)
M. BONNETERRE
M. BOULU
Mme BOUXIN-METRO (représentant l'INSERM)
Mme BRUNET
M. CARLIER
M. GALEZOWSKI suppléant de M. HANSLIK
M. GIROUD
M. IMBS
M. JACQUES
Mme JOLLIET
Mme JONVILLE-BERA suppléante de Mme AUTRET-LECA
Mme JOUAN-FLAHAULT
M. KANTELIP suppléant de M. MERLE
Mme LEMER MALLE
Mme LILLO LE LOUET suppléante de Mme SGRO
Mme MIREMONT-SALAME suppléante de Mme COSTAGLIOLA
M. MONTASTRUC (pour les dossiers MEDIATOR®, CELANCE® et ZYVOXID®)
M. MUNERA
M. PELLETIER
M. SCHMITT
Mme SGRO
M. VIAL

Unité de Pharmacovigilance :
Mme KREFT-JAIS
Mme CARDONA
Mme HALLE
Mme OUARET
Mme PAGE-LECOMPTE
Mme POROKHOV
Mme ROBINE

Interne en Pharmacie :
Mlle VERMILLARD

CRPV :
Mme BEYENS
Mme DAVID-LAROCHE
Mme LE BELLER

Etaient excusés :
M. DOUARD
M. ESCHALIER
M. HANSLIK
M. LIOTE
M. VERNOIS

SURBUM :
M. FAGOT
Mme ROULEAU

Unité Psychotropes et Stupéfiants :
Mme CELESTIN

Unité PTC 2 :
Mme HAY
Mme REY-QUINIO

Unité Affaires réglementaires :
Mme FOSSET

Stagiaire
M. MCHAIK

Annexe 3-72

DOSSIERS TRAITES PAR LABORATOIRES

- **MEDIATOR® (CHLORHYDRATE DE BENFLUOREX)**

LABORATOIRE CONCERNE	*REPRESENTANTS*
SERVIER :	M. BAUDENA M. DEHESDIN M. FRANCILLARD Mme MAHLBERG GAUDIN M. MONTES Mme PARAIRE M. WAGNIART

- **ENQUETE OFFICIELLE DES CAS DE VALVULOPATHIES CARDIAQUES RAPPORTES AVEC CELANCE® (PERGOLIDE)**

LABORATOIRE CONCERNE	*REPRESENTANTS*
LILLY :	M. MEGLIO Mme MUZARD Mme SALAMA BIARD

- **SUIVI NATIONAL DE ZYBAN® (CHLORHYDRATE DE BUPROPION)**

LABORATOIRE CONCERNE	*REPRESENTANTS*
GLAXO SMITH KLINE :	M. DAURY Mme DECOUT Mme MALBEZIN

- **SUIVI NATIONAL D'ARIXTRA® (FONDAPARINUX)**

LABORATOIRE CONCERNE	*REPRESENTANTS*
GLAXO SMITH KLINE :	Mme CHAUMERLIAC M. DAURY Mme MALBEZIN

GESTION DES CONFLITS D'INTERETS

Aucune situation de conflit d'intérêt important, susceptible de faire obstacle à la participation des experts à la délibération, n'a été identifiée ni déclarée au cours de la séance de la Commission nationale de pharmacovigilance du 27 mars 2007.

II –MEDIATOR® (CHLORHYDRATE DE BENFLUOREX) : MISE A JOUR DES DONNEES DE PHARMACOVIGILANCE, RESULTATS DE LA REEVALUATION DU BENEFICE/RISQUE ET RESULTATS DE L'ETUDE D'UTILISATION

1 – Introduction

Nom commercial	MEDIATOR®
DCI	Chlorhydrate de benfluorex
Formes pharmaceutiques	Comprimé pelliculé à 150 mg
Classe pharmacologique	Hypolipidémiant
Procédure d'enregistrement	Procédure nationale
Titulaire de l'AMM	Laboratoires Servier

Date(s) de passage en Comité technique de pharmacovigilance : 13 mars 2007
Passage en Commission nationale de pharmacovigilance à la demande du Comité technique de pharmacovigilance
Nom(s) du(des) rapporteur(s) : Pr. J.P. KANTELIP / Dr M. DAVID-LAROCHE – Centre Régional de pharmacovigilance (CRPV) de Besançon

MEDIATOR® (chlorhydrate de benfluorex) a obtenu une AMM lors d'une procédure nationale d'enregistrement en 1974, modifiée en 1987 et 1990. Les indications actuelles sont :
- adjuvant du régime adapté dans les hypertriglycéridémies ;
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Ce médicament est commercialisé en France depuis 1976.

2 – Contexte

En décembre 2004, la notification de plusieurs cas d'effets indésirables, pouvant évoquer un effet de type amphétaminique avec MEDIATOR®, a conduit à une actualisation des données relatives aux effets indésirables neuro-psychiatriques observés avec cette spécialité. Par ailleurs, la notification d'un cas d'hypertension artérielle pulmonaire, rapportée lors du Comité Technique du 8 mars 2005, a justifié une extension de l'enquête aux hypertensions artérielles pulmonaires (HTAP).

Les résultats de cette enquête officielle ont été présentés par le CRPV de Besançon au Comité Technique de Pharmacovigilance le 07 juin 2005 et à la Commission Nationale de Pharmacovigilance le 29 novembre 2005. La Commission avait demandé la réévaluation de la balance bénéfice/risque de Médiator®, une étude d'utilisation/prescription, une étude expérimentale sur un modèle animal permettant d'étudier le potentiel du benfluorex à engendrer des HTAP et une étude au niveau des Centres d'Evaluation et d'Information sur la Pharmacodépendance (CEIP) afin d'identifier un éventuel problème de pharmacodépendance. La réalisation de cette dernière étude n'a pas été jugée immédiatement nécessaire à cette étape de l'évaluation du dossier en raison du fondement théorique de cette demande (substance de type amphétaminique) et de l'absence d'un signal clairement identifié dans les données notifiées.
Les données disponibles ont été présentées au Comité technique de pharmacovigilance du 13 mars 2007 puis à la Commission nationale de pharmacovigilance du 27 mars 2007.

3 - Actualisation de l'enquête de pharmacovigilance sur les HTAP et les troubles neuropsychiatriques

Le CRPV de Besançon a actualisé les données de pharmacovigilance du benfluorex concernant les HTAP et les effets indésirables neuropsychiatriques. Concernant les effets neuro-psychiatriques, 39 cas avaient été notifiés jusqu'à novembre 2005 auxquels s'ajoutent 4 nouveaux cas : 1 cas de dépression, 1 cas d'agitation et 2 cas de délire. Concernant les cas de délire, le premier concerne une femme de 33 ans sans antécédent psychiatrique, traitée par MEDIATOR® 3 comprimés par jour puis 2 comprimés par jour pendant 5 mois, qui a présenté sous traitement un délire de persécution avec confusion, traité par ZYPREXA®, TERCIAN® et XANAX®, d'imputabilité douteuse. Le deuxième cas de délire concerne un homme de 31 ans, avec psychose chronique, traité par MEDIATOR® 2 comprimés par jour pendant 3 ans, qui a présenté un délire avec agressivité, régressif à l'arrêt du traitement, d'imputabilité douteuse.

Concernant les HTAP, 3 nouveaux cas potentiels ont été notifiés et ont fait l'objet d'une expertise :

- Le premier cas concerne une femme de 50 ans avec un indice de masse corporelle (IMC) à 38kg/m2, un diabète de type 2, une hypothyroïdie et une HTA, traitée par MEDIATOR® 3 comprimés par jour de 2000 à 2003. En 2003, apparaît une dyspnée d'aggravation progressive. En octobre 2005, une HTAP pré-capillaire est mise en évidence et est jugée moyennement sévère avec une pression artérielle pulmonaire systolique (PAPs) à 79 mmHg. Une origine multifactorielle est évoquée car, à la prise de benfluorex, s'ajoutent une obésité et un déficit ventilatoire restrictif sur paralysie de la coupole diaphragmatique droite. L'expertise conclut à une HTAP idiopathique ;
- Le deuxième cas concerne une femme de 51 ans avec un IMC de 41 kg/m2, avec un syndrome d'apnée du sommeil, une BPCO post-tabagique, un diabète de type 2 et des antécédents de phlébite. Cette patiente, traitée par MEDIATOR® durant 3 mois 10 ans auparavant, présente en décembre 2006 une pression artérielle pulmonaire moyenne (PAPm) à 60 mmHg avec à la scintigraphie pulmonaire des séquelles minimes post-emboliques. L'expertise conclut à une possible HTAP idiopathique, mais, en l'état et compte tenu de la chronologie, les pathologies associées et les données sont insuffisantes pour retenir ce dossier.
- Le troisième cas concerne une femme de 58 ans avec un IMC à 49 kg/m2, un diabète de type 2 et une HTA. Cette patiente, traitée par MEDIATOR® pendant 10 ans, présente en décembre 2006 une PAPm à 46 mmHg. L'expertise considère que l'HTAP idiopathique est possible mais que le dossier est beaucoup trop succinct pour permettre de statuer.

Par ailleurs, un cas de valvulopathie a été notifié au CRPV de Toulouse.

Les conclusions de l'enquête concernant les troubles neuro-psychiatriques ne sont pas modifiées par les données additionnelles. Elles confirment la réalité de la survenue de confusions sous MEDIATOR® et la nécessité de détailler dans la rubrique « Effets indésirables » du RCP, le terme de confusion, comme cela a été proposé à la Commission nationale du 29 novembre 2005.
Le nombre de cas notifiés d'HTAP idiopathiques, après expertise et prise en compte des nouveaux cas d'HTAP rapportés depuis 2005, est de 3, soit 1 cas pour 41 841 426 boites vendues ou 1 cas pour 17 204 533 mois de traitement. L'incidence naturelle l'HTAP idiopathique est quant à elle de 1 à 2 cas par million et par an. Ainsi, selon l'avis du rapporteur et compte tenu de l'incidence naturelle des HTAP idiopathiques, le nombre de cas d'HTAP d'allure idiopathique retrouvés dans l'enquête ne constitue pas un signal significatif de toxicité du MEDIATOR® dans la classe organe cardiovasculaire.

4 - Etude expérimentale sur un modèle animal permettant d'étudier le potentiel du benfluorex à engendrer des HTAP

Concernant le projet de modèle expérimental chez l'animal, le laboratoire a déposé un projet d'étude chez le rat Fawn-hooded, modèle génétique susceptible de développer spontanément une HTAP (accélérée par l'hypoxie). Après analyse de ce projet d'étude, les conclusions rendues par le groupe de travail préclinique de la Commission d'AMM ont été qu'il n'existe pas de modèle expérimental animal adapté à la question posée.

5 - Revue des données d'efficacité. Conclusion du groupe DEUG

Le Département de l'évaluation thérapeutique des demandes d'AMM de l'Afssaps a présenté aux membres de la Commission nationale de pharmacovigilance une revue des données d'efficacité de MEDIATOR®, reflet des conclusions du Groupe de Travail Diabétologie/ Endocrinologie/ Urologie/ Gynécologie (GT DEUG) de la Commission d'AMM.

L'AMM de MEDIATOR® a été octroyée en plusieurs étapes, en 1987 pour les hypertriglycéridémies et en 1990 pour le diabète.

Action hypolipémiante
Le mécanisme d'action sur les lipides est difficile à préciser malgré les données soumises. *In vitro*, le benfluorex inhiberait la synthèse des acides gras entraînant une baisse des triglycérides (TG). *In vivo* chez l'animal, le benfluorex inhiberait l'acyl-coenzyme A cholestérol : acyltranférase (ACAT), mais le retentissement clinique n'est pas démontré (pas de baisse du LDL-cholestérol) de même que l'effet indépendant de la prise alimentaire.
Dix études cliniques ont été soumises :

- six études versus placebo réalisées entre 1978 et 2006 (au total 394 patients), anciennes à l'exception de l'étude Moulin. Méthodologiquement, il y a un faible nombre de patients, une grande variabilité de la dyslipidémie selon les études et le LDL-cholestérol n'est pas toujours disponible. Dans l'étude Moulin, la plus récente, on observe une diminution de 7% des TG et de 6% du LDL-cholestérol ;

- quatre études versus produits de référence, les fibrates, comprenant au total 163 patients avec une dyslipidémie (IIa, IIb et IV).

Une méta-analyse de l'efficacité de MEDIATOR® sur les TG a été réalisée ; elle comporte 6 études (Louvet, Tomassi, Moulin, Velusi, Del Prato et Biancchi), d'effectif varié de 10 à 242 patients, contre placebo avec tirage au sort. L'efficacité du benfluorex est très modeste sur les TG et non démontrée sur les autres paramètres lipidiques.

Action hypoglycémiante

Plusieurs mécanismes d'action sont évoqués : effet insulino-sensibilisateur chez l'Homme avec effet sur les transporteurs de glucose, effet direct sur le foie et réduction du contenu musculaire en TG.

Les études analysées en 1990, lors de la validation de l'indication dans le diabète sont anciennes: 3 études *versus* placebo où l'on observe une diminution de l'HbA1c de 0,8% (Tomassi) sous régime seul, de 0,9% sous régime seul et sulfamide (Velussi) et de 1,7% (Louvet) sous MEDIATOR® et sulfamide versus placebo et sulfamide. Une étude plus récente (1998), l'étude de Del Prato *versus* placebo et *versus* metformine montre une baisse de 0,86% entre le groupe placebo et le groupe benfluorex mais la qualité de tous ces essais est médiocre.

Finalement, l'étude Moulin est la plus récente. Il s'agit d'une étude multicentrique, randomisée en double aveugle de 18 semaines qui étudie l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex *versus* placebo chez 325 patients diabétiques de type 2 en surpoids (IMC entre 25 et 40 kg/~~m2~~m^2) mal équilibrés (HbA1c entre 7 et 10%) par un sulfamide à dose maximale tolérée depuis au moins 2 mois et intolérants ou ayant une contre-indication à la metformine. Trois sous-groupes ont été définis : HbA1c>8%, âge >65 ans et clairance de la créatinine < 80 ml/min. Cette étude comporte 2 phases : une période en double aveugle de 18 semaines pour démontrer la supériorité du benfluorex *versus* placebo sur l'HbA1c et une période en ouvert de 16 semaines centrée sur le profil de sécurité à long terme en association à un sulfamide ou à l'acarbose.

Les résultats ont montré une diminution de l'HbA1c de 0,82% dans le groupe benfluorex par rapport à la valeur de base et de 1% par rapport au placebo ($p< 0,001$). Cette baisse est significative dès la quatrième semaine et est maintenue jusqu'à 6 mois. On observe également une diminution significative de la glycémie à jeun dès la quatrième semaine sous benfluorex par rapport au placebo. Il existe une perte de poids respectivement de 1,3 kg et de 0,7 kg sous benfluorex et placebo avec une efficacité sur l'HbA1c indépendante de l'évolution pondérale. La baisse de l'HbA1c sous benfluorex par rapport à la valeur de base est plus importante pour les patients dont l'HbA1c de base est > 8% par rapport aux patients dont l'HbA1c ≤ 8%. Lors de la phase en ouvert, l'effet est reproductible dans le groupe initialement traité par placebo.

Au total, l'étude est conforme aux recommandations pour le développement des antidiabétiques oraux (EMEA 2002), et l'effet hypoglycémiant est notable avec une diminution de l'HbA1c de 1% *versus* placebo. Ces résultats sont par ailleurs cohérents avec les études antérieures. L'efficacité en seconde intention en association à un sulfamide semble donc démontrée et ceci indépendamment de la perte de poids, mais les experts ont soulevé des réserves méthodologiques. Par ailleurs, l'efficacité en prévention primaire et secondaire des complications de l'athérosclérose n'est pas démontrée.

En conclusion, le GT DEUG de la Commission d'AMM propose le retrait de l'indication de MEDIATOR® dans les dyslipidémies par insuffisance d'efficacité avec maintien de l'indication « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » dans l'attente de la soumission de résultats complémentaires d'études en cours devant permettre de positionner plus précisément ce produit dans l'arsenal thérapeutique du diabète de type 2.

6 – Résultats de l'étude de prescription/utilisation

Les laboratoires Servier ont présenté aux membres de la Commission les résultats de l'étude de prescription basée sur l'exploitation de l'observatoire Thalès. Deux périodes de 1 an ont été analysées : mai 2004 à mai 2005 et mai 2005 à mai 2006. Il apparaît que 80,3% des prescriptions de MEDIATOR® en 2004-2005 et 80,5% en 2005-2006 sont réalisées dans le cadre de l'AMM chez des patients dyslipidémiques et/ou diabétiques, et qu'environ 11% des prescriptions concernent des patients obèses, hors du cadre de l'AMM (11,5% en 2004-2005 et 10,7% en 2005-2006).Ces taux restent donc stables au cours du temps. Par ailleurs, il n'y a pas de saisonnalité des prescriptions, qu'elles soient destinées aux obèses seulement ou à l'ensemble des patients. Enfin, sur les deux périodes, le profil des patients concernés reste stable (âge, sexe, IMC).

7 - Discussions de la Commission nationale de pharmacovigilance

Les membres de la Commission considèrent que le libellé de l'indication retenue par le GT DEUG dans le diabète n'est ni clair, ni conforme aux données des études cliniques. Ils ont d'autre part tenu à souligner que les laboratoires SERVIER n'ont pas déposé de demande de renouvellement de l'AMM de benfluorex en Espagne et en Italie. Ils estiment par ailleurs nécessaire, par rapport à une efficacité du produit jugée modeste

par certains membres de la commission nationale, et étudie sur un critère principal (baisse de l'HbA1c) dans la seule étude méthodologiquement acceptable (étude Moulin), de tenir compte dans la réévaluation du rapport bénéficie risque du MEDIATOR® : i) du métabolisme du benfluorex, conduisant à la formation d'un dérivé fenfluraminique, ii) de ses effets indésirables neuropsychiatriques, iii) des rares cas d'HTAP et de valvulopathies notifiés ou décrits pouvant faire évoquer un problème qualitatif similaire à celui ayant amené au retrait du marché des anorexigènes fenfluraminiques sérotoninergiques, iv) d'une utilisation du produit essentiellement en France (88% des ventes). Certains membres de la Commission nationale ont par ailleurs tenu à faire connaître leur opinion en se prononçant pour un rapport bénéfice/risque défavorable du MEDIATOR®. Ce dossier sera présenté en Commission d'AMM le 5 avril 2007.

Annexe 3-72

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Saint-Jacques – 25030 BESANCON Cedex

MEDIATOR® (benfluorex)

ENQUETE OFFICIELLE

Troubles neuropsychiatriques

Hypertensions artérielles pulmonaires

Commission Nationale du 27 mars 2007

Confidentiel

M. DAVID-LAROCHE
J.P. KANTELIP

Le MEDIATOR® (chlorhydrate de benfluorex) est commercialisé en France depuis 1976 par les laboratoires SERVIER (Gidy/Orléans), sous forme de comprimés dosés à 150 mg.

Ses indications sont :

- adjuvant du régime adapté dans les hypertriglycéridémies
- adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Le benfluorex n'est pas classé dans les anorexigènes, mais lors de l'enquête sur les effets indésirables et les restrictions de délivrance de ces produits, le Comité Technique de Pharmacovigilance a craint une déviation de l'utilisation du benfluorex comme anorexigène. (Le benfluorex a d'ailleurs été inscrit dans la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes, 10 mai 1995).

Métabolisme :

- In vivo : Chez l'homme, le MEDIATOR® est hydrolysé très rapidement au niveau plasmatique et hépatique par des estérases en S422 (dérivé alcool), puis transformé en 8 métabolites majeurs identifiés parmi lesquels, par oxydation (S1475, dérivé acide) ou désalkylation (S585, norfenfluramine).
  Le métabolite majoritaire est le dérivé carboxylique : S1475.
  Le métabolite primaire S422 et la norfenfluramine sont retrouvés à des taux très inférieurs.

Après administration de benfluorex radioactif, on retrouve 87 à 99% de la radioactivité après 72 heures dans les urines. L'absence de quantité significative dans les fécès montre que le produit est bien absorbé.
Il n'existe pas de phénomène d'accumulation.

L'élimination se fait en 2 phases :
- une première phase rapide (60% en 3 ou 4 heures)
- une seconde phase lente de 36 heures environ.

- In vitro : Les travaux faits in vitro après incubation d'hépatocytes frais humains montrent que les principaux cytochromes P450 jouent un rôle très minoritaire dans le métabolisme du benfluorex.

Les effets indésirables mentionnés dans le RCP sont :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, **confusion**, somnolence, état vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles
- très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke
- élévation des enzymes hépatiques, hépatite (très rare)

Cette enquête officielle concernant les troubles neuro-psychiatriques et l'hypertension artérielle pulmonaire a été présentée à la Commission Nationale de Pharmacovigilance du 29 novembre 2005 dont les conclusions étaient:

- *les effets neuro-psychiatriques décrits dans le RCP sous le terme de « confusion » doivent être détaillées*
- *les données ne sont pas suffisantes pour affirmer l'existence d'un syndrome de sevrage*
- *le faible nombre de cas décrits d'HTAP idiopathique ne justifie pas sa mention dans le RCP*

Nous présentons ici une actualisation de cette enquête, le numéro des nouveaux cas étant inscrit en gras.

I - TROUBLES NEURO-PSYCHIATRIQUES :

A. Troubles psychiatriques lors du traitement

39 cas ont été rapportés, dont 4 déclarés depuis l'enquête présentée novembre 2005 :

- dépression : TO060262
- agitation : S06001505 : *non grave*
- délire de persécution : SE0600351
- délire : TO060409

Elles concernent 19 hommes (âge moyen : 57 ans) et 20 femmes (âge moyen : 58,3 ans).

Les troubles psychiatriques sont divers :

- agressivité (4), nervosité (3), irritabilité
- dépression (2), cauchemars (2), angoisse, stupeur,
- désorientation (7), *confusion* (5),* aggravation des troubles cognitifs
- agitation (4), trouble du comportement (3)
- délire (3), bouffée délirante aiguë (2)

(*) « confusion » est inclus dans le dernier RCP

Remarque : La responsabilité de la pathologie et des nombreux traitements associés ne peut être exclue dans la plupart des notifications.

1. Imputabilité :

4 cas sont imputés « vraisemblable » :

- NC9500171 : nervosité et nausées chez une femme de 50 ans, 1 à 2 h après la prise de 1 comprimé de MEDIATOR®.

- 128E22 : chez un homme de 72 ans , traité pour démence, prenant pendant plusieurs années MEDIATOR® pour troubles métaboliques et MODOPAR® pour maladie de Parkinson, est observée une amélioration de ses troubles cognitifs lors d'un arrêt fortuit du MEDIATOR® et une aggravation lors de la reprise du MEDIATOR®.

- S10010345 : désorientation et obnubilation, chez une femme de 80 ans. Le traitement a été arrêté après 13 jours. Une réadministration ultérieure a été positive (traitement associé : KERLONE® et MOGADON®).

- CN0000093 : désorientation temporo-spatiale et agitation chez un homme de 76 ans. Le délai d'apparition des troubles est inconnu, mais les signes cliniques se sont améliorés à l'arrêt du MEDIATOR® et la réadministration est positive. Les autres médicaments ne sont pas arrêtés (DAONIL®, LASILIX®, SINTROM®, MONICOR L.P®. et FOZIRETIC®). *(Cas décrit également paragraphe suivant « gravité »)*

5 cas sont imputés « plausible »

- NC9700094 : accès d'agitation et agressivité, chez une femme de 74 ans, pendant la prise de MEDIATOR® pendant 6 jours. Disparition des symptômes 12 heures après l'arrêt du MEDIATOR®.
- NC9300347 : irritabilité chez un homme de 39 ans, traité pendant 11 mois par MEDIATOR®. L'évolution est favorable à l'arrêt du médicament.
- MA9100069 : angoisse et palpitation, chez un homme de 40 ans, 2 heures après avoir ingéré 4 comprimés de MEDIATOR®.
- NC9300349 : dépression, chez un homme de 50 ans, traité pendant 9 mois par MEDIATOR®. L'évolution est favorable à l'arrêt du médicament.
- CF9000137 : désorientation chez une femme de 79 ans, traitée par MEDIATOR®, HALDOL®, SERESTA®, ZESTRIL®, CATAPRESSAN®, PRAXILENE®, SERMION®. L'évolution est favorable à l'arrêt de tous les médicaments.

30 cas ont été imputés « douteux » dont 13 (C2, S1).

2. Gravité

Les effets indésirables ont nécessité une hospitalisation dans 12 cas.

a) Confusion : 4 cas

SE9500017 : Un état confusionnel ayant duré 12 h est survenu chez une femme de 41 ans après 83 jours de traitement par MEDIATOR® (1cp/j) et INCITAL®, et 2 ans par LEXOMIL®. Elle avait été retrouvée errante sur la voie publique après une dispute avec son mari. (Imputabilité : C1, S1)

010326 : Un homme de 61 ans, traité par MEDIATOR® (dose et durée inconnues), FONZYLANE® et SINTROM®, est hospitalisé pour déshydratation avec fièvre et confusion. L'évolution est favorable après réhydratation et arrêt du MEDIATOR®.

120M85 : Un homme de 69 ans, traité par MEDIATOR®, 2 cp/j pendant 11 jours pour désordre métabolique est admis à l'hôpital pour malaises avec confusion et amnésie. Le MEDIATOR® est arrêté, mais les troubles de mémoire continuent. Le scanner cérébral montre une atrophie cortico-souscorticale.
Le traitement associé est PREVISCAN® et CORDARONE®.

S01000031 : Un homme de 63 ans a été hospitalisé à plusieurs reprises pour confusion mentale inexpliquée. Une recherche des médicaments sur l'urine par technique de polarisation de fluorescence révèle une réponse positive pour les dérivés amphétaminiques et une chromatographie gazeuse couplée à une spectrométrie de masse ne confirme pas l'abus d'amphétamines usuels (incluant l'ecstasy).
Cependant, la norfenfluramine est retrouvée à des concentrations de 687 ng/ml dans l'urine et 8.4 ng/mg dans les cheveux.
La présence de norfenfluramine et l'absence de fenfluramine sont en faveur d'un abus illicite de MEDIATOR® (dose inconnue). L'évolution est inconnue. (Imputabilité : C1, S1)
(Cas publié : Norfenfluramine : usage thérapeutique ou toxicomanie ? V.CIRIMELE et coll. Journal de Médecine Légale Droit Médical, 2001, Vol.44, N°1, 23-26.

b) Désorientation temporo-spatiale : 3 cas

10345 : Une femme de 80 ans, avec des séquelles d'accident vasculaire cérébral, traitée pour hypercholestérolémie par MEDIATOR® 3cp/j pendant 13 jours est hospitalisée pour désorientation temporo-spatiale et obnubilation avec hypotension artérielle. L'évolution est favorable à l'arrêt du MEDIATOR®. Le rechallenge est positif.
Le traitement associé est: KERLONE®, MOGADON®.

RE037148 : Une patiente de 66 ans, obèse et grabataire, est amenée à l'hôpital en raison de l'apparition d'un syndrome confusionnel avec état stuporeux et une hyperthermie à 40°. Ses antécédents sont assez chargés avec entre autres, un état dépressif, un asthme et une cardiopathie hypertensive. Le traitement par MEDIATOR® (3cp/j) avait débuté 10 à 12 jours avant son hospitalisation à raison de 3 cp/j. Après l'arrêt du MEDIATOR®, on note une amélioration en quelques jours de la désorientation temporo-spatiale. Le traitement habituel de la patiente est : ASPEGIC®, COAPROVEL®, CORVASAL®, DIFFU K®, MONOTILDIEM®, MOVICOL®, SEROPRAM®, TRINIPATCH®, MEDIATENSYL®, VASTEN®, SERETIDE® et VENTOLINE®. (Imputabilité : C2, S1)

CN0000093 : Chez un homme de 76 ans, traité depuis 2 ans par MEDIATOR®, 3 cp/j, est apparu une désorientation temporo-spatiale et agitation, dont le délai d'apparition des troubles est inconnu, mais les signes cliniques se sont améliorés à l'arrêt du MEDIATOR® et la réadministration a été positive. Les autres médicaments ne sont pas arrêtés (DAONIL®, LASILIX®, SINTROM®, MONICOR L.P.® et FOZIRETIC®) *(dossier imputé «C3, S1 » décrit paragraphe précédent).*

c) Bouffée délirante aiguë : 2 cas

RN9500096 : Une patiente de 59 ans, sans antécédent psychiatrique, en cure d'amaigrissement (perte de 10 kg) depuis 3 mois avec MEDIATOR® (3cp depuis 73j), LIPANTHYL®, Amfépramone®, Craetegus 100mg, PILOSURYL®, CANOL®, STRESAM®, OLIVIASE®, RELVENE® et TOP MAG® est hospitalisée pour bouffée délirante aiguë avec confusion, désorientation temporo-spatiale et agitation. L'évolution est favorable 8 jours après l'arrêt de tout le traitement et la mise sous neuroleptiques. (Imputabilité : C1, S2)

TO041306 : Une bouffée délirante aiguë à thème de persécution et de complot avec agitation extrême et opposition des soins a nécessité une hospitalisation sous contrainte chez un homme de 50 ans qui était traité par MEDIATOR® (1cp/j) depuis 29 mois, associé à COTAREG® et ZYLORIC®. Les troubles ont disparu en 24h sous SOLIAN IM®, TERCIAN IM® ET RIVOTRIL®. Le patient est sorti de l'hôpital avec SOLIAN® 400mg, 2 fois par jour. (Imputabilité : C1, S2)

d) Délire : 2 cas

SE0600351 : En avril 2006, un délire de persécution accompagné d'une inversion du rythme nycthéméral conduisant à une hospitalisation est apparu chez une femme de 33 ans sans antécédent psychiatrique. Elle était traitée par MEDIATOR, 3 cp/j depuis novembre 2005 puis 2 cp/j depuis mars 2006, alors qu'elle avait présenté en janvier 2006 un épisode de dépression.
Le MEDIATOR est arrêté. Le traitement est ZYPREXA, TERCIAN et XANAX. L'évolution est favorable et le traitement à visée psychiatrique est interrompu ensuite. (Imputabilité : C1, S1)

TO060409 : Un homme de 31 ans, avec des antécédents de psychose chronique traitée par halopéridol débute un traitement par MEDIATOR, 2 cp/j en 2002. En 2005, son état délirant augmente, il est accompagné d'excitation psychomotrice avec hétéro et auto-agressivité. Il est admis en mars 2006 à l'hôpital psychiatrique, son état psychique revient à l'état de base alors que le MEDIATOR est arrêté. On s'aperçoit que le patient se procure du MEDIATOR par lui-même, en augmentant a priori les doses. (Imputabilité : C1, S1)

e) Dépression:

TO060262 = Une femme de 37 ans dont les antécédents sont : diabète non insulino-dépendant traité par MEDIATOR, troubles dépressifs traités par SEROPRAM , DEPAKOTE et NEULEPTIL et hystérectomie, hypothyroïdie, est admise au Urgences en octobre 2005 pour décompensation dépressive, avec recrudescence des idéations suicidaires, fléchissement thymique et dévalorisation. L'évolution est inconnue (Imputabilité : C1, S2)

3. Tableau récapitulatif des observations : (voir pages suivantes)

Les nouveaux cas (5) notifiés depuis le rapport de novembre 2005 sont inscrits **en gras**.

Troubles psychiatriques lors du traitement (1)

N°	S/Age	Durée TTT	Posologie/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables
S01001236	M,54	17 jours	450 mg	C2,S1	TRANDATE, C1,S1		A	N	Agressivité, irritabilité, insomnie
LY9600963	M,45	1 mois	450 mg	C1,S1	LEXOMIL, C2,S1		A	N	agressivité
NC9700094	F,74	6 j	225 mg	C2,S2			A	N	agressivité
541173	F,45	8j	300 mg	C2,S1	CORENITEC,C1,S1 LYSANXIA		A		Agressivité + hallucination
NC9300347	M,39	11 mois	150 mg	C2,S2			A	N	Irritabilité
NC9500171	F,50	1 cp	150mg	C3,S2			A	N	Nervosité
MP9800179	F,47	11j	300 mg	C2,S1	LIPANOR, C1,S1		A	N	Nervosité
124G84	F,35	20 j	300 mg	C2,S1	MAXEPA LEVOTHYROX HYDROCORTISONE	Hypothyroïdie Insuffisance surrénale	A	N	Nervosité +excitation
MA9100069	M,40	1 j	600 mg	C2,S2			A	N	Angoisse
TS9500338	F,69	8 j	150 mg	C2,S1	DAONIL, C1,S1 ALPRESS BITILDIEM DIAMICRON...		A	N	Stupeur
LY8900392	M,52	20 j	450 mg	C2,S1	ASPEGIC, C1,S1 SOTALEX, C1,S1		A	N	Cauchemars
10540O46	M, ?	qq semaines	450 mg	C1,S1	ZOCOR, C1,S1 PERSANTINE MAXEPA TILDIEM DAONIL		A	N	Cauchemars
NC9300349	M,50	9 mois	450 mg	C2,S2	LOPRIL, C1,S1		A	N	Dépression Paresthésie, asthénie
TO060262	**F,37**	**?**	**?**	**C1,S2**	**DEPAKOTE LEVOTHYROX NEULEPTYL SEROPRAM**	**Syndrome dépressif**	**U**	**O**	**Décompensation dépressive**

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Troubles psychiatriques lors du traitement (2)

SE9500017	F,41	84 j	150 mg	C1,S1	INCITAL, C1,S1 LEXOMIL, C1,S1		A	O	confusion
010326	M,61	?	?	C1,S1	FONZYLANE, C1,S1 SINTROM, C1,S1		A	O	Confusion Autre cause !
120M85	M,70	11j	300 mg	C2,S1	PREVISCAN , C1,S1 CORDARONE, C1,S1	Scanner cérébral : atrophie cortico souscorticale	A	O	Confusion Troubles de la mémoire
000031	M,63	?	?		Drogue ?		U	O	Confusion
127V18	M,70	1 jour !	150 mg	C2,S1	TERALITHE LEXOMIL NOCTRAN	Syndrome dépressif	A	N	Confusion Somnolence
128E22	M,72	+ années	?	C3,S1	MODOPAR	Démence	A	N	Aggravation des troubles cognitifs
CF9000137	F,79		450 mg	C2,S2	HALDOL, C2,S2 SERESTA, C2,S2 ZESTRIL, C2,S2 CATAPRESSAN, C2,S2 PRAXILENE, C2,S2 SERMION, C2,S2		A	N	désorientation
010345	F,80	13 j	450 mg	C3,S1	MOGADON, C1,S1 KERLONE, C1,S1		A	O	Désorientation Obnubilation
060J96	F,80	?	?	C1,S1	RENITEC ADALATE HEMIDAONIL TILDIEM		A	N	Désorientation
060J13	F,82	1 mois	450 mg	C2,S1	DAONIL		A	N	Désorientation
120M52	M,60	2 j	150 mg	C2,S1	LIPANTHYL, C1,S1 ASPEGIC, C1,S1		A	N	Désorientation Somnolence
RE037148	F,66	13 j	450 mg	C2,S1		Syndrome dépressif	A	O	Désorientation temporospatiale Etat stuporeux
CN0000093	M,76	2 ans	450 mg	C3,S1	DAONIL, C1,S1 SINTROM, C1,S1 LASILIX, C1,S1 MONICOR L.P., C1,S1 FOZIRETIC, C1,S1		A	O	Désorientation temporospatiale Agitation

Troubles psychiatriques lors du traitement (3)

MA8900523	F,40		150 mg	C1,S1	ISOMERIDE, 1j, C2,S1		A	N	Agitation
DJ9800349	M,74	3 mois	450 mg	C2,S1			A	N	Agitation
PA0200221	F,70	1 j	3 cp en 1 prise	C1,S1			A	N	Agitation, paresthésie
S06001505	**F,77**	**5 j**	**150 mg**				**A**	**N**	**Agitation**
10060560	M,75	Plusieurs mois	450 mg	C2,S1	DAONIL		A	N	Trouble du comportement
GR0100547	F,44	4 mois	450 mg	C2,S1	OLIGOSOL, C2,S1	Syndrome dépressif	F	N	Trouble du comportement Hallucination, vertige
GR0100594	F, ?	9 mois	450 mg	C1,S1			U	N	Trouble du comportement
RN9500096	F,59	73 j	450 mg	C1,S2	LIPANTHYL, C1,S2 PILOSURYL, C1,S2 CANOL, C1,S2 OLIVIASE, C1,S2 Amfépramone, C1,S2		A	O	Bouffée délirante aiguë
GR8700216	M,45	16 j	450 mg	C1,S1	COLLAGENAN, C1,S1 NICOBION, C1,S1		A	N	délire
TO041306	M,50	29 mois	150 mg	C1,S2	COTAREG, C1,S1 ZYLORIC, C1,S1		B	O	Bouffée délirante aiguë
SE0600351	**F,33**	**5 mois**	**450 mg Puis 300 mg**	**C1,S1**			**A**	**O**	**Délire de persécution**
TO060409	**M,31**	**3 ans**	**300 mg (+ auto médication)**	**C1,S1**	**Halopéridol**	**Psychose chronique**	**A**	**O**	**Délire Agressivité Confusion mentale**

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Troubles psychiatriques apparaissant lors du sevrage

Aucune nouvelle notification n'a été rapportée depuis la Commission Nationale du 29 novembre 2005

10 notifications de troubles psychiatriques apparaissant lors du sevrage ont été rapportés, 6 par les CRPV, 4 par le laboratoire.

Ils concernent 2 hommes et 8 femmes, dont la moyenne d'âge est respectivement 30,5 ans (27-34) et 45,25 ans (30-65).

Le délai d'apparition des troubles après l'arrêt du MEDIATOR® est très variable : de 1 jour (après un traitement de 8 ans) à 3 semaines (après un traitement de 4 à 15 mois).

La durée de traitement par MEDIATOR® est de 1 mois à 8 ans.

Dans les 3 observations qui ont nécessité une hospitalisation (gravité = O dans le tableau page 10), il existe un terrain ou des antécédents prédisposants :

- LY0200303 : une femme de 36 ans, traitée par MEDIATOR® pendant 6 mois pour obésité avec hypercholestérolémie et PROZAC pendant 6 semaines pour syndrome dépressif, est hospitalisée en psychiatrie pour état anxiodépressif aigu avec crise de panique, 2 à 3 semaines après l'arrêt des 2 médicaments.
L'état de la patiente s'améliore rapidement sous SOLIAN® et STABLON®. (Imputabilité : C1,S1)

- LY0200036 : chez une femme de 34 ans, avec des troubles dysthymiques, suivie pour difficultés psychologiques de type border line, en rupture de traitement neuroleptique depuis plusieurs mois, apparaît une décompensation avec délire persécutif et anxiété, environ 3 semaines après un traitement de 4 mois par MEDIATOR®.
La patiente sera traitée pour troubles psychotiques, l'évolution est inconnue. (Imputabilité : C1,S1)

- LY0200037 : une femme de 53 ans, diabétique non insulino-dépendante, ayant fait 2 épisodes maniaques en 1985 et 1996 (ce deuxième épisode étant survenu à la suite d'un régime amaigrissant accompagné peut-être du benfluorex) est hospitalisée pour accès maniaque atypique environ 3 semaines après l'arrêt d'un traitement de 15 mois par MEDIATOR®. Il est a noté un amaigrissement de 20 kg en 1 an.
La patiente sera traitée pour troubles psychotiques, l'évolution est inconnue. (Imputabilité : C1,S1)

Les autres troubles sont identiques à ceux décrits pendant le traitement par MEDIATOR® :

- vertige (4), somnolence (2)
- cauchemar, angoisse (2)

Dans 1 cas, l'imputabilité de MEDIATOR® est « vraisemblable » :

- PA97355052 : il s'agit d'un syndrome de sevrage avec excitation chez un homme de 27 ans, sportif, qui consomme (sur prescription médicale) à doses croissantes (1cp/semaine au début jusqu'à 9 cp/j) du MEDIATOR® comme "dopant ».
Ce patient avait eu un épisode similaire quelques mois plus tôt. (Imputabilité : C3,S1)

Troubles psychiatriques apparaissant lors du sevrage

N°	S/Age	Durée TTT	Poso/j	Imput. MEDIATOR	TTT associé/ imputabilité	Antécédents Terrain	Evol.	Gravité	Effets indésirables	sevrage
MP0300791	F,58	8 ans	450 mg	C2,S2	LIPANTHYL ,C2,S1 LEVOTHYROX, C1,S1 EUPRESSYL, C1,S11		A	N	Vertige, somnolence	24h
060141	M,34	2 mois	300 mg	C2,S1			A	N	Vertige, sueur	2 jours
TO001223	F,30	3 mois	450 mg	C1,S1	SURGAM CLAMOXYL		A	N	Céphalalgie, malaise, somnolence	9 jours
2000276	F,34	1 mois	450 mg	C2,S1	XENICAL ESBERIVEN		A	N	Nausée, vertige , fatigue, cauchemar, tremblement	
LY0200303	F,36	6 mois	300 mg	C1,S1	PROZAC, C1,S1	Syndrome dépressif	B	O	Etat anxiodépressif	2 à 3 semaines
S03000265	F,52	+ années	450 mg	C1,S1	LEVOTHYROX LIPANTHYL		U	N	Angoisse, nervosité, vertiges	Quelques jours
10060219	F,65	2 ans		C1,S1			A	N	Bouffées d'angoisse	
PA9735052	M,27	6 mois		C3,S1	« 9 cp/j (dopant) »		U	N	Excitation	
LY0200036	F,34	4 mois		C1,S1		Troubles dysthymiques sur personnalité pathologique	U	O	Bouffées délirantes	3 semaines
LY0200037	F,53	15 mois		C1,S1	GLUCOR, C1,S1 STAGID, C1,S1 LEVOTHYROX, C1,S1	Troubles dysthymiques	U	O	Exaltation maniaque atypique	3 semaines

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B. HYPERTENSIONS PULMONAIRES

20 notifications (9 CRPV et 13 laboratoire) dont 2 doublons, ont été rapportées (dont **3 rapportées depuis la Commission Nationale du 29 novembre 2005**) :

1. Notifications où MEDIATOR® est associé à un anorexigène :

Lors de la présentation du rapport MEDIATOR® en décembre 1998, 11 notifications d'«Hypertension artérielle pulmonaire » avaient été rapportées.
(9 d'entre elles faisaient partie de l'enquête « Anorexigènes et hypertensions artérielles pulmonaires » présentée au Comité technique du 28 avril 1995)
Elles ont été expertisées par le Professeur WEITZENBLUM (Strasbourg) :

- 7 ont été classées en HTAP d'allure idiopathique
- 3 en HTAP post-capillaire
- 1 en HTAP post-embolique

Le MEDIATOR® n'était jamais prescrit seul : il était présent en association à un ou plusieurs anorexigènes :

- ISOMERIDE® : 7 fois
- ISOMERIDE® + PONDERAL® : 2 fois
- ISOMERIDE ®+ FENPROPOREX® : 1 fois
- DININTEL® + TENUATE DOSPAN® + FRINGANOR® : 1 fois

La durée de traitement par MEDIATOR® est précisée dans 7 cas sur 11 : elle est de plusieurs mois à 5 ans.

Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® est :

- concomitante dans 5 cas,
- antérieure dans 2 cas,
- imprécise dans 1 cas.
- postérieure dans 3 cas *(voir détail page suivante) :*

➢ 840255 :
Une femme, 57 ans, obèse depuis longtemps, ayant pris PONDERAL® pendant 2 mois en 1978 et ISOMERIDE® en 1986 (durée inconnue) est hospitalisée en janvier 1993 pour suspicion d'embolie pulmonaire. La scintigraphie pulmonaire est normale.
Le traitement habituel est VOLTARENE®, FELDENE® et DOLIPRANE® pour lombalgies.

En septembre 1993, lors d'une consultation cardiologique, on note une dyspnée stade 3 et un souffle systolique d'insuffisance tricuspidienne. Des signes d'hypertrophie ventriculaire droite sont retrouvés à l'électrocardiogramme.
La dyspnée s'aggravant progressivement, la patiente est hospitalisée en novembre 1993.
A noter que la patiente aurait pris MEDIATOR® , VEINOBIASE®, STILNOX® et XANAX® au cours du mois de septembre 1993.
A l'échodoppler cardiaque, la PAP systolique (PAPs) est estimée à 73 mmHg.
Le cathétérisme cardiaque confirme l'HTAP précapillaire.

En février 1994, l'échodoppler montre une aggravation de la PAPs à 95 mmHg, mais l'état clinique de la patiente est légèrement amélioré début juin 1994.

→ *Avis de l'expert : « HTAP idiopathique »*

➢ 840B65 :
Chez un homme de 48 ans, dont les antécédents sont une hypertension artérielle traitée par FLUDEX®, des glycémie, cholestérolémie et uricémie aux limites supérieures de la normale, un syndrome restrictif post-traumatique, un tabagisme interrompu depuis 1987 et une obésité traitée par ISOMERIDE® de septembre 1990 à avril 1991, est hospitalisé en février 1992 pour syndrome obstructif post-tabagique sévère et aggravation du syndrome restrictif. Une dyspnée d'effort est cotée stade 3-4.
Le traitement de sortie est : MEDIATOR®, VECTARION®, BRONCHODUAL® et BRONILIDE®. FLUDEX® est remplacé par ECAZIDE®, puis LUMITENS®.

Après une amélioration, la dyspnée s'est aggravée et le patient est hospitalisé à nouveau en mai 1993 pour bilan de l'hypoxémie.
A l'échocardiographie, les cavités droites sont très dilatées, comprimant les cavités gauches. La PAPs est estimée à 50 mmHg.
Le cathétérisme droit effectué en juin 1993 pose le diagnostic d'HTAP précapillaire avec une PAP systolique à 90 mmHg. Le patient décède 24 mois plus tard.

→ *Avis de l'expert : « HTAP idiopathique »*

➢ 840B19 :
Une femme de 51 ans, ayant une HTA, une obésité après une première grossesse en 1966, traitée par PONDINIL® en 1974, puis par ISOMERIDE® de 1985 à 1989 (2 fois 3 mois), une hyperlipidémie traitée par MEDIATOR® de 1989 à janvier 1995, est hospitalisée en août 1994 pour bilan d'un syndrome sec.

Une échocardiographie met en évidence une double atteinte aortique et mitrale et une HTAP. Le traitement antérieur comporte : LIPUR®, SECTRAL®, DEBRIDAT®, PRAGMAREL®, ENDOTELON®.

En décembre 1994, lors d'une échocardiographie de contrôle, la PAPs est estimée à 60-65 mmHg.
Le traitement de la patiente est alors : SECTRAL®, MODURETIC®, KALEORID®, RANIPLEX®, PREPULSID®.

En janvier 1995, l'état de la patiente est stable avec une PAPs évaluée à 55 mmHg.

→*Avis de l'expert : « probable HTAP secondaire à une cardiopathie gauche ».*

« Indications du MEDIATOR® n'est pas associé à un anorexigène » (modifié)

3 nouveaux cas notifiés depuis le rapport de novembre 2005 sont inscrits ***en gras.***

4 dossiers sont en cours d'expertise par le Professeur WEITZENBLUM, qui avait expertisé les cas précédents.

➢ PS9900385 :

Chez une femme de 50 ans, ayant comme antécédent une hypertension artérielle traitée par LOGIRENE®, 0,5 cp/j et TRIATEC® 2,5 cp/j et une hypercholestérolémie traitée par LIPANTHYL® 1 cp/j et MEDIATOR®, 1 cp/j, est découvert une hypertension artérielle pulmonaire.
Le début des symptômes remonte à décembre 1998 avec l'installation d'une dyspnée d'effort, qui s'est majorée après un an d'évolution.
Lors d'un bilan en mai 1999, la pression artérielle pulmonaire systolique (PAPs) est estimée à 91 mmHg à l'échographie cardiaque.
Un bilan en juin 1999 confirme une HTAP avec une coronarographie, une angiographie et une scintigraphie pulmonaire normales.
Au cathétérisme droit, la pression artérielle pulmonaire moyenne (PAPm) est à 51 mmHg.
Un traitement par FLOLAN® est instauré (21 juin 1999).

Un bilan réalisé à trois mois montre une réelle amélioration et la patiente reste stable cliniquement jusqu'en septembre 2001, où elle constate une réaggravation de la dyspnée d'effort mais la PAPm est alors stable à 55mmHg.

→ *Avis de l'expert : « HTAP idiopathique »*

➢ S02001877 :

Une patiente de 55 ans (BMI=32) est traitée pendant un an (juillet 2001-septembre 2002) par MEDIATOR® pour un diabète non insulino-dépendant et une dyslipidémie, associé à ALDACTONE®, LASILIX® et TERALITHE®.
En juin 2002, un cathétérisme cardiaque droit montre une hypertension précapillaire avec une PAP à 51 mmHg. L'échographie montre des cavités droites dilatées.
L'échodoppler des membres inférieurs et la scintigraphie pulmonaire sont normaux.

En octobre 2002, la patiente est hospitalisée avec une dyspnée de grade 3. Au cathétérisme cardiaque droit la PAPm est à 40 mmHg.
Les différents traitements pris par la patiente sont :
PREVISCAN®, LESCOL®, AMAREL®, STABLON®, ATARAX®, TEMESTA®, LIPANTHYL®, LIPUR®, TOCO®, GLUCOPHAGE®.
L'évolution est inconnue.

→ *Avis de l'expert : « probable HTAP idiopathique »*

➢ TO040278 :
Une femme de 36 ans, traitée pendant 2 ans par MEDIATOR®, 3cp/j, LEVOTHYROX®, GINKOR Fort®, PRAXINOR®, PROZAC®, HEPTAMYL® et CANOL® est hospitalisée le 25 novembre 2003 suite à une détresse respiratoire aiguë. Le diagnostic est un syndrome alvéolo-interstitiel bilatéral. Il n'y a pas de syndrome inflammatoire.
Les antécédents sont une hypothyroïdie, un tabagisme, un surpoids (BMI = 24) et une insuffisance aortique de grade 2 découverte un an auparavant.
L'échographie montre une fonction systolique ventriculaire gauche à 65%, avec un ventricule gauche dilaté, une insuffisance mitrale de grade 2 et une insuffisance aortique de grade 2.
Le doppler veineux ne montre pas de thrombose veineuse des membres inférieurs.

L'état de la patiente s'améliore [illegible] LEVOTHYROX®, PROZAC® et CANOL®.
Une échographie de contrôle réalisée après normalisation clinique et radiologique montre une oreillette gauche dilatée et des cavités droites non dilatées sans HTAP.
Conclusion du cardiologue: *« Décompensation cardiaque associée à une probable infection virale broncho-pulmonaire ».*
Le 5 janvier, la patiente est hospitalisée à nouveau pour récidive d'un subOAP sur valvulopathies aortique et mitrale à la faveur d'une virose.
La valvulopathie est recontrôlée par échographie par voie transthoracique : il existe alors une élévation des pressions artérielles pulmonaires avec une PAPs estimée à 50mmHg (N : 15 mmHg), le ventricule et l'oreillette gauches sont dilatées.
Le 23 janvier 2004, le remplacement des valves est effectué. On ne note aucun problème dans les suites de l'opération.
L'anatomopathologie des valves montre une lésion dégénérative aspécifique.

Le diagnostic différentiel élimine :
- une maladie rhumatismale : l'aspect échographique n'est pas en faveur
- une endocardite : la recherche est négative
- une maladie auto-immune : les autoanticorps et la recherche des phospholipides sont négatifs.

Il est à noter que la soeur de la patiente est suivie pour valvulopathie.
Le traitement de sortie est PREVISCAN®, RENITEC®, PROZAC®, LEVOTHYROX®.

→*Avis de l'expert*: *« cardiopathie valvulaire sévère, l'OAP ayant entraîné une HTAP post-capillaire. »*

➢ MP0500189 :

Une femme de 55 ans (BMI=35), traitée par MEDIATOR®, 1cp/j, depuis 31 mois est hospitalisée en janvier 2005 pour suspicion d'embolie pulmonaire, avec dyspnée d'effort importante, progressivement croissante depuis plusieurs mois.
A l'échographie cardiaque, la PAPs oscille entre 75 et 80 mmHg.
L'angioscanner thoracique ne met pas en évidence de signe d'embolie pulmonaire, mais il semble exister un caillot dans l'artère sous segmentaire gauche.
Les D Dimères sont élevés à 12000.
La scintigraphie pulmonaire de ventilation perfusion montre des troubles perfusionnels avec vraisemblablement un petit épanchement pleural gauche, faisant suspecter des épisodes emboliques multiples partiellement reperfusés
Conclusion du cardiologue : « *Possible embolie pulmonaire compliquée d'HTA pulmonaire importante avec à la scintigraphie des défects périphériques disséminés. Il s'agit possiblement de micro-embols d'installation progressive mais on ne peut exclure formellement une HTAP primitive de type veino-occlusif.* »

Dans les antécédents de la patiente, on note une embolie pulmonaire en 1981, suite à un accident de la voie publique, compliquée d'une phlébite, traitée par antivitamines K pendant un an, une HTA ancienne traitée par COTAREG® et un tabagisme modéré.
Le 31 janvier, l'échographie cardiaque de contrôle met en évidence une diminution de la PAPs à 65 mmHg, le ventricule droit est dilaté, l'insuffisance tricuspide est relativement importante.

Le 1 février 2005, la patiente est sortie avec une PAPs à 65 mmHg, le traitement de sortie étant PREVISCAN® (en prévention d'une embolie pulmonaire), COTAREG® et MOPRAL®.
Le 22 février 2005, elle est hospitalisée à nouveau avec altération de l'état général, des douleurs thoraciques, des vomissements et une dyspnée.
La pression artérielle pulmonaire est à 80-85 mmHG, Sa tension artérielle est à 120/90, mais elle chute dans la nuit suivante à 8/5.
La patiente fait une asystolie et décède le lendemain par arrêt cardio-circulatoire.

→*Avis de l'expert : « Vraisemblable HTAP post-embolique »*

Une femme de 59 ans, pesant 86 kg, traitée par MEDIATOR®, 3 cp/j pour un désordre métabolique lipidique depuis novembre 1992 associé à de nombreux médicaments est hospitalisée en mars ou avril 2002 pour dyspnée et malaise.
Une hypertension pulmonaire est diagnostiquée. Le MEDIATOR® est alors arrêté.
Les différents traitements associés sont : CAPTEA®, LOPRIL®, PROGYNOVA®, UTROGESTAN®, HUMORYL® et PRAXINOR®
L'évolution est inconnue et le dossier succinct.

- NT0500397 = S05001666 :

Un homme de 74 ans, avec un BMI=31, a comme antécédents : une cardiopathie hypertensive diagnostiquée en 1982 avec des épisodes de tachycardie paroxystique depuis 1977, une arythmie par fibrillation auriculaire et un souffle systolique mitral et aortique depuis 1982. Il est traité par MODURETIC® ET SELOKEN® depuis 1982, puis par KERLONE®, HYTACAND®, CHRONO-ADALATE® depuis plusieurs années (au moins 2003) et PREVISCAN® depuis 2001. D'autre part, ce patient prend du MEDIATOR®, 3cp/j pour dyslipidémie depuis 1996.
En 1982, il existe un souffle systolique avec foyers mitral, aortique et aux 2 carotides.

En 2004, lors d'une consultation cardiologique pour dyspnée d'effort et toux sèche persistante signalée depuis février 2003, et apparition récente d'œdèmes des membres inférieurs, la PAPs est estimée à 52 mmHg à l'échocardiographie. L'insuffisance mitrale est de grade I, les cavités droites sont dilatées avec une insuffisance tricuspidienne de grade II.
En juin 2005, la dyspnée s'est aggravée. L'échocardiographie est stable par rapport à 2004, l'insuffisance mitrale est peu importante, l'insuffisance tricuspidienne est importante, la PAPs est estimée à 55 mmHg.
Le 4 août 2005, le patient consulte un pneumologue, car il se plaint de toux survenant dans le primo-décubitus, qui ne semble qu'en partie liée à la cardiopathie, pour discuter du maintien des antihypertenseurs, notamment béta-bloquants et antagoniste de l'angiotensine II. On évoque la possibilité d'un reflux gastro-oesophagien, qui sera traité par OGAST® pendant 1 mois.

Le 30 août 2005, le MEDIATOR® est arrêté. L'état du patient s'améliore très rapidement avec disparition de la toux et de l'essoufflement. (le lendemain de l'arrêt du MEDIATOR®, selon le patient). *(expertise en cours)*

- **TO060957:**
-

Une femme de 50 ans présente une dyspnée qui parait avoir débuté en 2003. Celle-ci est devenue rapidement invalidante au moindre effort. Elle est présente dès la marche à allure normale en terrain plat et s'accompagne d'une désaturation en oxygène avec un passage de 92% à 84% en juillet 2005. Les antécédents sont une obésité (BMI=38) et un diabète non insulino-dépendant traités par MEDIATOR®, 3 cp/j pendant 3 ans (de 2000 à 2003), une hypothyroïdie et une hypertension artérielle.

En octobre 2005, l'HTAP précapillaire est moyennement sévère avec une PAPs à 79 mmHg au cathétérisme cardiaque. Une origine multifactorielle a été évoquée : obésité, hypoventilation, syndrome ventilatoire restrictif sur paralysie phrénique ou cause médicamenteuse.
En janvier 2006, l'échographie cardiaque montre une dilatation des cavités droites, ainsi que de l'oreillette gauche. Les valves mitrale et aortique sont morphologiquement normales. En avril 2006, le cœur droit parait normal par rapport au degré de l'HTAP, la PAPs est à 82 mmHg.
En mai 2006, un diagnostic de communication intra-auriculaire est porté avec : il existerait une ouverture entre les 2 oreillettes de 12 mm environ. *(expertise en cours).*

A la mi-décembre 2006, une HTAP précapillaire sévère à 60 mmHg de moyenne sans réponse au NO est diagnostiquée chez une femme de 51 ans, aux antécédents d'obésité (BMI= 41), syndrome d'apnée du sommeil, BPCO post-tabagique, diabète non insulino-dépendant et phlébites en 2002-2003.
Son traitement habituel est : NOVONORM®, HYTACAND®, ZYPREXA®, SYMBOCORT® et BRICANYL®.
Elle a pris du MEDIATOR® pendant 3 mois, 10 ans auparavant.
Les signes cliniques au moment du diagnostic sont une dyspnée d'effort (stade fonctionnel NYHA III) associé à un test de marche de 6 minutes à 265 m.
Le traitement institué comprend PREVISCAN®, 0,75 mg/j associé à TRACLEER® 62,5 mg, 2 cp/j. *(expertise en cours).*

➢ BR0700051:

Une HTAP, avec une PAPm à 46 mmHg, est découverte fortuitement à la mi-décembre 2006, au décours d'un bilan pulmonaire systématique, chez une femme de 58 ans, diabétique, qui a une obésité morbide (BMI= 49) et une hypertension artérielle.
Il n'est pas retrouvé d'argument en faveur d'une embolie pulmonaire. Un petit syndrome interstitiel fait évoquer une insuffisance cardiaque gauche. Un traitement diurétique améliore la PO_2 et l'image radiologique.
La scintigraphie (ventilation et perfusion) est normale, ainsi que le scanner thoracique et l'endoscopie bronchique. L'échocardiographie s'est dégradée depuis 2002. Au moment du diagnostic, la patiente prenait : LANTUS® , metformine, TEMERIT® APROVEL® LASILIX® et MEDIATOR® (depuis 10 ans).
Le traitement institué comprend PREVISCAN®, 1 cp/j associé à TRACLEER® 62,5 mg, 2 cp/j. *(expertise en cours).*

Depuis le début de la commercialisation de MEDIATOR© à décembre 2006, le nombre de boites de 30 comprimés vendues est de : 125 524 279 correspondant à 51 613 601 mois de traitement*.

Les 2 derniers cas (BR0700050 et BR0700051) nous ayant été rapportés récemment, le 13 mars 2007, ils sont en cours d'expertise auprès de Monsieur le Professeur WEITZENBLUM, ainsi que le cas de Toulouse. La fréquence de survenue des HTAP idiopathiques vous sera donc présentée lors de la Commission Nationale du 27 mars 2007.

Lors du précédent rapport de novembre 2005, elle était de :

- 1 cas pour 11 069 333 boites vendues
- ou 1 cas pour 4 551 534 mois de traitement

(*) Mois de traitement : estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés (1 mois = 30,4 jours).

III – CONCLUSIONS :

- **Troubles neuropsychiatriques :**

Cette actualisation de l'enquête de Pharmacovigilance n'apporte rien de nouveau par rapport à l'enquête présentée le 29 novembre 2005.
Il permet de confirmer la réalité des *confusions* qui peuvent apparaître sous MEDIATOR. Cet effet est déjà présent dans le RCP, mais il avait été demandé lors de cette Commission Nationale de novembre 2005 de développer le terme *« confusion »* en détaillant les symptômes tels que : Troubles des fonctions cognitives : *désorientation temporo-spatiale,* troubles du comportement *: agitation, délire,* troubles de la perception : *hallucinations*

- **Hypertensions artérielles pulmonaires :**

Compte tenu de l'incidence des HTAP d'allure idiopathique (1 à 2 cas par millions et par an), le nombre de cas d'HTAP d'allure idiopathique rapporté dans l'enquête, *en attendant l'avis de l'expert pneumologue*, ne constitue pas un signal significatif de toxicité du MEDIATOR dans la classe organe cardiovasculaire.

Hypertensions artérielles pulmonaires (1)

N°	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
PP890081	F,42	1 an	DININTEL TENUATE DOSPAN FRINGANOR	5 ans 5 ans 5 ans	Concomitant	U	
NC9300007 = 052454	M,48	4 ans	ISOMERIDE ZYLORIC LIPANTHYL	3 ans 6 ans	Concomitant	D	
10052455	F,46	25 mois	ISOMERIDE CORGARD BUSPAR VELITEN ALDACTONE	580 jours	Concomitant	F	
10052733	F,71	60 mois	ISOMERIDE	45 jours	Antérieur	F	HTAP post-capil
10840193	F,47	?	ISOMERIDE COVERSYL LASILIX GLUCOPHAGE	730 jours	Concomitant	F	
10840255	F,57	?	ISOMERIDE PONDERAL STILNOX XANAX VEINOBIASE	? 2 mois	Postérieur	F	
10840663	M,48	+ mois	ISOMERIDE FLUDEX	210 jours	Postérieur	F	
10840770	F,66		ISOMERIDE FENPROPOREX	1 mois	Antérieur	F	HTA post-emb
10840954	F,54		ISOMERIDE STAGID DIAMICRON	1-2 semaines	Inconnu	A	HTA post-cap
10840B19	F,51	5 ans ?	ISOMERIDE SECTRAL MODURETIC KALEORID LEXOMIL RANIPLEX PREPULSID	6 mois	Postérieur	F	HTAP post-cap
10840D01	F,59	4 ans	ISOMERIDE PONDERAL ZOCOR PROGESTOGEL SPIROCTAN	Environ 12 mois Environ 6 mois	Concomitant	D	

Hypertensions artérielles pulmonaires (2)

N°	S/Age	BMI	Durée TTT	TTT associé	Evolution	Commentaires
PS9900385	F,50	24	4 à 5 ans	LOGIRENE TRIATEC Fenofibrate	U	
S02001877	F,55	32	1 an	TERALITHE ALDACTONE LASILIX LESCOL PREVISCAN LIPANTHYL, LIPUR GLUCOPHAGE...	U	
TO040278	F,36	24	2 ans		B	HTAP post-capillaire
MP0500189	F,55	35	31 mois	MOPRAL PREVISCAN COTAREG VIOXX	D	HTAP post-embolique
S02001046	F,59	*?* *(poids=86kg)*	9,5 ans	CAPTEA LOPRIL HUMORYL PRAXINOR PROGYNOVA UTROGESTAN	U	Dossier peu informatif
NT0500397 = S05001666	M, 74	31	9 ans	HYTACAND CHRONO-ADALATE KERLONE PREVISCAN	B	**Expertise en cours**
TO060957	**F,50**	**38**	**3 ans**	**LEVOTHYROX**	**F**	**Expertise en cours**
BR000050	**F,51**	**41**	**3 mois** **(il y a 10 ans)**		**B**	**Expertise en cours**
BR000051	**F,58**	**49**	**10 ans**		**B**	**Expertise en cours**

Les nouveaux cas notifiés depuis le rapport de novembre 2005 est inscrit ***en gras***

Servier CN PV 27/03/07

Objectif de l'étude

Étude d'utilisation / prescription de MEDIATOR

2021

Annexe 3-72

Choix méthodologique : observatoire THALES

- L'observatoire épidémiologique permanent THALES :

  - est fondé sur l'activité régulière d'un échantillon national représentatif de médecins généralistes libéraux (1 200 MG) informatisés équipés du logiciel Doc'ware

  - permet de recueillir et d'analyser longitudinalement des données anonymes et codées issues de dossiers patients en étudiant précisément le contexte de la prescription dans la pratique courante

Méthodologie de l'étude MEDIATOR

- Analyse de la prescription de MEDIATOR chez les médecins généralistes en fonction des indications pour lesquelles il a été prescrit.
- Période analysée :
  - mai 2004 – avril 2005
  - mai 2005 – avril 2006
- Nous avons distingué 5 groupes exclusifs de patients :

A : Patients diagnostiqués **dyslipidémiques** dans l'année (non diagnostiqués diabétiques)

B : Patients diagnostiqués **diabétiques** dans l'année (non diagnostiqués dyslipidémiques)

C : Patients diagnostiqués **diabétiques et dyslipidémiques** dans l'année

D : Patients **non diabétiques**, **non dyslipidémiques** ayant reçu un diagnostic « **obèses** », « **surcharge pondérale** », « **prise de poids** », associé à la prescription de MEDIATOR

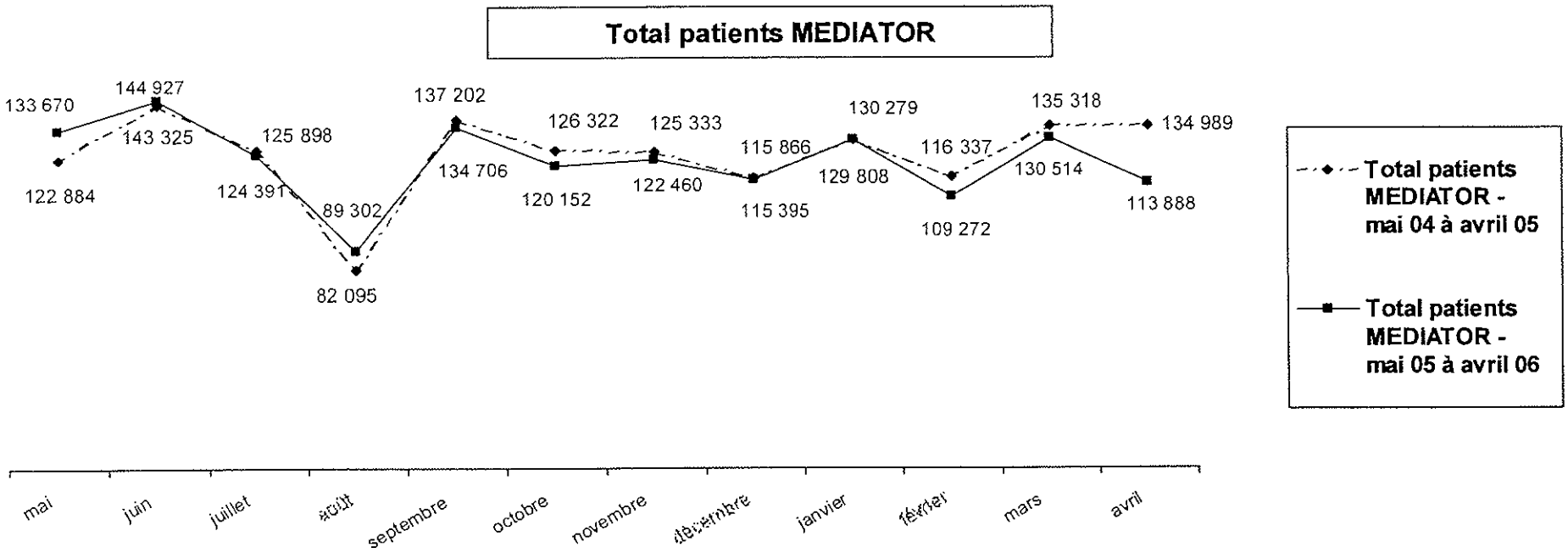
E : **Autres patients non diabétiques**, **non dyslipidémiques** ayant reçu d '**autres diagnostics** associés à la prescription de MEDIATOR

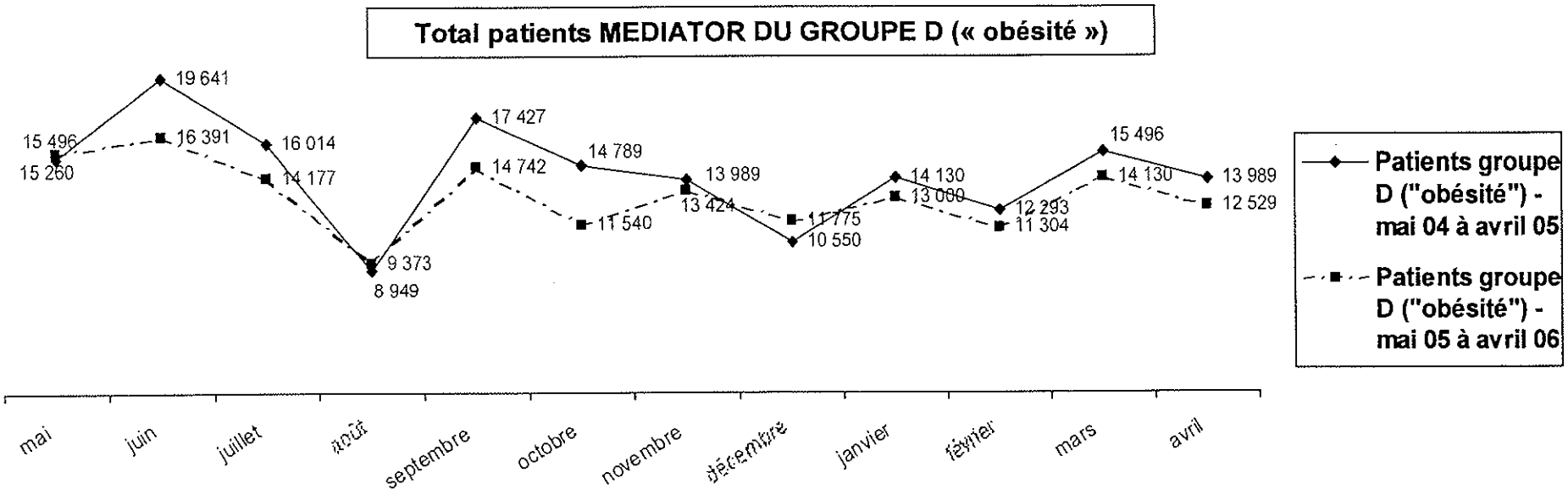
Répartition du nombre de prescriptions et de patients traités par MEDIATOR en fonction du diagnostic

(Valeurs extrapolées à partir des données brutes)

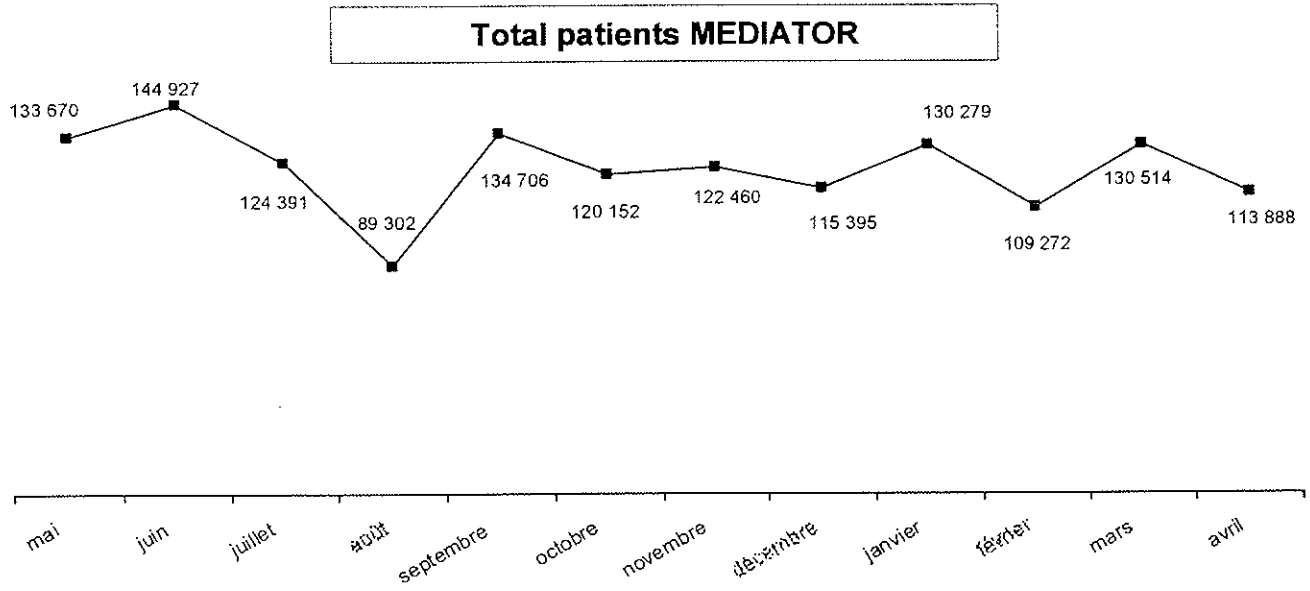
		de mai 2004 à fin avril 2005		de mai 2005 à fin avril 2006	
		Nombre de patients MEDIATOR	Nombre de prescriptions MEDIATOR générées	Nombre de patients MEDIATOR	Nombre de prescriptions MEDIATOR générées
A	Patients dyslipidémiques	270 307 **50,6%**	669 998 **44,8%**	266 869 **51,0%**	668 490 **45,5%**
B	Patients diabétiques	63 161 **11,8%**	223 395 **14,9%**	58 969 **11,3%**	213 551 **14,5%**
C	Patients dyslipidémiques et diabétiques	81 389 **15,2%**	308 222 **20,6%**	80 682 **15,4%**	301 770 **20,5%**
D	Patients avec diagnostic obésité / surcharge pondérale associé à la prescription	76 443 **14,3%**	172 527 **11,5%**	73 193 **14,0%**	157 879 **10,7%**
E	Patients avec d'autres diagnostics associés à la prescription de MEDIATOR	43 049 **8,1%**	121 235 **8,1%**	43 615 **8,3%**	127 264 **8,7%**
Total MEDIATOR		**534 350** **100,0%**	**1 495 378** **100,0%**	**523 328** **100,0%**	**1 468 955** **100,0%**

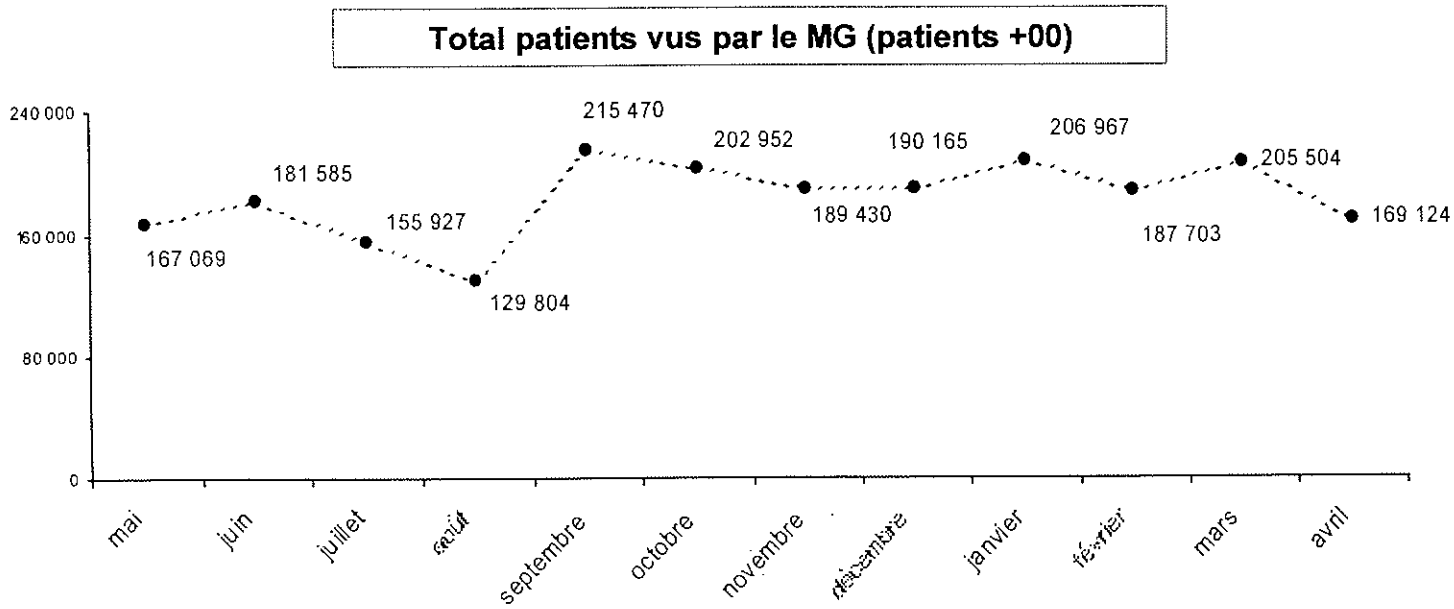
Analyse graphique de la saisonnalité des patients MEDIATOR





Comparaison de la saisonnalité des patients MEDIATOR vs. Total patients vus par les MG (mai 2005 à avril 2006)





Analyse de l'IMC des patients MEDIATOR du groupe D (« obésité »)

	mai 2005 à avril 2006							
	Total patients Groupe D		Total Hommes		Femmes de moins de 50 ans		Femmes de 50 ans et plus	
	Nbre	%	Nbre	%	Nbre	%	Nbre	%
- IMC[25 à 28[	12 293	16,8%	1 036	9,7%	7 301	17,6%	3 956	18,9%
- IMC [28 à 30[	7 960	10,9%	1 696	15,9%	3 533	8,5%	2 732	13,0%
- IMC > 30	24 021	32,8%	4 616	43,4%	13 141	31,6%	6 264	29,9%
- IMC non renseigné dans l'année	28 919	39,5%	3 297	31,0%	17 615	42,4%	8 007	38,2%
patients avec diag de Surpoids	20 536	28,1%	2 261	21,2%	12 670	30,5%	5 605	26,7%
patients avec diag Obésité	8 384	11,5%	1 036	9,7%	4 946	11,9%	2 402	11,5%
Total patients du groupe D (obèse/surpoids)	**73 193**	**100,0%**	**10 645**	**100,0%**	**41 589**	**100,0%**	**20 960**	**100,0%**

*** Liminaire méthodologique : l'IMC a été calculé chez les patients ayant eu à une même date le poids et la taille de renseignés**

Profil signalétique des patients MEDIATOR selon l'âge et le sexe

(base : total patients MEDIATOR en médecine générale)

	Mai 2004 à Avril 2005			
	Total patients MEDIATOR		Groupe D Patients obèses / surcharge pondérale	
	Nbre	%	Nbre	%
Hommes	182 654	34,2%	11 116	14,5%
Hommes de moins de 50 ans	52 988	9,9%	6 782	8,9%
Hommes de 50 ans et plus	129 666	24,3%	4 333	5,7%
Femmes	351 696	65,8%	65 328	85,5%
Femmes de moins de 50 ans	150 720	28,2%	44 086	57,7%
Femmes de 50 ans et plus	200 976	37,6%	21 242	27,8%
Total patients MEDIATOR	**534 350**	**100,0%**	**76 443**	**100,0%**

	Mai 2005 à Avril 2006			
	Total patients MEDIATOR		Groupe D Patients obèses / surcharge pondérale	
	Nbre	%	Nbre	%
Hommes	177 803	34,0%	10 645	14,5%
Hommes de moins de 50 ans	51 527	9,8%	7 065	9,7%
Hommes de 50 ans et plus	126 275	24,1%	3 580	4,9%
Femmes	345 526	66,0%	62 549	85,5%
Femmes de moins de 50 ans	141 300	27,0%	41 589	56,8%
Femmes de 50 ans et plus	204 226	39,0%	20 960	28,6%
Total patients MEDIATOR	**523 328**	**100,0%**	**73 193**	**100,0%**

CONCLUSION

- Environ 80 % des prescriptions de MEDIATOR sont réalisées chez des patients dyslipidémiques et / ou diabétiques

  (80,3 % en 2004-2005 / 80,5 % en 2005-2006)

  Environ 11 % des prescriptions MEDIATOR sont réalisées chez des patients « obèses »

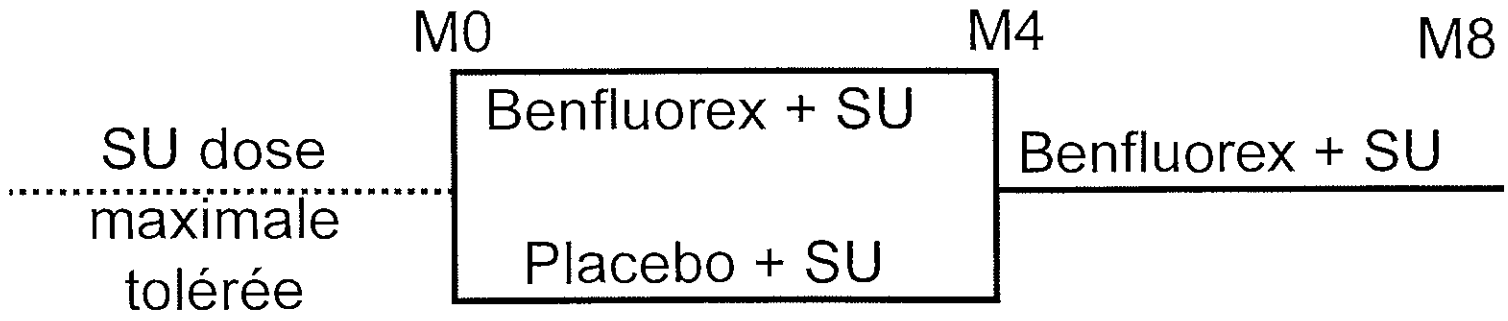
  (11,5 % en 2004-2005 / 10,7 % en 2005-2006)

  Ces taux restent stables au cours du temps

- Concernant la saisonnalité des prescriptions de MEDIATOR, l'analyse n'a pas montré de différences entre le groupe « obésité » et le total patients MEDIATOR

- Le profil des patients MEDIATOR (âge/sexe/IMC) reste stable sur les deux périodes

MEDIATOR EN ASSOCIATION AUX SULFONYLURÉES CHEZ DES PATIENTS AVEC UN DÉSÉQUILIBRE GLYCÉMIQUE IMPORTANT ET UNE INTOLÉRANCE OU CONTRE-INDICATION A LA METFORMINE



Inclusion : diabétiques de type 2

Age > 18 ans

Surpoids : IMC de 25 à 40 kg/m^2

Insuffisamment contrôlés : HbA1c de 7 à 10 %

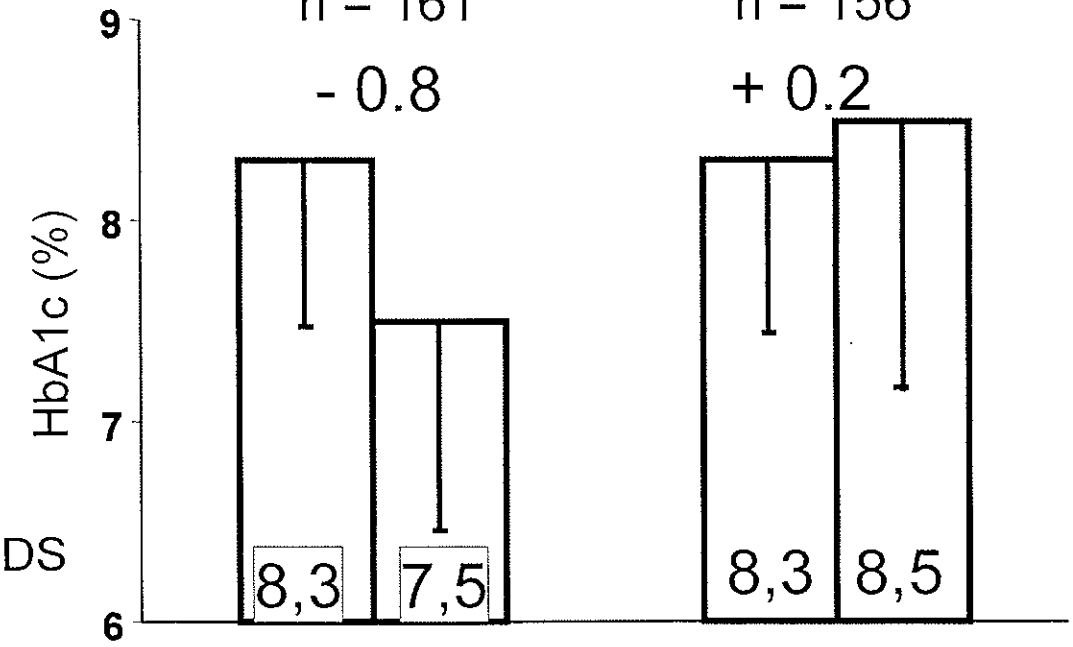
Sous dose maximale tolérée sulfonylurées depuis 2 mois

Intolérance ou contre-indication à la metformine

EFFICACITE : HBA1C – ITT

benfluorex versus placebo
en ITT : 97% des inclus

Δ HbA1c: - 1.0%
p < 0,001

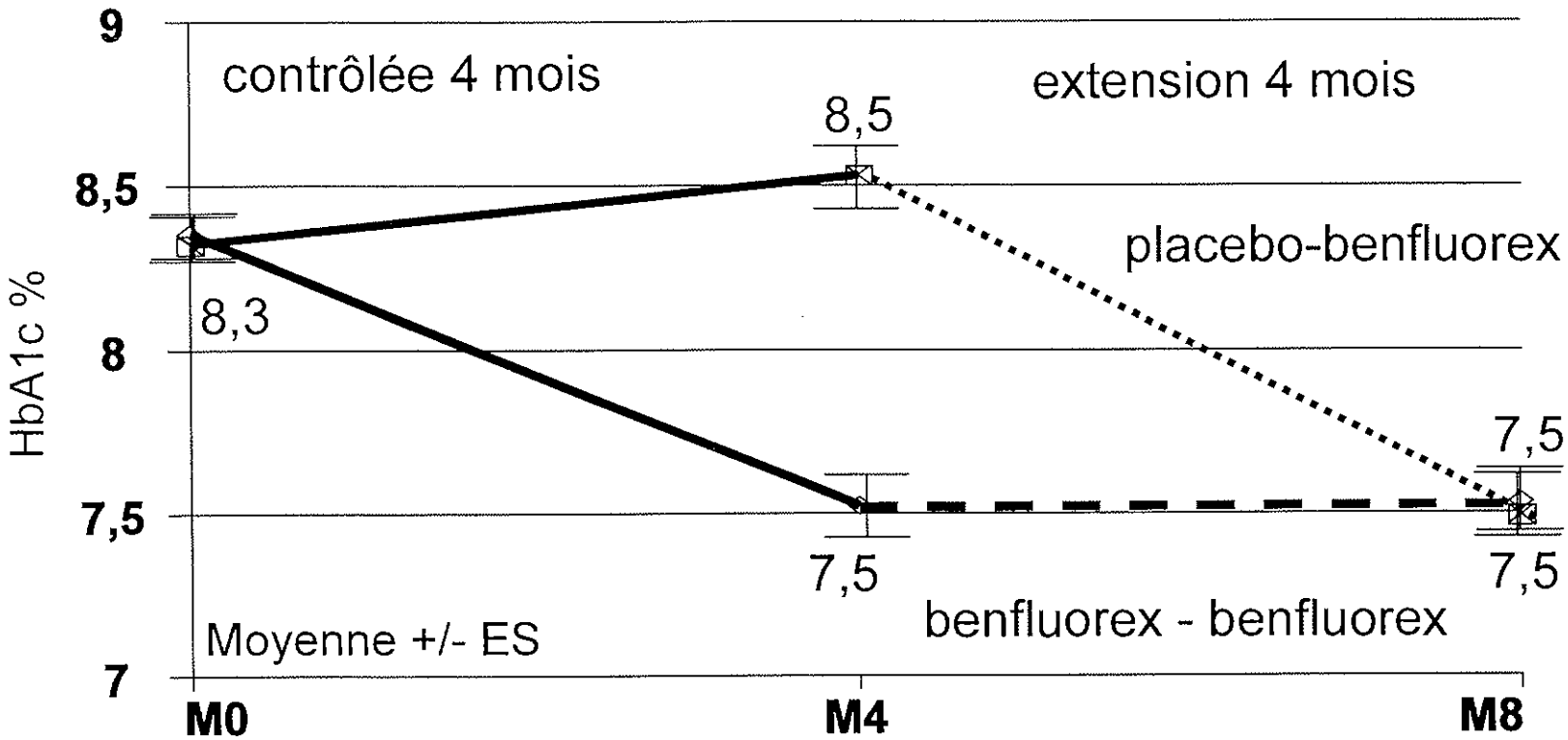


Moyenne +/- DS

	n	HbA1c initiale	Δ vs placebo
Per Protocol :	265	8.3	- 1.1
Age > 65 ans	152	8.3	- 0.8
HbA1c > 8%	182	**8.9**	- 1.1

EVOLUTION DE L'HbA1c

Effet maintenu jusqu'à 8 mois



L'effet de benfluorex est reproductible dans le groupe initialement traité par placebo

TOLERANCE

- Evènements indésirables

  Troubles gastro-intestinaux :

  - Total 15% versus 10%
  - Patients avec intolérance digestive à la metformine 15% versus 15%

  ⇒ <u>Pas d'intolérance croisée avec la metformine</u>

- Poids : - 0.6 Kg versus placebo

  ⇒ <u>Efficacité indépendante de l'évolution pondérale</u>

  HbA1c : différence versus placebo ajustée sur la variation pondérale – 0.96 %, p < 0,001
  (analyse principale non ajustée – 1.01%)

- Pression artérielle et fréq. cardiaque : stables
- ECG, biologie standard : pas de modifications

CONCLUSIONS DE L'ETUDE

- Données valides et pertinentes
  - Méthodologie rigoureuse, résultats robustes, population de diabétiques de type 2 représentative
- Quantité d'effet hypoglycémiant importante
  - HbA1c : diminution de 1% versus placebo,
    y compris chez les patients sévères
  - Cohérent avec les études antérieures
- Pas d'effet cliniquement pertinent sur le poids
  - Cohérent avec les études antérieures :
    Δ : - 0.4 à -1.0 Kg versus placebo

Modèle animal d'HTAP (1)

❑ Modèles développés pour étudier les mécanismes physiopathologiques et des thérapeutiques de l'HTAP :

1) stimuli pathophysiologiques :

ex. rat en hypoxie chronique

2) stimuli chimiques et toxiques :

ex. rat monocrotaline

3) modèles génétiques :

ex. rat Fawn-hooded

❑ Pas de modèle validé pour évaluer le potentiel d'un médicament à engendrer une HTAP

Modèle animal d'HTAP (2)

Rat Fawn-Hooded (FH) a été proposé :

- Rat susceptible de développer spontanément une HTAP (accélérée par l'hypoxie)

- Protocole :

  Rats FH traités en chronique (3 sem. + réversibilité)

  En normoxie ou hypoxie

  Evaluation : - hémodynamique (PAP, PAS)
  - hypertrophie ventriculaire droite
  - histologie (prolifération cellulaire et degré muscularisation artérioles)

2039

Annexe 3-73

Jean MARIMBERT - Rép. : Projet compte rendu de la Commission nationale de pharmacovigilance du 27 mars 2007

De : Jean-Hugues TROUVIN
À : Catherine REY-QUINIO; Jean MARIMBERT; Sophie FORNAIRON
Date : Mercredi 9 Mai 2007 07:23
Objet : Rép. : Projet compte rendu de la Commission nationale de pharmacovigilance du 27 mars 2007
CC : Anne CASTOT; Carmen KREFT-JAIS; Eric ABADIE

Concernant MEDIATOR, nous allons effectivement procéder par étape, avec en première priorité faire adopter par la commission d'AMM la recommandation de supprimer l'indication "triglycérides", et le démarrage de la procédure contradictoire y afférente, avec en sus la notification des questions résiduelles sur l'indication "diabète de type 2".
Une fois la procédure contradictoire achevée sur l'indication litigieuse, et le RCP rectifié en conséquence, nous pourrons alors libérer l'AMM du générique de Médiator, générique qui est actuellement "bloqué" dans sa notification et qui risque, si nous tardons trop à lui octroyer son AMM, de monter au créneau et soulever, à juste titre, un traitement inéquitable puisque le princeps continue à exploiter son médicament, avec le RCP actuel, et que lui ne peut pas exploiter le produit, qui est actuellement ouvert à la générication.
C'est pourquoi je crois plus prudent d'agir par étape, et de rectifier les AMM du princeps et du générique au fur et à mesure que les données sur Médiator se complètent.
Le retrait de l'indication triglycéride étant le sujet qui fait actuellement l'objet d'un consensus, c'est cette "décision" qu'il convient de mettre en oeuvre maintenant sans délai (mais dans le respect des formes et des procédures pour éviter le contentieux avec le titulaire du princeps !!) et notifier au génériqueur l'AMM ainsi "rectifiée", en l'informant que d'autres modifications sont en cours sur l'AMM du Médiator et qu'il aura à les mettre en oeuvre dès qu'elles seront notifiées aux titulaires des AMM.
JH

>>> Jean MARIMBERT 07/05/07 18.40 >>>
J'ai pris connaissance du document tramsmis par Catherine à la suite de mes remarques sur l'avant-projet de compte-rendu de la CNPHV du 27 mars.
Il faut que nous puissions dans le courant du mois de mai, en amont de la validation finale et de la publication du compte-rendu de PHV, valider et déclencher les suites de l'avis de la Commission d'AMM, notamment la procédure contradictoire de suppression d'une indication, la modification du RCP pour ajouter des EI en 4.8, et la préparation de la communication sur l'indication qui resterait ainsi que-et c'est peut-être plus épineux- sur l'usage hors-AMM.
J.M.

>>> Catherine REY-QUINIO 02/05/2007 10:23 >>>
Monsieur,

Faisant suite à vos remarques sur le compte rendu de la CNPV au sujet de MEDIATOR, veuillez trouver ci joint le relevé d'avis tél qu'il a été rédigé après la COM d'AMM du 5 avril dernier. Lors de cette COM , les conclusions de la CNPV et celles du groupe DEUG ont été présentées.
Voir essentiellement pages 18 et 19.

Cordialement,

C Rey-Quinio

>> Jean MARIMBERT 05/01/07 8:22 >>>
Quelques remarques sur ce projet de compte-rendu bien étoffé.
S'agissant de MEDIATOR,la mention en termes trés nets aux lignes 55 et 56 de la page 8 d'un désaccord entre la CNPHV et le GT DEUG quant au libellé de lindication, mais aussi du fait que le renouvellement de l'autorisation de Benfluorex n'a pa été accordé en Espagne et en Italie, rend indispensable de pouvoir

compléter le compte-rendu avant sa publication par l'exposition de la position prise par la Comission d'AMM et de préférence aussi de la décision de l'Agence, sachant qu'à ce jour je n'ai pas de visibilité sur les termes du choix tel qu'il se présente aprés examlen par la Commission d'AMM.
S'agissant de Pergolide, il me semble qu'il y a eu au moment de la CNPHV ou juste aprés une communication de l'EMEA que nous avons reprise.Le compte-rendu devrait si tel a bien été le cas être complété par une mention de ce message.
S'agissant du Zyban, j'ai été un peu intrigué par l'écart apparent entre l'affirmation de la ligne 16 de a page 16 suivant laquelle"L'étude n'a as montré d'augmentation du risque suicidaire en résence de Zyban par rapport au placebo mais les effectifs sont insuffisants" et le chiffre d'OR de 3, 27 qui figure en première ligne/dernière colonne du tableau pour les actes suicidaires dans l'indication de dépression.
Par ailleurs, il faudra que nous nous voyions un moment avant la publication pour voir si l'Agence suit la proposition unanime de la Commission tendant à arrêter le suivi national , afin de pouvoir faire état de la décision dans le CR.
S'agissant d'Arixtra, écrire"pallier les problèmes" en première ligne de la page 19.Par ailleurs, pourrait-on expliquer en français ce qu'est une "line listing" (ligne 20) ?
A la ligne 46 de la page 20, je suppose qu'il manque un vingt entre quatre et six.
Sur le fond, le lecteur est frappé par la fréquence nettement plus élevée semble-t-il en France des accidents hémorragiques.Das ce contexte, il paraît souhaitable de diffuser rapidement aux professionnels de santé l 'information que la Commision appelle de ses voeux, sans attendre sans doute l'aboutissement de l'évaluation au niveau européen de la demande d'extension d'indication pour l'infarctus du myocarde.
J.M.

****
Docteur Catherine REY-QUINIO
Responsable de l'Unité PTC2
DEMEB/Afssaps
Tel : 01.55.87.34.45/Fax : 01.55.87.34.42.
catherine.rey-quinio@afssaps.sante.fr
****

>>> Annabelle PAGE 26/04/2007 15:58 >>>
Bonjour,

Nous vous prions de bien vouloir trouver ci-joint le projet de compte rendu de la Commission nationale de pharmacovigilance du 27 mars 2007, pour avis et commentaires, si possible au plus tard le **lundi 30 avril, midi.**

Nous vous remercions par avance.

Cordialement,

Diane HALLE et Annabelle PAGE
SESAC PV
Unité de pharmacovigilance
DEMEB

mars 2008

IX – TOUR DE TABLE DES CAS MARQUANTS

N° des cas	Date de survenue	Sexe / Age	Médicaments suspects	Effets observés	Evol.	Imput	EI présent dans le RCP (ou le VIDAL)	G	N	E	Inter. BNPV	Commentaires Interaction
CRPV de BORDEAUX												
BX080 0191 BX080 0192 BX080 0193			Hypnovel® midazolam	Mesusage, erreur EI : bradypnée	A		Sans objet	O	?	N		Utilisation en prémédication pré-opératoire po (ou sublingual ?) Erreur d'administration (ampoule à 50mg au lieu de 5 mg) S'utiliserait aussi en intra-nasal ???
	Dans ces cas le midazolam, forme injectable, a été utilisé en prémédication anesthésique par voie orale. Une conférence de consensus datant de 2002, utilisant la méthodologie ANAES, recommande l'utilisation du midazolam *per os* mais également par voie intra-nasale. Les recommandations de cette conférence de consensus provenant de la Société française d'anesthésie et de réanimation (en collaboration avec la Société française d'oto-rhino-laryngologie) seraient trés suivies par un certain nombre d'hôpitaux. **=> Le Groupe de Travail Neuro-Psy-Anesthésiste (GTNPA) va être saisi afin de savoir s'il s'agit d'un problème fréquent ou d'un cas particulier de la Réunion.**											
CRPV de BREST												
BR200 80051	juin-07	F 50 A	MEDIATOR NUTROPINAQ	Insuffisance mitro-aortique	Guérison avec séquelles	C1S1 C1S1	Non	Oui	N on	No n	Oui 2 cas en 2007: - MP20070034 - TO070121	Prise courte d'Isoméride (1 à 3 mois) il y a 20 ans. Echocardiographie quasi- normale en 2001 dans le cadre d'un bilan diabétique. Absence de symptomatologie cardio-respiratoire entre 2001 et 2006. Mise en route du ttt par somatotropine en mars 2007. Début de symptomatologie respiratoire (dyspnée) en mai-juin 2007. A noter que la somatotropine est poursuivie. Facteurs de risques cardio-vasculaires : -DNID - tabac
	A la suite de la décision de la commission d'autorisation de mise sur le marché, le MEDIATOR® n'est plus indiqué dans les dyslipidémies depuis le 25 juillet 2007. Deux autres cas d'insuffisance mitro-aortique sous MEDIATOR® avaient été précédemment déclarés. Les résultats de l'anatomopathologie seraient concluants. **=> le CRPV doit récupérer le compte-rendu de l'anatomopathologie qui permettrait de confirmer le diagnostic.**											

2041

Annexe 3-74

	survenue	Age	suspects				le RCP (ou le VIDAL)					Interaction
CRPV de LIMOGES												
LM0800063	22/02/2008	F/54	OCTAGAM 50 mg/mL	Neutropénie	F	C1S1	N	O	N	Discussion lors d'un tour de table des cas marquants au CT du 07/11/06	BS0500429 (neutropénie) PP20070164 (leucopénie) BX0600311 (leucopénie)	Traitement associé : RIVOTRIL, INEGY, Insuline/pompe. Neutropénie survenant au 3ème jour de la 1ère cure d'OCTAGAM Lots injectés pendant la cure : 9 flacons B751E8431 et un flacon B748C8431. Les perfusions sont bien tolérées. Pas d'administration d'immunoglobulines auparavant.
	En 2006, une DMI a été déposé par le laboratoire LFB pour la TEGELINE® à la suite de la description de 17 cas de neutropénies dont 7 cas dans la BNPV. La rubrique "Effets indésirables" du RCP de la TEGELINE® comprend maintenant la mention suivante :"Une leuconeutropénie asymptomatique, de survenue précoce et rapidement réversible, peut être observée, en particulier chez les patients traités par de fortes doses." Cependant le RCP d'Octagam® ne comporte pas cette mention. **=> Le Comité Technique propose une surveillance des cas de leuconeutropénies sous OCTAGAM®.**											
LM0800045	2007	M/62	GLIVEC (imatinib)	Hypoglycémie	F	C1S1	N	O	O	?	N	Patient diabétique insulino-dépendant depuis 28 ans, bien équilibré, traité par GLIVEC depuis juin 2007. Depuis l'instauration du ttt, il présente des hypoglycémies à 0,25 g/L. En janvier 2008, posologie GLIVEC augmentée à 400 mg/J et aggravation hypoglycémies.
	=> Le CRPV de Limoges vérifiera dans quelle indication, le GLIVEC® était ici utilisé car les hypoglycémies sont fréquentes lors de tumeurs gastriques. De plus, les CRPV de Limoges et de Montpellier étudieront ensemble quel pourrait être le mécanisme d'action du GLIVEC® responsable d'hypoglycémie.											

Evolution : selon le code OMS : A, F, B, U, D, C, N
Pour Gravité, Nouveauté, Enquête : répondre par Oui ou Non

Evolution : selon le code OMS : A, F, B, U, D, C, N
Pour Gravité, Nouveauté, Enquête : répondre par Oui ou Non

Annexe 3-75

DIRECTION DE L'EVALUATION
DES MEDICAMENTS ET DES PRODUITS BIOLOGIQUES
DEPARTEMENT DE PHARMACOVIGILANCE

Saint-Denis, le 02 Juin 2009

COMITE TECHNIQUE DE PHARMACOVIGILANCE
COMPTE RENDU DE LA REUNION DU MARDI 5 MAI 2009

Etaient présents :

Membres du Comité Technique de pharmacovigilance :

M. MERLE (président)
Mme LAINE-CESSAC (vice-présidente)
Mme KREFT-JAIS (représentant la Direction Générale de l'AFSSAPS)
Mme BOUXIN-METRO (représentant le Directeur général de l'INSERM)
Mme ALLAIN-VEYRAC (suppléante de Mme JOLLIET)
M. ANDREJAK
Mme BALDIN (suppléante de Mme CHICHMANIAN)
Mme BAVOUX
M. BIOUR
M. CARON
Mme DE LA GASTINE (suppléante de M. COQUEREL)
Mme EFTEKHARI
M. ESCHALIER
M. GILLET
Mme HILLAIRE-BUYS (suppléante de M. BLAYAC)
Mme JEAN-PASTOR
Mme JONVILLE-BERA (suppléante de Mme AUTRET-LECA)
M. KANTELIP
Mme LATES (suppléante de Mme WELSCH)
Mme LEBELLER (suppléante de Mme LILLO-LE LOUET)
M. LE LOUET
M. MALLARET
Mme MIREMONT-SALAME (suppléante de Mme HARAMBURU)
M. MONTASTRUC
Mme PERAULT-POCHAT
M. RICHE
M. TRENQUE
M. VIAL
Mme WAROT (suppléante de Mme LEBRUN-VIGNES)

Département de Pharmacovigilance :
Mme DELEAU
Mme OUARET
Mme PAGE

AFSSAPS :
M. BOUCAUD-MAITRE
Mme COURNE
Mme DEGUINES
Mme REY-QUINIO
Mme VILLANOVA

Internes :
Mme CAVEE
Mme RIBEIRO-CRESPEL

Etaient excusés :
Mme DELOFFRE
Mme NOBLET
M. OLLAGNIER

Stagiaire :
Mme PIZZOGLIO

CRPV :
Mme BOUTARD
Mme DAVID-LAROCHE
Mme DEVOTI
Mme GOURAUD
Mme GINISTY
Mme MOACHON
Mme VALNET-RABIER

EXPERTS :

5 GESTION DES CONFLITS D'INTERETS

Aucune situation de conflit d'intérêt n'a été retenue ni déclarée au cours de la séance du Comité technique de pharmacovigilance du 5 mai 2009.

Annexe 3-75

TABLE DES MATIERES

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I - ADOPTION DU COMPTE RENDU DE LA SEANCE DU MARDI 5 MAI 2009

Dossier suivi par Annabelle PAGE-LECOMPTE

Page 40 : IX – Tour de table des cas marquants et littérature
Ligne 5 : remplacer « désormais réservé en pas première intention dans le traitement de l'arthrose, PR et SpA » par « désormais le piroxicam ne doit pas être utilisé en première intention dans le traitement de l'arthrose, PR et SpA, lorsqu'un traitement par AINS est indiqué ».

II - POINT SUR LE SUIVI NATIONAL DE PHARMACOVIGILANCE DU METHYLPHENIDATE

Dossier suivi par : Claire Ferard
CRPV rapporteur : Dr Thierry Trenque– CRPV Reims

DCI	Méthylphénidate
Nom commercial / Titulaire AMM / Procédure	Ritaline® 10 mg*, Ritaline LP® 20 mg, 30 mg et 40 mg / Novartis Pharma / Procédure nationale Concerta LP® 18 mg, 27mg (non commercialisée), 36 mg, 54 mg / Janssen Cilag / Reconnaissance Mutuelle Méthylphénidate Rubio® 5mg, 10mg, 20mg (non commercialisées) /Rubio SA / Reconnaissance Mutuelle Quasym LP® 10mg, 20mg, 30 mg (non commercialisées) / UCB Pharma / Reconnaissance Mutuelle
Indication	Trouble déficitaire de l'attention avec hyperactivité (TDAH) chez l'enfant de plus de 6 ans. Narcolepsie avec ou sans cataplexie, en cas d'inefficacité du modafinil, chez l'adulte et l'enfant de plus de 6 ans*.
Conditions de prescription et de délivrance	Prescription limitée à 28 jours Prescription initiale hospitalière annuelle réservée aux spécialistes en neurologie, psychiatrie et pédiatrie, et aux centres du sommeil

I. Introduction

Un point sur le suivi national de pharmacovigilance du méthylphénidate avec une mise à jour des données françaises de sécurité d'emploi a été souhaité dans le cadre de l'arbitrage européen déclenché en juillet 2007 et concernant la réévaluation du rapport bénéfice/risque de l'ensemble des produits à base de méthylphénidate. Cet arbitrage a donné lieu à une évaluation par l'Agence Européenne (EMEA) de l'ensemble des données disponibles de sécurité concernant le méthylphénidate, et plus particulièrement les effets indésirables cardiaques, psychiatriques et neurologiques, les effets à long terme sur la croissance et la maturation sexuelle. Suite à cette évaluation européenne, de nouvelles recommandations ont été établies par l'EMEA afin de limiter les risques liés à l'administration du méthylphénidate (cf point d'information Afssaps 23 janvier 2009), et les résumés des caractéristiques du produit (RCPs) de l'ensemble des spécialités à base de méthylphénidate ont été harmonisés.

Ce point fait suite à celui du 19 décembre 2000 (Ritaline®), et du 7 février 2006 (Ritaline®, Ritaline LP®, Concerta LP®).

II. Méthode

Le CRPV de Reims a analysé :
- les données enregistrées dans la base nationale de pharmacovigilance (BNPV) sur la période du 07 février 2006 au 31 décembre 2008 (méthylphénidate considéré 'suspect' selon les critères d'imputabilité de l'OMS)
- les données nationales et internationales pour la période du 01 janvier 2006 au 31 décembre 2008 fournies par les laboratoires commercialisant le méthylphénidate (Novartis, Janssen-Cilag).

Résultats et discussion :

- **Cas notifiés en France depuis le 01 janvier 2006**

	Cas notifiés aux CRPVs du 07/02/06 au 31/12/08	Cas notifiés aux laboratoires du 01/01/06 au 31/12/08	Total
Ritaline® et Ritaline LP®	21	113 (49 graves)	134
Concerta LP®	20	66 (20 graves)	86
Total	41	179 (dont 10 doublons avec la BNPV)	220

Les effets indésirables les plus fréquents sont essentiellement de type neuropsychiatrique, cutané, et cardiovasculaire.

- **Données de la BNPV**

Les effets indésirables neuropsychiatriques sont les plus fréquents (n=17) et généralement d'évolution favorable : tics, troubles du sommeil, hallucinations, crise tonico-clonique, céphalées, convulsions, vertiges, agitation psychomotrice ; sauf un cas de suicide chez un garçon de 11 ans notifié avec Concerta LP®. Les données françaises mettent aussi en évidence 8 cas de toxicité cardiovasculaire (majoration d'extrasystoles ventriculaires, tachycardie, hypertension artérielle, dyspnée d'effort), une toxicité cutanée (n=11), une toxicité hématologique (n=2) et un cas de retard de croissance avec cassure de la courbe de poids et âge osseux diminué. Un cas de dépendance est notifié avec Ritaline® et Ritaline LP®. Par ailleurs, sur les 41 notifications, 15 concernent des indications hors AMM.

- **Données des laboratoires Novartis et Janssen-Cilag**

Les effets indésirables neuropsychiatriques sont les plus fréquents (n=62) avec 36 cas de troubles psychiatriques : dépression, phobie, angoisse, agitation, comportement impulsif, tics, troubles du sommeil, agitation psychomotrice, hallucinations, logorrhée. Les effets cardiovasculaires rapportés (n=9) sont essentiellement : tachycardie et hypertension artérielle. Les troubles cutanés correspondent à des érythèmes, alopécies, anomalies des ongles, éruptions, avec 1 cas de syndrome de Stevens-Johnson d'évolution favorable à l'arrêt du traitement.
Pour Ritaline® et Ritaline LP®, il est à noter aussi des atteintes thyroïdiennes (n=3), des abus médicamenteux (n=3), des retards de croissance (n=2), un syndrome de Wolff Parkinson White. Pour Concerta LP®, on note aussi des atteintes thyroïdiennes (n=2), des atteintes hépatiques biologiques (n=2), des cas d'abus (n=4), et un accident vasculaire cérébral d'évolution favorable chez un enfant de 14 ans aux antécédents cardiovasculaires.
Par ailleurs, sur les 179 notifications, 38 concernent des indications hors AMM.

- **Cas notifiés en France depuis la commercialisation du méthylphénidate**

Depuis le début de la commercialisation du méthylphénidate (1991) jusqu'au 31 décembre 2008 :

- 90 notifications ont été enregistrées dans la base nationale de pharmacovigilance, chez 61 garçons et 13 filles de moins de 18 ans (âge moyen de 10 ans +/- 3 ans) et 16 adultes (9 hommes, 7 femmes).
- 437 notifications ont été enregistrées par les laboratoires Novartis et Janssen-Cilag.

Le profil d'effet indésirable est similaire pour les deux formes de méthylphénidate (forme à libération rapide et forme à libération prolongée). Les effets indésirables rapportés sont des effets attendus. Les manifestations neuropsychiatriques sont les plus fréquentes avec en particulier des convulsions, des troubles du comportement, des hallucinations et des syndromes dépressifs.

- **Données d'utilisation**

En terme de chiffres de vente, les données GERS (ville et hôpital) montrent, pour Ritaline® et Ritaline LP®, une baisse du nombre de boîtes vendues en 2005 (de 227 263 en 2004 à 186 033 boîtes vendues en 2005) puis une progression constante entre 2006 et 2008 (de 218 213 à 282 939 boîtes vendues). Cette baisse de 2004 à 2005 n'est pas expliquée. Le nombre de boîtes vendues dans les établissements de soins a diminué d'environ 13% en 10 ans. Le nombre de patients traités pendant la période étudiée a évolué de 10 119 patients-années en 2004 à 18 106 patients-années en 2007.
Les données GERS concernant Concerta LP ® n'ont pas été communiquées au CRPV.
En termes de remboursement (données des organismes de base de l'Assurance Maladie), le nombre de boîtes de méthylphénidate remboursées par l'Assurance Maladie a augmenté de 33% de 2004 à 2007 avec une progression de la forme à libération prolongée au détriment de la forme à libération immédiate
Une différence existe entre le nombre de boîtes remboursées par l'Assurance Maladie et le nombre de boîtes vendues qui varie de 20% à 27% en fonction des années (22% en 2007 soit 57 955 boîtes). Normalement, cette différence devrait être inférieure à 10% vu les modalités de prescription de ces spécialités.

III. <u>Conclusions et propositions du rapporteur :</u>

Les précédents rapports ont permis de mettre l'accent sur différents points concernant la sécurité d'emploi du méthylphénidate, comme les manifestations psychiatriques, cardiovasculaires, les conduites addictives, les retards de croissance, et l'éventualité d'apparition d'accidents vasculaires cérébraux ou de toxicité tumorale. Ces deux derniers points ne sont pas confirmés par cette mise à jour des données de pharmacovigilance du méthylphénidate. Par ailleurs, les atteintes thyroïdiennes apparaissent comme un nouveau signal à surveiller.

Une modification des RCPs des différentes spécialités à base de méthylphénidate a été adoptée à la suite de l'arbitrage européen, avec élaboration de recommandations concernant les pathologies et les antécédents cardiaques, les manifestations psychiatriques, ainsi que la surveillance de la croissance. Ainsi, les données de pharmacovigilance provenant de la notification française sont en accord avec le RCP de l'ensemble des spécialités à base de méthylphénidate harmonisé lors de l'arbitrage européen, ainsi qu'avec le PGR européen qui comprend l'élaboration d'études à long terme et la surveillance des effets indésirables psychiatriques, cardiovasculaires, addictifs, et le retentissement sur la croissance et la maturation sexuelle.

Cependant, certaines interrogations formulées dans les deux précédents rapports restent identiques et concernent :

- la prescription du méthylphénidate (croissance des prescriptions chez l'adulte qui paraît associée à un glissement des prescriptions vers des indications hors AMM ; indication pour une pathologie dont les critères diagnostiques sont basés sur deux classifications différentes, dont la population cible reste à être précisée et aux facteurs de comorbidité confondants)
- sa délivrance (différence entre le nombre de boîtes vendues et remboursées)

Le CRPV de Reims propose la mise en place d'un plan de gestion des risques national, en complément du PGR européen, comprenant :

- La poursuite du suivi national de pharmacovigilance.
- La mise en place d'un suivi prospectif des enfants traités par méthylphénidate L'élaboration de recommandations sur le bon usage des traitements du TDAH (Trouble Déficitaire de l'Attention avec Hyperactivité)
- La mise en place d'études d'utilisation (prescription et délivrance)

IV. Conclusions du comité technique :

Le comité technique du 05 mai 2009 a adopté les conclusions et propositions du CRPV de Reims, et souligne la nécessité d'obtention de données françaises d'utilisation du méthylphénidate, et de données sur les effets à long terme (retentissement sur la croissance, risque de pharmacodépendance, effets cardiovasculaires…). Le CT souhaite que la possibilité de mettre en place sur une longue période une cohorte française d'enfants traités par méthylphénidate soit étudiée, et que soit mis en place par l'Afssaps un groupe d'experts chargé d'élaborer des recommandations sur le bon usage du méthylphénidate.

III - SUIVI NATIONAL DE MINIRIN® (DESMOPRESSINE) : TROISIEME RAPPORT

Dossier suivi par Béatrice POROKHOV

1 – Introduction

Nom commercial	MINIRIN®, MINIRIN SPRAY®, MINIRINMELT®
DCI	desmopressine
Forme pharmaceutique	Comprimé, solution pour administration endonasale, lyophilisat oral
Classe pharmacologique	Hormone antidiurétique
Procédure d'enregistrement	Procédures nationales
Titulaire de l'AMM	FERRING SAS

Le suivi national concernant les effets indésirables graves observés sous desmopressine fait suite à une enquête réalisée en 2004 qui avait conduit à retirer l'indication énurésie nocturne primaire pour les formes intra-nasales. De plus, des informations pour une meilleure prévention et un dépistage plus précoce des intoxications par l'eau avaient été ajoutées dans les RCP de Minirin®.

Ce suivi était justifié par :

- la nécessité d'évaluer l'impact des mesures prises après l'enquête et diffusées par une lettre aux prescripteurs (avril 2006)
- la commercialisation en juillet 2006, d'une forme d'administration sublinguale de desmopressine, le Minirinmelt® dosé à 60 et 120 µg, puis en avril 2007 de la spécialité dosée à 240 µg.

Ce troisième rapport de suivi a porté sur la notification entre avril 2008 et mars 2009 de:

- toutes les observations concernant la desmopressine notifiées en France provenant de la BNPV et du laboratoire Ferring.
- les observations internationales graves transmises par le laboratoire Ferring.

Afin de disposer d'éléments relatifs à l'indication « nycturie », ont été réalisées 1) une enquête de prescription dans cette indication auprès des urologues de Basse-Normandie (BN) et 2) une analyse des données de la CNAM en Haute-Normandie (HN) et BN, relatives à tous les patients de 45 ans et plus ayant eu une prescription de desmopressine entre août 2006 et septembre 2008.

2 – Résultats du troisième rapport de suivi national de pharmacovigilance

a) Données générales :

- Au total: dans la BNPV, 10 notifications concernant la desmopressine dont 6 intoxications par l'eau certaines et 3 possibles, dont 7 cas graves (tous des intoxications par l'eau).
- Et dans la base de données Ferring, 64 observations dont 46 intoxications par l'eau (32 certaines et 14 possibles), 51 cas graves dont 40 intoxications par l'eau (31 certaines, 9 possibles).
- Pour l'ensemble des cas français : **23 observations** dont 7 intoxications par l'eau prouvées et 8 possibles, et au total 7 effets graves. Cela fait une incidence moyenne de 2 notifications par mois pour la desmopressine dont au moins une intoxication par l'eau (incidence identique à celle des deux précédents suivis).
- 16 observations concernant le Minirinmelt® dont 6 françaises. Parmi ces observations, 10 cas graves ; 15 cas d'intoxication par l'eau dont 9 graves (5 certaines et 10 possibles).

b) Observations en rapport avec une intoxication par l'eau :

- pour la France : 7 cas avérés d'intoxication et 8 cas possibles avec par ordre de fréquence décroissant les indications suivantes : 8 énurésie (dont 2 cas d'intoxications par l'eau avérés), 6 nycturies (dont 4 intoxications par l'eau avérés), 1 indication diabète insipide. La voie d'administration le plus souvent retrouvée est la voie sublinguale (6 cas sur 15), suivie des voies orale et intra-nasale (4 cas pour chacune).
- pour les autres pays : 40 cas graves dont 31 cas d'intoxication par l'eau avérés et 9 cas possibles, l'indication majoritaire est le diabète insipide (18 cas) suivie de l'énurésie (12 cas) et de la nycturie (5 cas). La voie d'administration le plus souvent en cause reste la voie intra-nasale (15 cas) suivie de la voie sublinguale (9 cas) et orale (6 cas).
- *concernant le traitement de l'énurésie* : en France, 2 cas d'intoxication par l'eau avérés (dont un grave), 6 possibles. Aucun cas ne concernait la voie intra-nasale. La voie sublinguale était retrouvée dans 6 cas non graves (dont 1 cas avéré), les deux autres cas concernant la forme comprimé. Dans les autres pays, 12 observations graves dont 5 avec la voie intra-nasale (soit 42%, versus 65% dans le précédent rapport de suivi). Trois mises en jeu du pronostic vital (2 avec la voie IN et une avec le Minirinmelt®). Sept cas étaient des intoxications avérées et 5 possibles.

- *concernant le traitement de la nycturie* : en France, 6 cas d'intoxication par l'eau dont 5 graves (2 mises en jeu du pronostic vital), 100% correspondaient à un usage hors AMM (patients de plus de 65 ans) parmi lesquels 4 doubles mésusages (utilisation de la forme IN). Pour les autres pays, 5 cas graves dont 3 concernaient la forme comprimé et 2 le Minirinmelt®. L'âge était supérieur à 65 ans chez tous les patients.
  Une association à un autre médicament inducteur d'hyponatrémie était retrouvée chez 4 patients français sur 6 et 4 sur 5 pour les autres pays.

c) Enquête de prescription dans la nycturie auprès des urologues de Basse-Normandie : envoi de 17 questionnaires, 8 réponses: 2 prescrivent parfois la desmopressine dans cette indication, 2 exceptionnellement, 4 jamais. Un seul médecin la prescrit parfois malgré l'âge des patients dépassant 65 ans. Deux sont assez satisfaits de ce médicament dans cette indication, 1 un peu et 2 pas du tout.

d) Analyse des données de la CPAM en Haute et Basse-Normandie: 340 patients en HN et 264 en BN ont été traités par desmopressine, parmi lesquels respectivement 146 (43%) et 119 (45%) avaient 65 ans ou plus. Les résultats qui suivent concernent les patients de plus de 65 ans. L'indication nycturie est vraisemblable chez 134 patients de HN et 111 de BN. La forme galénique la plus prescrite dans cette indication est le comprimé (72% en HN, 63% en BN) suivie du Minirinmelt® (16% et 23%) et du spray intra-nasal à 10 µg (12% et 14%). La durée moyenne de traitement est de 7,4 mois en HN et 6,8 mois en BN. Une proportion importante de patients est traitée pour instabilité vésicale ou hypertrophie de prostate: en HN, respectivement 50% des patients et 62% des hommes; en BN, 44% et 60%. Soixante cinq pourcent (65%) des patients en HN et 76% en BN reçoivent au moins une famille d'anti-HTA. Soixante dix sept (77) % des patients en HN et 85% en BN sont traités par au moins un autre médicament inducteur d'hyponatrémie, au premier rang desquels les anti-inflammatoires non stéroïdiens (AINS) (50% des patients en HN, 53% en BN), suivis des diurétiques (44% et 40%) et des inhibiteurs sélectifs de recapture de la sérotonine (ISRS) (23% et 31%).

e) Evolution des ventes : Poursuite d'une discrète diminution des ventes des formes intra-nasales par rapport à celles des formes orales et sublinguales. Augmentation des prescriptions des formes sublinguales qui sont en tête dans l'énurésie (47% chez les généralistes, 85% chez les pédiatres). Persistance de la baisse du nombre absolu de patients traités par desmopressine dans l'indication énurésie par les médecins généralistes (45 452 en 2008 versus 54 024 en 2007, soit moins 16%).

3 - Discussion et synthèse du CRPV Rapporteur

En France, l'estimation de l'incidence des cas graves d'intoxication par l'eau est de 8,5 pour 100 000 patients traités (8,9 pour 100 000 lors du deuxième rapport de suivi).
Dans l'indication *énurésie*, il n'y a pas de cas français d'intoxication par l'eau avec la forme intra-nasale. Avec le Minirinmelt®, la majorité des cas sont non graves (en augmentation), le nombre de cas graves étant stable. Il y a encore une prépondérance de cas graves avec la voie intra-nasale dans les autres pays, bien que la proportion diminue.
Le risque d'intoxication par l'eau lors du traitement de la *nycturie* semble en grande partie lié au mésusage qui concerne 100 % des notifications dans cette indication. Les intoxications sont souvent graves en raison du risque de chute lors d'une hyponatrémie, mettant parfois en jeu le pronostic vital des patients âgés.
Les données de la CNAM montrent l'importance des prescriptions hors AMM (près de la moitié des patients ont plus de 65 ans), l'utilisation probablement inadaptée de la desmopressine pour de nombreux patients (notamment en cas d'hypertrophie de prostate ou de vessie instable), le risque de déséquilibre d'une HTA puisque la majorité des patients sont hypertendus, et enfin le risque d'hyponatrémie majoré par le grand âge et l'utilisation fréquente d'autres médicaments inducteurs d'hyponatrémie.
De plus, l'utilisation de la desmopressine dans la nycturie avait été déconseillée à deux reprises lors des commissions de transparence de mars 2004 et janvier 2006, sur la base d'un effet seulement symptomatique, d'une indication chez les patients de moins de 65 ans en contradiction avec le terrain de la nycturie (la nycturie étant plus fréquente en vieillissant), d'une efficacité non démontrée et d'un risque important d'hyponatrémie. De plus, la place de ce médicament dans la stratégie thérapeutique a été jugée marginale, justifiant l'octroi d'un niveau de Service Médical Rendu (SMR) insuffisant et le refus du remboursement par la HAS.

4 - Propositions du rapporteur

- Réévaluation du rapport bénéfice / risque de la desmopressine dans l'indication nycturie
- Arrêt du suivi national compte tenu de la stabilité des résultats par rapport aux deux précédents rapports de suivi.

5 – Discussion et conclusions du Comité technique de pharmacovigilance

Les mesures de prévention et de précocité du diagnostic d'intoxication par l'eau et leur support de communication ont eu un impact positif sur la sécurité d'utilisation du Minirin®. Cependant, concernant l'indication nycturie, on ne dispose pas de l'évolution des ventes ni de la répartition selon l'âge, avant ou après 65 ans, des patients traités pour nycturie. Ces données seront demandées au laboratoire Ferring (base IMS).
La poursuite de l'étude observationnelle (MENUI) accompagnant la mise sur le marché du MinirinMelt® sera discutée compte-tenu de l'insuffisance des inclusions et de l'impossibilité d'atteindre les objectifs.

Ce troisième rapport de suivi national de pharmacovigilance de la desmopressine sera présenté à la Commission Nationale de pharmacovigilance. Des données complémentaires concernant la nycturie y seront présentées.

IV - ENQUETE OFFICIELLE RELATIVE AUX HYPERTENSIONS ARTERIELLES PULMONAIRES ET AUX VALVULOPATHIES OBSERVEES AVEC MEDIATOR® (CHLORYDRATE DE BENFLUOREX): MISE A JOUR DES DONNEES DE PHARMACOVIGILANCE

Dossier suivi par Béatrice POROKHOV / Virginie RIBEIRO-CRESPEL

1 – Introduction

Nom commercial	MEDIATOR®
DCI	Chlorhydrate de benfluorex
Formes pharmaceutiques	Comprimé pelliculé à 150 mg
Classe pharmacologique	Antidiabétique
Procédure d'enregistrement	Procédure nationale
Titulaire de l'AMM	Laboratoires Servier

MEDIATOR® (chlorhydrate de benfluorex) a obtenu une AMM lors d'une procédure nationale d'enregistrement en 1974 et est commercialisé en France depuis 1976.
Sa seule indication est: « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ».
L'indication « adjuvant du régime adapté dans les hypertriglycéridémies » a été supprimée suite aux conclusions de la Commission Nationale de Pharmacovigilance du 27 mars 2007.

2 – Contexte

En décembre 2004, la notification de plusieurs cas d'effets indésirables, évoquant un effet de type amphétaminique avec MEDIATOR®, a conduit à une actualisation des effets indésirables neuropsychiatriques observés. Par ailleurs, la notification d'un cas d'hypertension artérielle pulmonaire, présenté au Comité Technique du 8 mars 2005, a justifié une extension de l'enquête aux hypertensions artérielles pulmonaires (HTAP).

Les résultats de cette enquête officielle ont été présentés par le CRPV de Besançon au Comité Technique de Pharmacovigilance du 07 juin 2005 et à la Commission Nationale de Pharmacovigilance du 29 novembre 2005. La Commission a alors demandé : i) la réévaluation de la balance bénéfice/risque de MEDIATOR®, ii) une étude d'utilisation/prescription, iii) une étude expérimentale sur un modèle animal permettant d'étudier le potentiel du benfluorex à induire des HTAP et iiii) une étude au niveau des Centres d'Evaluation et d'Information sur la Pharmacodépendance (CEIP) afin d'identifier un éventuel problème de pharmacodépendance.
Ces données, hormis l'interrogation des CEIPs, ont été présentées au Comité Technique de pharmacovigilance du 13 mars 2007 puis à la Commission Nationale de pharmacovigilance du 27 mars 2007. Les conclusions de la Commission Nationale ont conduit à la suppression de l'indication « adjuvant du régime adapté dans les hypertriglycéridémies » par la Commission d'AMM du 5 avril 2007.

Ce rapport présente les résultats actualisés de l'enquête sur le risque d'HTAP et de valvulopathie cardiaque sous MEDIATOR® ainsi que les données d'une publication récente sur ce sujet : K.Boutet et coll. *« Fenfluramine-like cardiovascular side-effects of benfluorex »* en mars 2009, rapportant 5 cas d'hypertension artérielle pulmonaire (HTAP) et un cas de valvulopathie cardiaque chez des patients ayant été exposés au benfluorex.

3 - Actualisation des données de l'enquête sur les HTAP

28 cas d'HTAP ont été notifiés, dont 8 nouveaux depuis la Commission Nationale du 27 mars 2007.

3.1 – Notifications où Médiator® est associé à un anorexigène : 13 cas

• 11 cas déjà présentés lors de la CN du 27 mars 2007 et expertisés par le Pr. Weitzenblum, dont 7 cas d'HTAP jugés d'allure idiopathique.

• 2 nouveaux cas d'allure idiopathique ont été rapportés *BR20080383* (publication de Boutet et Al., cas n°5) : Femme de 55 ans, BMI=41 kg/m^2, HTAP modérée. Prise d'ISOMERIDE® très ancienne et pendant moins de 3 mois et de MEDIATOR® pendant plusieurs années, arrêté 1 an avant le diagnostic.

PB0700302 (cas rétrospectif de 2002) : Femme de 65 ans. Prise d'ISOMERIDE® de 1992 à 1993, et de MEDIATOR® de 1996 à 1999.

3.2 – Notifications où Médiator® est non associé à un anorexigène: 15 cas

- 9 cas déjà présentés à la CN du 27 mars 2007 et expertisés par le Pr. Weitzenblum. Aux 3 cas jugés alors idiopathiques (*PS9900385, PB20090105, TO060957*), s'ajoute un cas incomplet en 2007 et confirmé depuis :
  BR0700051 (publication Boutet et Al., cas n°4) : Femme de 58 ans, DNID, HTA et BMI=49 kg/m². Prise de MEDIATOR® pendant 10ans.

- 6 nouveaux cas ont été rapportés. Leur analyse ne permet de retenir aucun cas d'HTAP d'allure idiopathique.

- 3 de ces 15 cas d'HTAP non idiopathiques sont associés au développement, après exposition au benfluorex, d'une valvulopathie. Ils seront donc classés comme valvulopathies sous MEDIATOR®.

3.3 – Conclusions sur les cas d'HTAP

Depuis le dernier rapport de 2007, le nombre d'HTAP d'allure idiopathique sous Mediator® non associé à un autre anorexigène passe de 3 à 4 (*PS9900385, PB20090105, TO060957* et *BR0700051*).
La fréquence des HTAP imputables au MEDIATOR® reste donc stable par rapport à 2007 (1 cas sur 8 738 542 boîtes vendues contre 1 cas sur 9 655 713 boîtes vendues en 2007).
Compte tenu de l'incidence des HTAP d'allure idiopathique dans la population générale (1 à 2 cas par millions et par an), le nombre de cas d'HTAP d'allure idiopathique rapporté dans l'enquête ne constitue pas un signal significatif de la toxicité du MEDIATOR®.

4 - Actualisation de l'enquête sur les valvulopathies

En France, 30 cas ont été notifiés entre 1998 et 2009 :
- 19 notifications spontanées (NS) : dont 3 cas rapportés également dans les HTAP post-capillaires.
- 11 cas identifiés par le CRPV de Brest par l'intermédiaire de l'interrogation du PMSI (Programme de médicalisation des systèmes d'information).

4.1 – Caractéristiques des patients atteints de valvulopathie

	NS : 19	**Brest PMSI : 11**
Sexe	Femmes : 24, hommes : 6	
Age moyen de survenue (ans) *Femmes* : 54,6 *Hommes* : 62,2	 53,7 54,6	 56,4 69,7
BMI (kg/m²) *18,5 à 24,9* : 5 cas *25 à 29,9* : 7 cas *≥ 30* : 8 cas	 3 5 4	 ~~3~~ 2 2 4
Durée moyenne de traitement (ans) 5,3	5,6	4,6
Antécédents / Terrain (nombre) *Tabac* : 13 *Hypothyroïdie* : 9	 10 7	 3 2
Antécédent/Terrain cardiaque (nombre)	15	

Médicaments associés (nombre) *Levothyroxine* *Antidépresseur IRS*	 9 7

4.2 – Type et localisation des valvulopathies

Concernant la nature des valvulopathies (30 cas), elles sont monovalvulaires dans 6 cas, bivalvulaires dans 16 cas et trivalvulaires dans 8 cas. Par ailleurs, en terme de localisation, une insuffisance mitrale est présente dans 28 cas (sévère dans 17 cas), une insuffisance aortique dans 24 cas et une insuffisance tricuspide dans 11 cas (sévère dans 4 cas).

4.3 – Aspects anatomo-pathologiques des valvulopathies opérées

Des données anatomo-pathologiques précises sont disponibles chez 6 patients opérés : 5 cas de patients français, ainsi qu'un cas espagnol rapporté dans une publication (Rafel Ribera J.) par le laboratoire Servier *S03000422*.

a) 4 cas dont l'aspect anatomo-pathologique serait compatible avec celui décrit avec les anorexigènes

TO060355 (Publication Noize 2006) : femme de 48 ans, BMI=25 kg/m^2, MEDIATOR® pendant 7 ans pour intolérance aux glucides.

BR20080051 (Publication de Boutet, cas n°6) : femme de 50 ans, diagnostic en novembre 2007, BMI=34 kg/m^2, diabète de type 2, MEDIATOR® de 2001 à septembre 2007, ISOMERIDE® pendant 1 à 3 mois 20 ans auparavant.

BR20090080 (Brest PMSI) : femme de 54 ans, BMI=30 kg/m^2, MEDIATOR® de septembre 2007 à décembre 2008, diagnostic en décembre 2007, prise d'amphetamine 7 à 8 ans jusqu'en 1986.

S03000422 (Cas espagnol publié par R. Ribera J. 2003) : femme de 50 ans, 12 mois par intermittence sous MEDIATOR®.

b) Autres cas

Dans 2 cas l'anatomopathologie n'est pas spécifique : TO051212 TO0400278

Les autres cas ne disposent que de données échographiques insuffisantes.

4 – Discussion et conclusions du Comité Technique

La fréquence des cas d'HTAP idiopathiques sous MEDIATOR® est stable par rapport aux données présentées en mars 2007. De plus, celle-ci n'est pas supérieure à l'incidence naturelle des cas d'HTAP idiopathiques. Les membres du CT recommandent une surveillance simple des notifications spontanées des cas d'HTAP dans la population générale.

L'identification de 30 cas de valvulopathies à partir de la notification spontanée et de la recherche dans le PMSI effectuée par le CRPV de Brest, constitue un signal de sécurité d'emploi du MEDIATOR® qui doit être exploré. La rareté de cet évènement et la non-spécificité des données anatomopathologiques et cliniques, conduisent à choisir plutôt une étude rétrospective cas/témoins plutôt qu'une étude prospective. Dans cette optique l'exploitation du codage PMSI est une possibilité intéressante, mais qui reste à être modélisée avant validation afin de la rendre reproductible et extrapolable à d'autres problématiques. A cette fin, ce projet sera présenté lors de la deuxième réunion du groupe de pharmaco-épidémiologie du 3 juin 2009.

Ce rapport ainsi que les propositions du groupe de pharmaco-épidémiologie qui se réunira le 3 juin feront l'objet d'une présentation en Commission Nationale de Pharmacovigilance.

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Annexe 3-75

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Saint-Jacques – 25030 BESANCON Cedex

MEDIATOR® (benfluorex)

Enquête officielle

Hypertensions artérielles pulmonaires

Et

Point sur

Valvulopathies

Comité technique du 5 mai 2009

Confidentiel

M. DAVID-LAROCHE
J.P. KANTELIP

Suite à la publication de K. Boutet et coll. *« Fenfluramine-like cardiovascular side-effects of benfluorex »,* rapportant 5 cas d'hypertension artérielle pulmonaire (HTAP) et un cas de valvulopathies cardiaques chez des patients ayant été exposés au benfluorex, le Comité Technique a demandé d'actualiser l'enquête officielle sur les HTAP sous benfluorex.
Un cas de valvulopathie étant rapporté dans cette article, nous faisons également le point sur les cas de valvulopathies dans lesquelles, il a été retrouvé un traitement par benfluorex.
Nous y avons ajouté les cas d'HTAP post-capillaires, lorsque la valvulopathie parait être postérieure à la prise de benfluorex.

Le MEDIATOR® (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés, dosés à 150 mg.

La seule indication est : « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale », car l'indication, « adjuvant du régime adapté dans les hypertriglycéridémies » a été supprimée, suite aux conclusions de la Commission Nationale de Pharmacovigilance du 27 mars 2007.

Le nombre d'HTAP d'allure idiopathique retrouvé dans l'enquête présentée à cette commission, ne constituait pas un signal significatif de toxicité du MEDIATOR® dans la classe organe cardiovasculaire.

Métabolisme : (rappel)

- In vivo : Chez l'homme, le MEDIATOR® est hydrolysé très rapidement au niveau plasmatique et hépatique par des estérases en S422 (dérivé alcool), puis transformé en 8 métabolites majeurs, par oxydation (S1475, dérivé acide) ou désalkylation (S585, norfenfluramine).
  Le métabolite majoritaire est le dérivé carboxylique : S1475.
  Le métabolite primaire S422 et la norfenfluramine sont retrouvés à des taux très inférieurs.

Après administration de benfluorex radioactif, on retrouve 87 à 99% de la radioactivité après 72 heures dans les urines. L'absence de quantité significative dans les fécès montre que le produit est bien absorbé.
Il n'existe pas de phénomène d'accumulation.

L'élimination se fait en 2 phases :
- une première phase rapide (60% en 3 ou 4 heures)
- une seconde phase lente de 36 heures environ.

- In vitro : Après incubation d'hépatocytes frais humains, il a été montré que les principaux cytochromes P450 jouent un rôle très minoritaire dans le métabolisme du benfluorex.

Annexe 3-75

I. Hypertensions Artérielles Pulmonaires

28 notifications ont été rapportées (dont 8 depuis la Commission Nationale du 27 mars 2007) :

1. Notifications où MEDIATOR® est associé à un anorexigène :

13 notifications d'«Hypertension artérielle pulmonaire » ont été rapportées.

- 11 d'entre elles, expertisées par le Professeur WEITZENBLUM (Strasbourg), faisaient partie de l'enquête «Anorexigènes et hypertensions artérielles pulmonaires» présentée à la Commission Nationale du 27 mars 2007
Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® est :

- antérieure dans 2 cas : 1 HTAP post-capillaire (10052733)
  1 HTAP post-embolique (10840770)

- concomitante dans 5 cas : 5 HTAP d'allure idiopathique (PP890081, NC9300007, 10052455, 10840193, 10840D01)

- inconnue dans 1 cas : 1 HTAP post-capillaire (10840954)

- postérieure dans 3 cas : 2 HTAP d'allure idiopathique (10840255, 10840663)
  1 HTAP post-capillaire (1084B19)

- 2 nouveaux cas ont été rapportés :

BR20080383 : (cas n°5 de la publication de K. Boutet et al)

Femme de 55 ans, obèse (BMI= 41), diabétique et dépressive, prise en charge pour une dyspnée d'effort associée à un syndrome d'obésité/hypoventilation et d'apnée du sommeil, appareillée en avril 2006.
Lors d'une visite de suivi, on découvre à l'échocardiographie une dilatation des cavités droites.
La PAPs est évaluée à 59 mmHg.
Le cathétérisme (janvier 2007) montre une PAPm à 28 mmHg. L'HTAP modérée est prise en charge sans traitement médical.
En 2008, l'état clinique de la patiente est stable.
Le dossier médical retient une prise d'ISOMERIDE®, très ancienne, pendant moins de 3 mois et de MEDIATOR® pendant plusieurs années, arrêté 1 an avant le diagnostic d'HTAP.

PB0700302 :

Ce cas, très succinct, datant de 2002 est rapporté rétrospectivement.
Diagnostic d'HTAP précapillaire, chez une femme de 65 ans, alors qu'elle avait pris de l'ISOMERIDE® de 1992 à 1993 et du MEDIATOR® de 1996 à 1999. Au moment de la notification, la patiente n'était pas rétablie.

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2. Notifications où MEDIATOR® n'est pas associé à un anorexigène :

15 notifications d'«Hypertension artérielle pulmonaire » ont été rapportées.

- 9 d'entre elles, expertisées par le Professeur WEITZENBLUM (Strasbourg), faisaient partie de l'enquête «Anorexigènes et hypertensions artérielles pulmonaires» présentée à la Commission Nationale du 27 mars 2007.

  - 1 HTAP post-embolique
    - MP0500189 →*Avis de l'expert : « Vraisemblable HTAP post-embolique »*

  - 2 HTAP post-capillaires :

    - TO040278 :

    →*Avis de l'expert*: *« cardiopathie valvulaire sévère, l'OAP ayant entraîné une HTAP post-capillaire. »*

    - NT0500397 = S05001666 :

    → *Avis de l'expert : « HTAP probablement post-capillaire, peu documentée »*

  - 6 HTAP d'allure idiopathique

    - 2 cas non pris en compte lors de la Commission Nationale (CN) du 27 mars 2007 :

    - S02001046 : dossier trop succinct.
    - BR0700050 (publication K. Boutet, cas n°3) : → *Avis de l'expert : « HTAP idiopathique »*, mais la patiente a été traitée par MEDIATOR® pendant 3 mois, 10 ans auparavant.

    - Les 3 cas retenus lors de la CN du 27 mars 2007 sont :

    - PS9900385 : cas n° 1 de la publication de K. Boutet et coll.
    - S02001877 = PB20090105 : cas n° 2 de la publication de K. Boutet et coll.
    - TO060957

    - Le cas de BR0700051 (publication K. Boutet, cas n°4) était incomplet lors de la CN et l'avis de l'expert *était : « probable HTAP idiopathique mais documentation incomplète » (manque cathétérisme cardiaque)*
    Depuis nous avons reçu, le résultat du cathétérisme cardiaque droit retrouvant une pression artérielle pulmonaire moyenne à 46 mmHg (systolique à 98 mmHg et diastolique à 30 mmHg).
    Il s'agit d'une femme de 58 ans, ayant un DNID, une HTA et une obésité morbide (BMI= 49), qui la fait passer du lit au fauteuil toute la journée et ce depuis plusieurs années.
    Elle a pris du MEDIATOR® pendant 10 ans. Au moment du diagnostic, la patiente prenait LANTUS®, metformine, TEMERIT®, APROVEL® et LASILIX®.
    Elle sort de l'hôpital avec un traitement comportant en plus TRACLEER® et DIAMOX®.

- 6 nouveaux cas notifiés depuis le rapport de mars 2007.

Ces cas n'ont pas été expertisés par le Professeur Weitzenblum, comme les cas antérieurs, mais :

- dans 1 cas, (MA20070346), il s'agit d'une patiente de 52 ans, ayant un BMI = 25,8, traitée pour une hypercholestérolémie par MEDIATOR® depuis 8 ans avec adjonction ensuite de LIPANTHYL®, qui souffre d'une dyspnée d'effort depuis 1 an. L'échocardiographie montre un ventricule droit non dilaté, la pression pulmonaire systolique (PAPs) est estimée à 45 mmHg. Le MEDIATOR® est arrêté. Une échographie cardiaque de contrôle, moins de 3 mois plus tard, montre la normalisation des PAPs, ainsi que l'absence d'insuffisance cardiaque clinique. Un cathétérisme cardiaque n'a pas été effectué.
Il est donc difficile de retenir ce cas comme HTAP d'allure idiopathique.

- dans 1 cas, une HTAP post-embolique est évoquée, (MA20070231) : la patiente âgée de 37 ans est hospitalisée pour péricardite chronique et pneumopathie interstitielle. Elle avait été traitée pendant 1 an par MEDIATOR®, qui a été arrêté 6,5 ans avant la survenue de l'HTAP. La scintigraphie pulmonaire est en faveur d'embolies pulmonaires.

- dans 4 cas, il existe une valvulopathie associée à l'HTAP.

Remarque : parmi ces 4 cas, lorsque le traitement par MEDIATOR semble antérieur à la valvulopathie : MP0700281 et BX20080964, ces cas seront repris dans la partie « II. Valvulopathies » (avec le cas *TO040278 rapporté antérieurement).*

Le nombre d'HTAP d'allure idiopathique passe de 3 à 4, depuis le dernier rapport de mars 2007, en comptant le cas BR0700051.

3. Fréquence :

Depuis le début de la commercialisation de MEDIATOR® à décembre 2008, le nombre de boites de 30 comprimés vendues est de : 139 816 678 correspondant à 57 490 410 mois de traitement*.

En prenant en compte toutes les HTAP, avec ou sans anorexigènes associés, et après élimination des HTAP post-emboliques (3) et post-capillaires (9), il reste 16 cas d'HTAP idiopathique soit :

- 1 cas pour 8 738 542 boites vendues
- ou 1 cas pour 3 593 150 mois de traitement.

Lors du précédent rapport de mars 2007, elle était de :

- 1 cas pour 9 655 713 boites vendues
- ou 1 cas pour 3 970 277 mois de traitement.

(*) Mois de traitement : estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés (1 mois = 30,4 jours).

Après élimination des 9 HTAP idiopathiques survenues lors de traitement par MEDIATOR® associé à un anorexigène, 3 dossiers succincts ou de chronologie douteuse :S02001046, MA20070346 (évolution favorable en 3 mois) et BR0700050 (3 mois de traitement par MEDIATOR®, 10 ans auparavant), il reste 4 cas d'HTAP d'allure idiopathique (PS9900385, S02001877, TO060957 et BR0700051) soit :

- 1 cas pour 34 954 169 boites vendues
- ou 1 cas pour 14 372 602 mois de traitement.

Lors du précédent rapport de mars 2007, elle était de :

- 1 cas pour 41 841 426 boites vendues
- ou 1 cas pour 17 204 533 mois de traitement.

4. Conclusion :

Compte tenu de l'incidence des HTAP d'allure idiopathique (1 à 2 cas par millions et par an), le nombre de cas d'HTAP d'allure idiopathique rapporté dans l'enquête, ne constitue pas un signal significatif de toxicité du MEDIATOR dans la classe organe cardiovasculaire.

Hypertensions artérielles pulmonaires (1) (avec anorexigènes associés)

HTAP d'allure idiopathique							
N° Année survenue	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
PP890081= 540V06 (1988)	F, 42	1 an	Dinintel Tenuate Dospan Fringanor	5 ans 5 ans 5 ans	Concomitant	U	
NC9300007 = 052454 (1991)	M, 48	4 ans	ISOMERIDE Zyloric Lipanthyl	3 ans 6 ans	Concomitant	D	
10052455 (1993)	F, 46	25 mois	ISOMERIDE Corgard Buspar Veliten Aldactone	580 jours	Concomitant	F	
10840193 (1993)	F, 47	?	ISOMERIDE Coversyl Lasilix Glucophage	730 jours	Concomitant	F	
10840D01 (1995)	F, 59	4 ans	ISOMERIDE PONDERAL Zocor Progestogel Spiroctan	Environ 12 mois Environ 6 mois	Concomitant	D	
10840255 (1993)	F, 57	1 mois! (sept. 1993)	ISOMERIDE (1986) PONDERAL (1978) Stilnox Xanax Veinobiase	? 2 mois	Postérieur	F	Novembre 1993 : PAPs = 73 mmHg Février 1994 : PAPs = 95 mmHg
10840663 (1993)	M, 48	Plusieurs mois (depuis février 1992)	ISOMERIDE (1990-1991) Fludex	210 jours	Postérieur	Décès	Février 1992 : dyspnée d'effort stade 3-4 Mai 1993 : PAPs= 50 mmHg

N° Année survenue	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
HTAP d'allure idiopathique (nouveaux dossiers)							
BR20080383 = S08005656 (2007)	**F, 55 BMI: 41**	**Plusieurs années Arrêté 1 an avant HTAP**	**ISOMERIDE Anafranil Imovane Lysanxia Glucophage**	**Moins de 3 mois Il y a plusieurs années**	**Postérieur**	**B**	**PAPm : 28 mmHg** *Public. Boutet n°5*
PB0700302 = S07002196 (2002)	**F, 65 BMI: 39**	**3 ans (1996-1999)**	**ISOMERIDE**	**1 an (1992/93)**	**Postérieur**	**B**	**HTAP (2002)**
HTAP post-embolique							
10840770 (1991)	F,66		ISOMERIDE Fenproporex	1 mois	Antérieur	F	HTAP post-embolique
HTAP post-capillaires							
10840954 (1994)	F,54		ISOMERIDE Stagid Diamicron	1-2 semaines	Inconnu	A	HTAP post-capillaire
10052733 (1993)	F,71	60 mois	ISOMERIDE	45 jours	Antérieur	F	HTAP post-capillaire
10840B19 (1994)	F, 51	5 ans ?	ISOMERIDE Sectral Moduretic Kaleorid Lexomil Raniplex Prepulsid	2 X 3 mois	Postérieur	F	HTAP post-capillaire

Les nouveaux cas notifiés depuis le rapport de mars 2007 sont inscrits ***en gras***

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Hypertensions artérielles pulmonaires (2) (sans anorexigènes retrouvés!)

N° Année suvenue	S/Age	BMI	Durée TTT	ATCD	TTT associé	Evolution	Commentaires
HTAP d'allure idiopathique							
PS9900385 = 126V79 (1998)	F, 50	24	4 à 5 ans	Hypercholestérolémie Diabète HTA	Logirène Triatec Fenofibrate	B	*Pub. Boutet n°1*
S02001877 = PB20090105 (2002)	F,55	32	3 ans	Dyslipidémie Dépression DNID	Teralithe Aldactone Lasilix Lescol Previscan Lipanthyl, Lipur, Glucophage…	B	*Pub. Boutet n°2*
TO060957 = S06002671 (2005)	F,50	38	3 ans	DNID Hypothyroïdie HTA Obésité	Levothyrox	F	
BR0700051 = S07001172 (2006)	F,58	49	10 ans	Diabète HTA Obésité	Lantus Metformine Aprovel Temerit Lasilix	B	*Dossier succinct* *Pub. Boutet n°4*
S02001046 (2002)	F,59	? Poids= 86 Kg	9.5 ans	Hyperlipidémie HTA Dépression	Captea Lopril Humoryl Praxinor Progynova Utrogestan	U	*Dossier succinct*
BR0700050 = S07001089 (2006)	F,51	41	3 mois (il y a 10 ans)	DNID BPCO Thrombose veineuse profonde Synd. d'apnée du sommeil Obésité	Hytacand Novonorm Zyprexa Symbocort Bricanyl	B	*Chronologie!!* *Pub. Boutet n°3*
MA20070346 = S007003637 (2007)	**F, 52**	**26**	**8 ans**	**Hypercholestérolémie**	**Lipanthyl**	**A**	Evolution favorable en 3 mois

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N° Année suvenue	S/Age	BMI	Durée TTT	ATCD	TTT associé	Evolution	Commentaires
HTAP post-emboliques							
MP0500189 = S05000620 (2005)	F,55	35	31 mois	Hypertriglycéridémie Embolie pulmonaire HTA Obésité	Mopral Previscan Cotareg Vioxx	D	HTAP post-embolique
MA20070231 = S08001396 (2007)	**F,37**		**1 an arrêté depuis 6,5 ans**	**DNID Dyslipidémie Péricardite chronique Pneumopathie interstitielle Syndrome dépressif Psychose ! Tabac**	**Glucophage Amarel Paroxétine Abilify Haldol Théralène Lexomil**	**F** Par poussées	HTAP post-embolique !
HTAP post-capillaires (valvulopathies antérieures à MEDIATOR®)							
NT0500397 = S05001666 (2005)	M, 74	31	9 ans	Dyslipidémie Scléroses valvulaires mitrale et aortique Arythmie HTA	Hytacand Chrono-adalate Kerlone Previscan	B	Valvulopathies évoluant depuis 10 ans avant la prise de MEDIATOR
MP0700282 = S07002383 (2007)	**F,72**	**35**	**?**	**Valvulopathie mitrale**	**Coversyl Lasilix Cordarone Cardensiel Inexium**	**F**	HTAP : 15 mars2007 Embolie pulmonaire : 26 avril 2007 HTAP Post-capillaire (Insuffisance mitrale) Ou post-embolique ?
MP20080211 = S08001458 (2007)	**F, 62**	**Pds= 54 kg**	**Début juillet 2007 Continué pdt 7 mois**	**Dyslipidémie Cardiopathie ischémique Infarctus du myocarde (1999) HTA sévère**	**Ticlid Bitildiem Elisor Clarityne**	**F**	Insuffisance aortique

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N° Année suvenue	S/Age	BMI	Durée TTT	ATCD	TTT associé	Evolution	Commentaires
HTAP post-capillaires (dossiers classés également en valvulopathies)							
MP0700281 = S07002370 (1999)	**M,67**	**35**	**5 ans Arrêté depuis 2 ans (1997)**	**Infarctus du myocarde (1980) → Insuffisance cardiaque Fibrillation auriculaire Cirrhose (1981) Tabagisme Obésité**	**Levothyrox Previscan Hemigoxine Ikorel Coversyl Lasilix Ogast**	F	Insuffisance mitrale
BX20080964 = S08005674 (2008)	**F, 78**	**36**	**15 ans**	**Diabète type 2 Hypertriglycéridémie HTA Fibrillation auriculaire**	**Aprovel Hyperium Amlor Zocor**	**F**	Insuffisances mitrale et aortique
TO040278 = S04000348 (2003)	F,36	24	8 mois (Continué 2 ans)	Hypothyroïdie HTA Tabac	Levothyrox Prozac Canol Ginkor fort Hept a myl	B	Insuffisances mitrale et aortique

2067

Les nouveaux cas notifiés depuis le rapport de mars 2007 sont inscrits ***en gras***

Annexe 3-75

II. Valvulopathies

En France, 30 notifications ont été rapportées entre 1998 et 2009:
(Un cas espagnol rapporté par le laboratoire sera pris en compte dans la partie «8. Aspect des valves, page 15»: publication de Rafel Ribera J.)

- 19 notifications spontanées : 16 valvulopathies + 3 HTAP post-capillaires rapportées ci-dessus
- 11 notifications recueillies intensivement par le CRPV de Brest par l'intermédiaire du PMSI.

A. Notifications

1. Sexe/ Age :

Les notifications de valvulopathies concernent 24 femmes et 6 hommes.

a) Femmes :

La moyenne d'âge de survenue des valvulopathies est de 54,6 ans:
- 53,7 ans (de 34 à 78 ans) pour les notifications spontanées
- 56,4 ans (de 49 à 72 ans) pour les cas de Brest (PMSI)

b) Hommes

La moyenne d'âge de survenue des valvulopathies est de 62,2 ans:
- 54,6 ans (43, 54 et 67 ans) pour les notifications spontanées
- 69,7 ans (60, 70 et 79 ans) pour les cas de Brest (PMSI)

2. BMI : connu dans 20 cas

Dans 3/4 des cas, le BMI indique un surpoids ou une obésité.

BMI entre 18,5-24,9 : 5 cas
- Notifications spontanées : 3 femmes
- Brest PMSI: 2 (1homme, 1 femme)

Entre 25-29,9 (surpoids) : 7 cas
- Notifications spontanées : 5 cas (1 homme, 4 femmes)
- Brest PMSI: 2 femmes

Supérieur à 30 (obésité) : 8 cas
- Notifications spontanées : 4 (1 homme, 3 femmes)
  - BMI = 33 et 34 concernant 2 valvulopathies
  - BMI = 35 et 36 concernant 2 HTAP
- Brest PMSI: 4 femmes
  - BMI : 30, 32, 34, 44

3. Durée de traitement : (dates imprécises dans 4 cas)

La moyenne des durées de traitement est de 5,3
- 5,6 ans (8 mois à 15 ans) pour les notifications spontanées
- 4,6 ans (de 1 à 10 ans) pour les cas de Brest (PMSI)

4. Antécédents et terrain:

a) Tabac :

Un tabagisme est connu chez 13 patients :
- 10 fois dans les notifications spontanées. Il concerne 9 femmes et 1homme
- 3 fois dans les cas de Brest PMSI. Il concerne 2 femmes et 1 homme.

b) Hypothyroïdie

Une hypothyroïdie traitée par levothyroxine est connue dans 9 cas:
- 7 cas pour les notifications spontanées
- 2 cas pour les cas de Brest (PMSI)

c) Antécédents ou terrain cardiaque :

- Hypertension artérielle: rapportée 9 fois
- Infarctus du myocarde : 2 cas
- Angine de poitrine : 1 cas
- Thrombo-embolie : 1 cas
- Cardiomyopathie dilatée (avec HTA) : 1 cas
- Décompensation cardiaque sur bronchopathie (avec HTA) : 1 cas
- Insuffisance cardiaque non précisé mais traitement cardiaque connu dans 2 cas

d) divers

- Angines dans l'enfance sans RAA connu : rapportées 4 fois
- Polyarthrite rhumatoïde : 2 cas
- BPCO : 1 cas

5. Médicaments associés :

- Levothyroxine (9 fois : cf. ci-dessus)
- Antidépresseurs inhibiteurs de la recapture de la sérotonine (IRS)
  - Fluoxétine : 3 fois
  - Paroxétine : 2 fois
  - Vinlafaxine : 2 fois

Remarque : un antidépresseur (IRS) est connu dans 5 cas sur 11 pour Brest PMSI.

6. Insuffisances valvulaires :

a) Localisation :

En ce qui concerne les notifications spontanées, sur 19 cas:

- Insuffisance mitrale dans 4 cas
- Insuffisance aortique dans 2 cas
- Insuffisances mitrale + aortique dans 9 cas
- Insuffisances mitrale + tricuspide dans 1 cas
- Insuffisances mitrale + aortique + tricuspide dans 3 cas

En ce qui concerne les cas de Brest PMSI, sur 11 cas :

- Insuffisances mitrale + aortique dans 5 cas
- Insuffisances mitrale + tricuspide dans 1 cas
- Insuffisances mitrale + aortique + tricuspide dans 5 cas

b) Gravité :

- Une insuffisance mitrale (IM) est présente dans 28 cas sur 30.
  Remarque: Une IM sévère de grade 2-3 à 3 est rapportée dans 9 cas sur 15 pour les notifications spontanées et dans 8 cas sur 11 pour Brest (PMSI)
- Une insuffisance aortique (IAO) est présente dans 24 cas sur 30.
  Remarque :
  Une IAO de grade 1 et 2 est rapportée dans 11 cas sur 14 pour les notifications spontanées et dans 6 cas sur 11 pour Brest (PMSI)
  Dans 2 cas, il n'existe qu'une insuffisance aortique isolée, modérée.
- Une insuffisance tricuspide (IT) est présente dans 11 cas sur 28.
  Remarque : Une IT de grade 1 à 2 est rapportée dans 7 cas : (2 cas de valvulopathies et dans 5 cas sur 11 de Brest (PMSI))
  Une IT sévère de grade 3 est rapportée dans 4 cas : (2 cas de valvulopathies et dans 2 cas 11 de Brest PMSI)

7. Evolution des valvulopathies

- 4 valvulopathies sont bien tolérées sans traitement (dont 3/11de Brest PMSI), 5 ont nécessité un traitement médical ou changement du traitement.

- Dans 4 dossiers, l'évolution est inconnue et 5 dossiers sont en cours.

- Une chirurgie valvulaire a été effectuée dans 10 cas (dont 5 cas sur 11 pour les dossiers de Brest PMSI), elle est prévue dans 2 cas (cf. BR20090086 et GR20090107) décrits ici:

GR20090107
Une échographie cardiaque, début décembre 2008, découvre une HTAP de repos à près de 75 mmHG, chez une femme de 57 ans, pesant 105 Kg, qui a une HTA, une hypothyroïdie, une insuffisance mitrale et une fibrillation auriculaire, traitée par cardioversion externe. Son traitement habituel est HEMIGOXINE®, LEVOTHYROX®, LOGIRENE®, CORDARONE®, PREVISCAN® et FLECAINE®.
Elle a pris du MEDIATOR® d'octobre à décembre 2002, de janvier à avril 2004 et en 2008.
Le cathétérisme cardiaque réalisé en janvier 2009 retrouve une PAPs à 60 mmHG. L'insuffisance mitrale de grade 2 est plutôt centrale, la fuite va jusque dans les veines pulmonaires. L'oreillette gauche est dilatée en rythme sinusal. L'insuffisance mitrale sera traitée dans un premier temps avec des IEC et un diurétique en attendant un remplacement valvulaire.

BR20090086 (Brest PMSI)
Il s'agit d'une femme de 60 ans, ayant un BMI=27, qui présente à l'échocardiographie en mars 2008, un rétrécissement mitral avec insuffisance mitrale de grade 3, une insuffisance aortique de grade 1 et une HTAP. La pression artérielle pulmonaire systolique (PAPs) est égale à 44 mmHg). La valve mitrale est notée de mobilité réduite, épaissie et remaniée.
L'examen clinique retrouve un épanchement pleural droit récidivant de type transsudat. Dans ses antécédents, on retrouve des angines fréquentes sans RAA, une hypothyroïdie, une dépression, un alcoolisme sevré et un tabagisme. Son traitement habituel est LEVOTHYROX®, TAHOR®, PROZAC®, NEULEPTIL®, LAROXYL®, NOCTRAN®, ART 50®. Elle a pris du MEDIATOR® pendant une dizaine d'années (jusqu'en 2008)

Le bilan d'auto-immunité retrouve des IgM antihistones positives mais pas d'anticorps antiphospholipides.

La décision opératoire est en attente, elle permettra d'éliminer une maladie rhumatismale.

8. Aspects morphologique, macroscopique et microscopique des valves :

8.1. Valvulopathies opérées:

Nous rapportons ici les 10 cas de patients français ayant subi une chirurgie valvulaire, ainsi que le cas espagnol, publication de Rafel Ribera J, qui est rapporté par le laboratoire (S03000422).

a) cas où l'anatomo-pathologie serait compatible avec les anorexigènes : 4 cas

- TO060355=S06001104: Cas publié par P. Noize (2006)

Femme de 48 ans, dont le BMI est de 25, traitée par MEDIATOR® pendant 7 ans, dans le cadre d'une intolérance au sucre responsable d'hypoglycémies répétées jusqu'à décembre 2005. Dans ces antécédents, on note une BPCO et un tabagisme important depuis l'âge de 19 ans, sevré fin octobre 2005 avec la survenue d'une dyspnée.
L'échodoppler montre une insuffisance mitrale de grade 3, une insuffisance tricuspide de grade 2 et pas d'insuffisance aortique. L'échographie montre un épaississement de la grande valve qui reste bien mobile et rétraction de la valve postérieure.

Anatomopathologie, histologie :
1° avis : *« Sclérose collagénique englobant cordages et pilier*
Lésions histologiques inhabituelles. Sclérose dense, pauci cellulaire, fortement collagénisée, remaniée par des microfissures.
Valve : fibrose associée à de petits territoires d'œdème mixoïde.
Tissu sous-valvulaire : fibrose particulièrement dense qui englobe en monobloc des cordages mal identifiés et le pilier charnu ».

2° avis : « *Valve épaissie par une fibrose constituée d'accumulation de matrice extra-cellulaire avec peu de cellules fusiformes dans le territoire de l'endocarde, sans inflammation, sans néo-vaisseaux, sans calcifications, sans altération des tuniques sous-jacentes :*
Aspect non spécifique dans l'absolu de la toxicité des anorexigènes, mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes ».

- BR20080051= S08002916: Cas n°6 de la publication de Boutet K. (2009)

Femme de 50 ans, avec un BMI = 34, découverte en novembre 2007 d'une valvulopathie fuyante mitro-aortique responsable d'une décompensation cardiaque. Dans ses antécédents, on note une insuffisance hypophysaire, un DNID et un tabagisme. Elle est traitée par levothyroxine, ramipril, somatropine et depuis 6 ans (de 2001 à septembre 2007) par MEDIATOR®. L'insuffisance mitrale est de grade 3 et l'insuffisance aortique de grade 3. Il existe une HTAP (PAPs= 49 mmHg). L'histoire clinique de la patiente retient qu'elle a pris de l'ISOMERIDE® pendant 1 à 3 mois, 20 ans auparavant.

Anatomopathologie, histologie:
« Epaississement et rétraction des valves (particulièrement de la valve mitrale)
Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire ».

BR20090080 (Brest PMSI)

Femme de 54 ans, avec un BMI = 30, traitée pendant 15 mois par MEDIATOR® (de septembre 2007 à décembre 2008) et pour une dépression par LAROXYL® en 2006 et par EFFEXOR® en 2001 et 2008. Le traitement associé est : CARDENSIEL®, TRIATEC®, LASILIX®, HEMIGOXINE® ET ATARAX®.
En octobre 2005, l'échographie cardiaque était normale avec absence de valvulopathie.
En décembre 2007, 3 mois après le début du traitement par MEDIATOR®, l'échocardiographie montre une insuffisance mitrale et une insuffisance aortique de grade 1.
En octobre 2008, une nouvelle échocardiographie conclut à une altération de la fonction ventriculaire gauche (52%), une insuffisance mitrale de grade 3, une insuffisance aortique de grade 3 et une insuffisance tricuspide de grade 1. La PAPs est à 44 mmHg.
En mars 2009, la dyspnée de grade IV entraîne la décision opératoire avec double remplacement valvulaire.
Il est a noté que la patiente avait pris des amphétamines (biphetamine) pour contrôle du poids pendant 7 à 8 ans jusqu'en 1986.

Anatomopathologie, histologie :
Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique.
Valve aortique :remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques. Présence d'un petit foyer de calcification non spécifique.

S03000422 : Cas espagnol publié par Rafel Ribera J (2003)

Ce cas rapporte une atteinte des 3 valves mitrale, aortique et tricuspide, associée à une HTAP (PAPs: 72 mmHg) chez une femme de 50 ans (BMI non précisé) qui a été traitée pendant 12 mois par intermittence par benfluorex.

Anatomopathologie, histologie :
« Fibrose diffuse avec raccourcissement des cordages de la valve mitrale, une valve tricuspide épaissie et des sigmoïdes aortiques rétractées.
Les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves ».

b) 2 cas où l'anatomopathologie n'est pas spécifique :

TO051212=S05002371

Femme de 49 ans, (BMI inconnu), ayant une hypothyroïdie traitée par LEVOTHYROX® ayant débuté un traitement par MEDIATOR® en 2002.
Pendant ses vacances en Egypte apparaît alors une dyspnée.
En août 2005, elle est hospitalisée pour pneumopathie de la base droite.
En octobre 2005, elle présente une insuffisance mitrale de grade 3, sans rupture de cordage, qui est opérée en novembre 2005. La PAPm est à 22 mmHg. MEDIATOR® est alors arrêté.
Conclusion du cardiologue : *« il s'agit vraisemblablement d'une insuffisance mitrale qui a évoluée à bas bruits pendant de nombreuses années et qui devient symptomatique actuellement »*
Une pathologie post-rhumatismale est évoquée.

Anatomopathologie, histologie :
Les valves sont légèrement indurées sans végétations.
Les remaniements tissulaires associent des plages de fibrose cicatricielle dense, fortement collagénisée, à des territoires oedémateux et myxoïdes de caractère dégénératif, occupés par de nombreux fibroblastes.
On observe des micro-fissures et de rares îlots adipocytaires.
Il n'y a ni dépôt calcique, ni infiltrat inflammatoire, ni bourgeonnement capillaire.
Absence de lésions spécifiques.

S04000348= TO0400278 (dossier classé également dans les HTAP post-capillaires)

Il s'agit d'une femme de 36 ans, avec un BMI = 24, des antécédents d'hypothyroïdie traitée par LEVOTHYROX®, d'HTA et de tabagisme. Elle est traitée par MEDIATOR® de 2002 à 2004 et par PROZAC®, CANOL®, GINKOR FORT®, PRAXINOR®, HEPT A MYL®.
8 mois après l'introduction de MEDIATOR® (2003), est découverte une insuffisance aortique de grade 2 avec insuffisance mitrale minime.
La patiente est hospitalisée en décembre 2003 pour décompensation cardiaque avec une double insuffisance mitrale grade 3 et aortique grade 2, qui sera opérée en janvier 2004. La PAPs est à 50 mmHg.

Remarque : la sœur de la patiente est suivie également pour valvulopathie.

Anatomopathologie, histologie :
Lésions dégénératives non spécifiques.

c) 5 cas sans résultat d'anatomopathologie:

GR20090108

Une insuffisance mitrale de grade 3, associée à une HTAP (PAPs évaluée à 70-75 mmHg) est découverte chez une femme de 56 ans, (BMI inconnu) qui a été traitée pendant 14 ans (1994-2009) par MEDIATOR® pour dyslipidémie et diabète de type 2 associé à fenofibrate, GLUCOPHAGE® et CORDARONE®. Dans ses antécédents, on trouve une dépression, un tabagisme actif et des angines à 20 ans traitées par perfusion intraveineuse.

Aspect des valves :
Valve mitrale remaniée, épaissie, non calcifiée
Grande valve mitrale : aspect en crosse de hockey

BR20090084 (Brest PMSI)

Une double valvulopathie (mitrale et aortique) est découverte en 1998, chez une femme de 51 ans, ayant un BMI=32, qui a pris ISOMERIDE® pendant au moins un an en 1989, MEDIATOR® en 1988, 1999, et quelques mois en 2004. Elle a été traitée également pour état dépressif par PROZAC® pendant 4 ou 5 ans jusqu'en 1995.
En août 2004, l'examen cardiologique relève une valve aortique remaniée avec insuffisance aortique de grade 3, une insuffisance mitrale de grade 3 non calcifiée. Une insuffisance tricuspide et une ACFA sont rapportées.
Un double remplacement valvulaire est réalisé en novembre 2004.

BR20090079 (Brest PMSI)

Il s'agit d'un homme de 60 ans, diabétique chez lequel on a découvert une insuffisance mitrale sévère en septembre 2002. Un traitement par CARDENSIEL®, TRIATEC®, DIGOXINE®, LASILIX® et KALEORID® est instauré.
En mars 2003 l'échographie montre une insuffisance mitrale de grade 3 et une insuffisance aortique de grade 2, sans HTAP. Le traitement chirurgical est réalisé en mai 2003.
Le patient aurait pris du MEDIATOR® pendant une dizaine d'années jusqu'en mars 2003.
Il est suivi en 2009 pour insuffisance tricuspide.

Aspect des valves :
Petite valve mitrale rétractée

BR20090087 (Brest PMSI)

Début 2003, chez un homme de 79 ans, ayant un BMI = 24, une coronarographie réalisée dans le cadre d'une angine de poitrine conduit à une angioplastie et pontage de IVA. Ses antécédents sont un diabète, une hypercholestérolémie, une pancréatite et un tabagisme.
Son traitement habituel (durée inconnue) est PLAVIX®, KARDEGIC®, ZYLORIC®, TRIATEC®, LIPANTHYL®, LASILIX®, CARDENSIEL® et MEDIATOR®.

En juin 2003, lors d'un OAP, l'échographie cardiaque montre une insuffisance mitrale de grade 3, une insuffisance aortique de grade 1, une insuffisance tricuspide de grade 1 et une HTAP (PAPs: 77 mmHg). Une hypothèse rhumatismale non ischémique est évoquée.
Une intervention chirurgicale pour plastie et reconstruction valvulaire est réalisée en octobre 2003.
En février 2005, les bons résultats de la plastie sont notés, la valve aortique parait remaniée et une insuffisance tricuspide de grade 2 est rapportée.

Aspect des valves :
2003 : Cordages de la petite valve uniformément rétractées, mais encore souples et bien individualises
Le mécanisme de l'insuffisance mitrale est un basculement de la petite valve dans le VG. Elle est attirée par des cordages raccourcis.

BR20090078 (Brest PMSI)

En 2002, lors d'une consultation pour hypertension artérielle est noté une insuffisance mitrale de grade1 chez une femme de 53 ans, ayant un BMI= 21, traitée par LIPANTHYL® pour une hypercholestérolémie. Un diabète découvert en 2002 est traité par MEDIATOR® et GLUCOPHAGE® ;
En juin 2004, une échocardiographie met en évidence une insuffisance mitrale de grade 3, une insuffisance aortique de grade 2, une insuffisance tricuspide de grade 3 et une HTAP (PAPs: 90 mmHg).
Un double remplacement valvulaire est réalisé en août 2004.
On note dans ses antécédents, une amygdalectomie à l'âge de 18 ans, suite à de nombreuses angines et une dépression. Son traitement habituel comprend également LASILIX®, DIFFU K®, APROVEL®, PREVISCAN®, DIANTALVIC®, XANAX®, IMOVANE®, ELISOR® et DEROXAT®.

Aspect des valves :
Mitrale :
Epaississement fibreux des grandes et petites valves
Soudure de la commissure antérieure
Rétraction importante de l'appareil sous-valvulaire avec des valves et cordages irrécupérables.
Aortique :
Epaississement des sigmoïdes
Athérome minime à la coronarographie

8.2. Valvulopathies non opérées

TO020331 :

Il s'agit d'une femme de 60 ans, avec comme antécédents : diabète de type 2, hypercholestérolémie, macroadénome hypophysaire, hypothyroïdie, syndrome dépressif, obésité ancienne et dipsomanie, traitée par de nombreux médicaments dont MEDIATOR®, depuis 3 ans, LEVOTHYROX® et EFFEXOR®.
Lors de l'exploration d'un souffle cardiaque, est découvert une insuffisance aortique de grade 2, ainsi qu'une insuffisance mitrale de grade 1-2, et une faible insuffisance tricuspide.
L'évolution est inconnue.

Aspect des valves :
Grande valve mitrale légèrement ballonisée
Décalcification des sigmoïdes aortiques avec diminution de leur mobilité
Ouverture sigmoïdienne mesurée à 16 mm
Pas de rétrécissement aortique

TO070121 :

Femme de 44 ans, en surpoids (BMI= 25), tabagique modérée, traitée pour hypercholestérolémie par MEDIATOR® pendant 9 mois, hospitalisée pour décompensation cardiaque gauche. L'échocardiographie permet de découvrir une insuffisance aortique de grade 4 et une insuffisance mitrale de grade 3. Il existe un minime épanchement péricardique sans HTAP. L'angio-scanner élimine une embolie pulmonaire mais note une infiltration des septas pulmonaires. La patiente sort avec un traitement par LASILIX®, COVERSYL®, MOPRAL® et régime peu salé. Le MEDIATOR® est arrêté.

Aspect des valves :
Echocardiographie : Epaississement valvulaire sur la grande valve mitrale avec une image compatible avec une végétation mesurant environ 10 mm.
Echographie trans-oesophagienne : insuffisance mitrale de grade 2, centrale et commissure antérieure sur restriction du jeu valvulaire avec une rigidité du feuillet antérieur et une restriction du feuillet postérieur.
L'appareil sous-valvulaire est d'aspect brillant.
On note une insuffisance aortique centrale sur une valve à trois cuspides de grade 2 sur 4.

MP20080857 :

Patiente de 77 ans, obèse (BMI= 32,9), hypertendue, ayant une hypercholestérolémie et une hypertriglycéridémie, de multiples antécédents chirurgicaux (colectomie partielle, 4 éventrations, cholécystectomie, hernie et prolapsus) hospitalisée en octobre 2008 pour aggravation d'une dyspnée. Son traitement habituel est HYTACAND®, pravastatine, PLAVIX® et MEDIATOR® depuis plusieurs années. L'aortographie trouve une fuite aortique de grade 2-3 et une insuffisance mitrale de grade 2 confirmée par le cathétérisme. Un éventuel remplacement valvulaire est discuté, vu l'âge de la patiente.

Aspect des valves :
Rétraction de la petite valve mitrale
Calcification sur l'anneau

BR20090085 (Brest PMSI)

Femme de 49 ans, (BMI= 28), ayant dans ses antécédents, un AVC, une splénectomie, un tabagisme et un PTI. Son traitement habituel est : LIORESAL®, OGAST®, NEURONTIN®, URBANYL® et CORTANCYL®. Elle a pris du MEDIATOR® en 2002 et en 2003.
En 2002, lors d'une transfusion pour PTI, une suspicion d'OAP entraîne la réalisation d'une échographie cardiaque qui montre une insuffisance mitrale de grade 2 et une insuffisance aortique de grade 2.
En août 2003, suite à un OAP brutal, l'échocardiographie retrouve cette double valvulopathie avec un rétrécissement mitral non serré ainsi qu'une insuffisance tricuspide.

Aspect des valves :
Remaniement valvulaire au niveau des sigmoïdes et de la mitrale
Valve mitrale un peu épaissie et sténosante
Rétrécissement mitral lâche avec petite valve immobile.

BR20090092 (Brest PMSI)

Femme de 55 ans, hospitalisée en urgence en 2001 pour aggravation d'une dyspnée et suspicion d'OAP. Elle a une insuffisance aortique de grade 1. L'évolution est favorable sous diurétiques. Ses antécédents sont une obésité (BMI= 34), une HTA traitée par CELECTOL® et une cholécystectomie.
Un bilan en 2003 trouve une double fuite aortique et mitrale de grade 2.
En mars 2009, l'échocardiographie montre un aspect stable de la double valvulopathie.
La patiente prend du MEDIATOR® depuis au moins 1998 pour contrôler son poids et ne désire pas arrêté.

Aspect des valves :
Remaniement et rétraction de l'appareil sous-valvulaire sans calcification (en 2003)

S06001337 :

Homme, 54 ans traité pour dyslipidémie par MEDIATOR® de mars 2003 à septembre 2005. Le traitement associé est VASTEN®, KARDEGIC® et TENORMINE®. Suite à un épisode de tachycardie avec insuffisance cardiaque en septembre 2005, une coronarographie et une échocardiographie montrent une insuffisance mitrale de grade 2-3, une insuffisance aortique modérée, une sténose de 70% de l'artère coronaire droite et une hypokinésie du ventricule gauche. Le patient subit une angioplastie de l'artère coronaire avec insertion d'un stent.

Aspect des valves :
Pas d'anomalie sur valves à l'échocardiographie.

Remarque : dans 12 cas, nous n'avons aucune information sur les valves

9. Aspects des valves dans la publication de H. Conolly et coll. intitulée « Valvular heart disease associated with fenfluramine-phentermine».

La valve mitrale est scintillante et épaisse. La valve antérieure a une mobilité préservée tandis que la valve postérieure est immobile. Les cordages sont épaissis et raccourcis.
La valve aortique est épaisse.
L'histopathologie montre des plaques de myofibroblastes dans une matrice extracellulaire abondante de collagène.
L'aspect est semblable aux valvulopathies dues ergotamine et aux maladies valvulaires carcinoïdes.

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Annexe 3-75

Valvulopathies : Aspects morphologique, macroscopique, microscopique

N° Dossiers	Année de survenue		Aspects morphologique, macroscopique, microscopique
MA9900176 = 125P75	1998	I.A I.M. modérée	
TO020331	2002	I.M. grade 1-2 I.A.grade 2 I.T. minime	Grande valve mitrale légèrement ballonisée Décalcification des sigmoïdes aortiques avec diminution de leur mobilité Ouverture sigmoïdienne mesurée à 16 mm Pas de rétrécissement aortique
MP0500087 = S05000405	2004	Aggravation d'1 Valvulopathie (HTAP à Isoméride)	
TO051212 = S05002371	2005	I.M. majeure	Trame valvulaire dégénérative, Absence de lésions spécifiques Les valves sont légèrement indurées sans végétations *Les remaniements tissulaires associent des plages de fibrose cicatricielle dense, fortement collagénisée, à des territoires oedémateux et myxoïdes de caractère dégénératif, occupés par de nombreux fibroblastes.* *On observe des micro-fissures et de rares îlots adipocytaires* *Il n'y a ni dépôt calcique, ni infiltrat inflammatoire, ni bourgeonnement capillaire*
TO060355 = S06001104	2005	I.M.	**Cas publié : Noize P. 2006** 1° avis : Sclérose collagénique englobant cordages et pilier *Lésions histologiques inhabituelles. Sclérose dense, pauci cellulaire, fortement collagénisée, remaniée par des microfissures.* *Niveau valve : fibrose associée à de petits territoires d'œdème mixoïde.* *Tissu sous-valvulaire :fibrose particulièrement dense qui englobe en monobloc des cordages mal identifiés et le pilier charnu* 2° avis : *valve épaissie par une fibrose constituée d'accumulation de matrice extra-cellulaire avec peu de cellules fusiformes dans le territoire de l'endocarde, sans inflammation, sans néo-vaisseaux, sans calcifications, sans altération des tuniques sous-jacentes : aspect non spécifique dans l'absolu de la toxicité des anorexigènes), mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes.*
S06001337	2005	I.M. grade 2-3	Pas d'anomalies sur valves
TO070121 = S07000845	2006	I. M. grade 3 I. A. sévère	Epaississement valvulaire sur la grande valve mitrale avec une image compatible avec une végétation ETO : Commissure antérieure sur restriction du jeu valvulaire avec une rigidité du feuillet antérieur et une restriction du feuillet postérieur. L'appareil sous-valvulaire est d'aspect brillant.
BR20080051 = S08002916	2007	I. M. grade 3 I. A. grade3	**Cas publié : Boutet K. 2009.** Epaississement et rétraction des valves (particulièrement de la valve mitrale) Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire Isoméride 20 ans auparavant
MP20070034 = S07002863	2007	I.A. modérée	Etat stable *Dossier complet mais succinct*
NT20080555 = S09000197	2007	I. M. I. A.	*Dossier complet mais succinct*
CN20080152 =S08002252	2008	I.A. modérée	*Dossier complet mais succinct*
NT20080556 = S09000205	2008	I. M. grade 2 I. A. grade 2 I. Tricuspide grade 3	
MP20080857 =S08006172	2008	IM grade 2 IA grade 2-3	IM: rétraction petite valve Calcification de l'anneau
GR20090107	2008	IM grade 2	
GR20090108	2009	I.M.	Valve mitrale remaniée, épaissie, non calcifiée Grande valve mitrale : aspect en crosse de hockey
GR20090109	2009	I.M. grade 2 IA grade 2	

Dossiers classées également en HTAP post-capillaires			
MP0700281 = S07002370	1999	I.M. 2-3	
S04000348 = TO0400278	2003	I. M. grade 3 I. A. grade 2	Lésions dégénératives non spécifiques Valvulopathie familiale (sœur)
S08005674 = BX20080964	2008	I.M. grade 2 I.A. grade 1	
Valvulopathies : cas CRPV Brest (PMSI)			
BR20090084	1998	I.M. grade 3 I.A. grade 3 I.T.	(Isoméride associé)
BR20090079	2002	I.M. grade 3 I.A. grade 2-3	Petite valve mitrale rétractée
BR20090085	2002	I.M. grade 2 I.A. grade2 I.T.	Remaniement valvulaire au niveau des sigmoïdes et de la mitrale Valve mitrale un peu épaissie et sténosante Rétrécissement mitral lâche avec petite valve immobile
BR20090088	2002	I.M grade 1. I.A. grade 3	
BR20090087	2003	I.M. grade 3 I.A. grade 1 I.T. grade 1	2003 : Cordages de la petite valve uniformément rétractées, mais encore souples et bien individualises Le mécanisme de l'insuffisance mitrale est un basculement de la petite valve dans le VG. Elle est attirée par des cordages raccourcis 2005 : Valve aortique remaniée
BR20090092	2003	I.M. grade 2 I.A. grade 2	Remaniement et rétraction de l'appareil sous-valvulaire sans calcification
BR20090078	2004	I.M. grade 3 I.A. grade 2 I.T. grade 3	Niveau mitral : Epaississement fibreux des grandes et petites valves Soudure de la commissure antérieure Rétraction importante de l'appareil sous-valvulaire avec des valves et cordages irrécupérables. Niveau aortique : Epaississement des sigmoïdes avec défaut de coaptation des sigmoïdes Athérome minime à la coronarographie Pas d'anatomopathologie
BR20090089	2005	I.M. grade 3 I.T. grade 1	
BR20090082	2007	I.M. grade 2-3 I.A. modérée	
BR20090080	2008	I.M. grade 3 I.A. grade 3 I.T. grade I	Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique. Valve aortique :remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques. Présence d'un petit foyer de calcification non spécifique.
BR20090086	2008	I.M. grade 3 I.A. grade 1	Rétrécissement mitral Valve mitrale: mobilité réduite, épaissie et remaniée
Valvulopathies : Cas espagnol publié par Rafel Ribera J			
S03000422	2002 ou 2003	I. M. I. A. I. Tricuspide	Fibrose diffuse avec raccourcissement des cordes mitrales Une valve tricuspide épaissie et des sigmoïdes aortiques rétractées Les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves

VALVULOPATHIES (classées par année de survenue)

Valvulopathies : Notifications spontanées

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
MA9900176 = 125P75 (1998)	M, 43	26	6 ans (1992-1998)	Hypercholestérolémie Surpoids Infarctus du myocarde Insuffisance mitrale minime Tabagisme	Tenormine Vasten Aspirine	I. A. I.M. modérée		IA bien tolérée	ATCD : Infarctus du myocarde
TO020331 (2002)	F, 60	27	3 ans (1998- début 2002)	Diabète type 2 Hypercholestérolémie Obésité ancienne Hypothyroïdie Macroadénome hypophysaire Alcoolisme chronique Syndrome dépressif	Levothyrox Zyrtec Zocor Effexor Stilnox Noctamide	I. M. grade 1-2 I. A. grade 2 I. Tricuspide faible	Pas d'HTAP	U	Décalcification des sigmoïdes aortiques postérieures Grande valve mitrale ballonisée
MP0500087 = S05000405 (2004)	F, 42	22	8 ans (1996-2004)	Hyperlipidémie Hypothyroïdie Tabagisme ancien	Levothyrox Lasilix	Aggravation d'1 Valvulopathie I.M. grade 3 I.A. grade 2 I.T. grade 3	PAPs : 50	TTT médical	ATCD :valvulopathies, HTAP sous ISOMERIDE
TO051212= S05002371 (2005)	F, 49	?	3 ans (2002-2005)	Hypothyroïdie	Levothyrox	I. M. grade 3	PAPm : 22	Chirurgie	Dyspnée débute en même temps que MEDIATOR (Voyage en Egypte) Pathologie post-rhumatismale évoquée Trame valvulaire dégénérative Absence de lésions spécifiques
TO060355= S06001104 (2005)	F, 48	25	7 ans (fin : 2005)	Intolérance au sucre BPCO Tabagisme		I. M.grade 3 I.T. grade 2	PAPm=24	Chirurgie	Cas publié : P. Noize 2006 Sclérose collagénique englobant cordages et pilier Lésions de fibrose (*)

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Annexe 3-75

Valvulopathies : Notifications spontanées (suite)

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
S06001337 (2005)	M, 54	? P=88 kg	2,5 ans (2003-2005)	Dyslipidémie	Vasten Tenormine Kardegic	I. M.grade 2-3 I. A. modérée		U	Pas d'anomalies sur valves
TO070121 = S07000845 (2006)	F, 44	25	9 mois (2006-2007)	Hypercholestérolémie Surpoids Tabagisme modéré		I. M. grade 3 I. A. grade 4	PAPs= 35	U	Début des symptômes : 8 mois Epaississement de la grande valve mitrale
BR20080051 **= S08002916** **(2007)**	F, 50	34	6 ans (2001-2007)	Hypopituitarisme DNID Obésité Tabagisme	Levothyrox Ramipril Somatropine	I. M. grade 3 I. A. grade 3	PAPs : 49	Chirurgie	Anatomopathologie, histologie (**) Isoméride 20 ans Auparavant *Public Boutet n°6*
MP20070034 **= S07002863** **(2007)**	F, 68	26	5 ans (2001-2007)	HTA Cardiomyopathie dilatée primitive Surpoids	Fludex	I.A. modérée		TTT médical	Etat stable
NT20080555 **= S09000197** **(2007)**	F, 56	?	10 ans (1998-2008)	Hypertriglycéridémie		I. M. I. A.		F	Dossier complet mais succinct
CN20080152 **= S08002252** **(2008)**	F, 34	22	4 ans (2004-2008)	Hyperlipidémie Dépression Tabagisme Alcoolisme	Noctamide Lysanxia	I.A. modérée		F	Automédication abusive Demande en cours pour anorexigènes
NT20080556 **= S09000205** **(2008)**	F, 57	?	3 ans (fin : 2008)	Dyslipidémie HTA Angine dans l'enfance		I. M. grade 2 I. A. grade 2 I. Tricuspide grade 3	PAPs : 55	F	
MP20080857= **S08006172** **(2008)**	F, 77	33	Plusieurs années (fin : 2008)	Hypercholestérolémie Hypertriglycéridémie Obésité HTA Surcharge athéromateuse des axes carotidiens Sténose sous-clavière D	Hytacand Pravastatine Plavix	IM grade 2 IA grade 2-3	PAPs: 60	U	IM: rétraction petite valve Calcification de l'anneau

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Annexe 3-75

Valvulopathies : Notifications spontanées (fin)

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
GR20090107 **(2008)**	F, 57	? P: 105 Kg	2 à 3 mois en 2002, 2004 , 2008	Insuffisance mitrale Fibrillation auriculaire HTA Hypothyroïdie	Hemigoxine Logirène Cordarone Previscan Flecaine Levothyrox	I.M. grade 2	PAPs : 60	Chirurgie prévue	
GR20090108 **(2009)**	F, 56	?	14 ans (1994-2009)	Dyslipidémie Diabète type 2 Dépression Tabagisme actif Angine à 20 ans	Fenofibrate Glucophage Cordarone	I.M. grade 3	PAPs : 70-75	Chirurgie	Valve mitrale remaniée, épaissie, non calcifiée Grande valve mitrale : aspect en crosse de hockey
GR20090109 **(2009)**	F, 48		8 mois (fin : début 2009)	Insuffisance mitrale Polyarthrite rhumatoïde HTA Synd. Gougerot-Sjögren Tabagisme Syndrome dépressif Splénectomie pour PTI		I.M. grade 2 I.A. grade 2	PAPs : 48	En cours	Prise d'Isoméride pendant plusieurs années Consultation prévue en juin 2009 en pneumologie

Dossiers classés également dans HTAP

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
MP0700281 = **S07002370** **(1999)**	M, 67	35	5 ans (arrêté depuis 2 ans : 1997)	Infarctus du myocarde (1980) → Insuffisance cardiaque Fibrillation auriculaire Hypothyroïdie Cirrhose (1981) Tabagisme sevré (1980) Obésité	Levothyrox Previscan Hemigoxine Ikorel Coversyl Lasilix Ogast	I.M. 2-3	PAPs: 100	F	Non opérable car HTAP trop importante
S04000348 = TO0400278 (2003)	F, 36	24	2 ans (2002-2004) (Début des symptômes à 8 mois : 2003))	Hypothyroïdie HTA Tabagisme	Levothyrox Prozac Canol Ginkor fort Hept a myl	I. M. grade 3 I. A. grade 2	PAPs :50	Chirurgie	Lésions dégénératives non spécifiques) Valvulopathie familiale (sœur)
S08005674 = **BX20080964** **(2008)**	F, 78	36	15 ans (1994-2008)	Décompensation cardiaque sur bronchopathie HTA Diabète type 2 Hypertriglycéridémie Obésité Fibrillation auriculaire	Aprovel Hyperium Amlor Zocor	I.M. grade 2 I.A. grade 1	PAPs : 63	TTT médical	

Dossiers PMSI Brest

N° (Année survenue)	S, A	BMI	Durée TTT	ATCD	Méd associés		HTAP	Ev	Commentaires
BR20090084 **(1998)**	F, 51	32	1 an (1988) 1 an (1999) Quelques mois (2004)	Dépression	Prozac	I.M. grade 3 I.A. grade 3 I.T.		Chirurgie	Isoméride (1989) I.M, I.A.: 1998 Aggravation en 2004 : valve aortique remaniée
BR20090079 **(2002)**	M, 60		18 ans ? (1990-2002)	Diabète		I.M. grade 3 I.A. grade 2-3		Chirurgie	Petite valve mitrale rétractée I. Tricuspide en 2009

2082

Annexe 3-75

Dossiers PMSI Brest (suite)

N° (Année survenue)	S, A	BMI	Durée TTT	ATCD	Méd associés		HTAP	Ev	Commentaires
BR20090085 **(2002)**	F, 49	28	En 2002-2003	Rétrécissement mitral AVC PTI Splénectomie Tabagisme	Neurontin Ogast Lioresal Urbanyl Cortancyl	I.M. grade 2 I.A. grade2 I.T.		Stable	2002 : Valvulopathie Sept 2003 : Remaniement valvulaire au niveau des sigmoïdes et de la mitrale Valve mitrale un peu épaissie et sténosante Rétrécissement mitral lâche avec petite valve immobile
BR20090088 **(2002)**	M, 70		En 1997 En 1998 En 2003			I.M grade 1. I.A. grade 3 (en 2003)		Stable!	En 1999: I.M. grade 1 et HTAP
BR20090087 **(2003)**	M, 79	24	début : non précisé fin : juin 2003	Diabète Hypercholestérolémie Angine de poitrine Pancréatite Tabagisme	Plavix Kardégic Zyloric Triatec Lipanthyl Lasilix Cardensiel	I.M. grade 3 I.A. grade 1 I.T. grade 1	PAPs: 77	Chirurgie	2005: valve aortique remaniée, I.T. grade 2 Etiologie rhumatismale évoquée
BR20090092 **(2003)**	F, 55	34	10 ans (début avant 1998) Non arrêté	Obésité HTA Cholécystectomie	Celectol	I.M. grade 2 I.A. grade 2 (2003)		Stable	2001 : dyspnée, I.A. grade 1 2009: aspect stable Médiator non arrêté
BR20090078 **(2004)**	F, 53	21	3 ans (2002-2005)	Hypercholestérolémie DNID HTA Nombreuses angines Dépression	Glucophage Lasilix Diffu k Aprovel Previscan Diantalvic Xanax Imovane Elisor Deroxat	I.M. grade 3 I.A. grade 2 I.T. grade 3	PAPs: 85	Chirurgie	Epaississement fibreux des valves mitrales avec rétraction de l'appareil sous-valvulaire Epaississement des sigmoïdes aortiques Athérome minime à la coronarographie Pas d'anatomopathologie
BR20090089 **(2005)**	F, 57	44	3 ans (2003-2006)	Diabète Thromboembolie Obésité Dépression	Levothyrox Triatec Lasilix Foradil Paroxétine Xanax Diantalvic Diffu K	I.M. grade 3 I.T. grade 1 (en 2005)	PAPs:53	TTT médical	Début dyspnée: 2004 I.M. fonctionnelle évoquée

2083

Annexe 3-75

Dossiers PMSI Brest (suite et fin)

N° (Année survenue)	S, A	BMI	Durée TTT	ATCD	Méd associés		HTAP	Ev	Commentaires
BR20090082 **(2007)**	F, 72		4 ans (fin 2003-2008)	Polyarthrite rhumatoïde	Seroplex	I.M. grade 2-3 I.A. modérée	HTAP	TTT médical	2004 : I.A. modérée
BR20090080 **(2008)**	F, 54	30	15 mois	Dépression	Cardensiel Triatec Lasilix Hemigoxine Effexor Atarax	I.M. grade 3 I.A. grade 3 I.T. grade I		Chirurgie	Amphétamine: 7-8 ans (arrêtées en 1986) Début symptômes: 3 mois après benfluorex (I.A. grade 1) Anatomopathologie histologie (***)
BR20090086 **(2008)**	F, 60	27	10 ans	Angines fréquentes sans RAA Dépression Alcoolisme sevré Tabagisme	Levothyrox Tahor Prozac Neuleptil Laroxyl Noctran Art 50	I.M. grade 3 I.A. grade 1	PAPs: 44	Chirurgie prévue	IgM antihistones + Epanchement pleural Rétrécissement mitral

Cas publié espagnol : Rafel Ribera J

S03000422 (2002 ou 2003)	F, 50	?	12 mois TTT intermittent			I. M. I. A. I. Tricuspide	PAPs : 72	Chirurgie	Anatomopathologie, histologie (****)

(*) : aspect non spécifique dans l'absolu de la toxicité des anorexigènes, mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes.

(**) : épaississement et rétraction des valves (particulièrement de la valve mitrale)
Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire

(***) : Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique.
Valve aortique :remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques. Présence d'un petit foyer de calcification non spécifique.

(****) :Fibrose diffuse avec raccourcissement des cordes mitrales, une valve tricuspide épaissie et des sigmoïdes aortiques rétractées.
les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves.

Les nouveaux cas notifiés depuis mars 2007 sont inscrits ***en gras***

2084

Annexe 3-75

Annexe 3-75

MEDIATOR : benfluorex

Hypertensions artérielles pulmonaires
(HTAP)
(actualisation du rapport du 27 mars 2007)

Valvulopathies
(point)

Comité Technique
5 mai 2009

HTAP
28 notifications (20 en mars 2007)

Benfluorex associé à un anorexigène : 13

- 11 notifications : rapport décembre 1998
  - Antérieure: 2
  - Concomitante : 5
  - Inconnue: 1
  - Postérieure : 3
    - 2 HTAP idiopathique
    - 1 HTAP post-capillaire

Benfluorex associé à un anorexigène : 2 nouveaux cas

- BR20080383 (2007): K. Boutet n°5
  - F, 55 ans, BMI=41
  - Apnée du sommeil appareillée (2006)
  - PAPm: 28 mmHg
  - Etat stable sans traitement médical
  - ISOMERIDE: < 3 mois, il y a longtemps
  - MEDIATOR + années, arrêté en 2006
- PB0700302 : cas rétrospectif (2002)
  - Cas très succinct
  - ISOMERIDE : 1992-1993, MEDIATOR: 1996-1999, HTAP: 2002

Benfluorex non associé à un anorexigène : 15

- 9 cas: CN 27 mars 2007 (Pr Weitzenblum)
  - 1 HTAP post-embolique
  - 2 HTAP post-capillaires
  - 6 HTAP d'allure idiopathique:
    - S02001046 : trop succinct
    - BR0700050: TTT 3 mois, 10 ans auparavant
    - PS9900385 : K. Boutet n°1
    - S02001877 = PB20090105 : K. Boutet n°2
    - TO060957
    - BR0700051: cathétérisme cardiaque

Benfluorex non associé à un anorexigène

- *6 nouveaux cas:*
  - *HTAP post-capillaire: 4 cas*
    - *valvulopathie associée*
  - *HTAP embolique: MA20070231*
    - *TTT pendant 1 an, arrêté depuis 6,5 ans*
  - *HTAP d'allure idiopathique !: MA20070346*
    - *F, 52 ans, MEDIATOR 8 ans, PAPs: 45 mmHg*
    - *Evolution favorable en 3 mois*
    - *Dossier succinct, pas de cathétérisme cardiaque*

Hypertensions artérielles pulmonaires
Fréquence avec ou sans anorexigènes

- 16/28 cas HTAP d'allure idiopathique
  (3 post-emboliques, 9 post-capillaires)

139 816 678 boites vendues
= 57 490 410 mois de traitement

1 cas pour
8 738 542 boites vendues (9 655 713 en 2007)
3 593 150 mois de traitement (3 970 277 en 2007)

Hypertensions artérielles pulmonaires
Fréquence sans anorexigènes (2)

- 4 cas HTAP idiopathique
  - 1cas pour

34 954 169 boites vendues

(41 841 426 en 2007)

14 372 602 mois de traitement

(17 204 533 en 2007)

HTAP : Conclusions

- 4 cas retenus:
  - 1998
  - 2002
  - 2005
  - 2006
- Incidence HTAP idiopathique :

  1 à 2 cas / million / an

Valvulopathies

- 30 valvulopathies : 1998 – 2009
- 19 notifications spontanées :
  - 16 valvulopathies
  - 3 HTAP post-capillaires
- 11 PMSI Brest

Valvulopathies : sexe/âge/durée TTT

- Femmes: 24
  - 54,6 ans : 53,7 ans (N.S.)
    : 56,4 ans (BR PMSI)
- Hommes: 6
  - 62,2 ans : 54,6 ans (N.S.)
    : 69,7 ans (BR PMSI)
- Durée TTT : 5,3 ans (8 mois à 15 ans)
  - 5,6 ans (N.S.)
  - 4,6 ans (BR PMSI)

Valvulopathies : Antécédents - Terrain

- Tabac : 13
- Hypothyroïdie : 9
- HTA : 9
- Infarctus du myocarde : 2
- Angines dans l'enfance : 4
- BMI : (/20)
  - Surpoids : 7
  - Obésité : 8

Valvulopathies :

	I.M.	I.A.	I.M. + I.A.	I.M. + I.T.	I.M + I.A. + I. T.
N.S.	4	2	9	1	3
Brest PMSI			5	1	5
Total	4	2	14	2	8

Valvulopathies : gravité

- I.M. : 28/30
  - Grade 2-3 à 3 : 17
    - 9/15 N.S.
    - 8/11 cas Brest PMSI
- I.A. : 24/30
  - Grade 1 à 2 : 17
    - 11/13 N.S.
    - 6 / 11 cas Brest PMSI
- I.T. : 11/28

Valvulopathies : évolution

- Chirurgie Valvulaire : 10 + 2 (prévues)
- Stable : 4
- Stable avec TTT : 5
- Inconnue : 4
- En cours : 5

Valvulopathies opérées

- Anatomopathologie non spécifique:
  - TO051212
  - TO0400278 (HTAP)
- Pas d'anatomopathologie
  - BR20090084 (1998)
  - BR20090079 (2002)
  - BR20090087 (2003)
  - BR20090078 (2004)
  - GR20090108 (2009)

Valvulopathies opérées

- Anapath. compatibles avec anorexigènes!: 4 cas*
  - TO060355 : Publication Noize
  - BR20080051 : Publication de Boutet
  - BR20090080
  - *S03000422** : *Publication espagnole Rafel Ribera*

Valvulopathies: anatomopathologie (1)

TO060355 : 1° avis : *valve mitrale*

- *« Sclérose collagénique englobant cordages et pilier*
- *Lésions histologiques inhabituelles. Sclérose dense, pauci cellulaire, fortement collagénisée, remaniée par des microfissure.*
- *Niveau valve : fibrose associée à de petits territoires d'œdème mixoïde.*
- *Tissu sous-valvulaire : fibrose particulièrement dense qui englobe en monobloc des cordages mal identifiés et le pilier charnu »*

Valvulopathies : anatomopathologie (1*)

TO060355: 2° avis

- *« Valve mitrale épaissie par une fibrose constituée d'accumulation de matrice extra-cellulaire avec peu de cellules fusiformes dans le territoire de l'endocarde, sans inflammation, sans néo-vaisseaux, sans calcifications, sans altération des tuniques sous-jacentes :*
- *aspect non spécifique dans l'absolu de la toxicité des anorexigènes, mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes »*

Valvulopathies: anatomopathologie (2)

BR20080051: publication de Boutet K (n°6)

- *« Epaississement et rétraction des valves (particulièrement de la valve mitrale)*
- *Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire ».*

Valvulopathies: anatomopathologie (3)

BR20090080 (Brest PMSI)

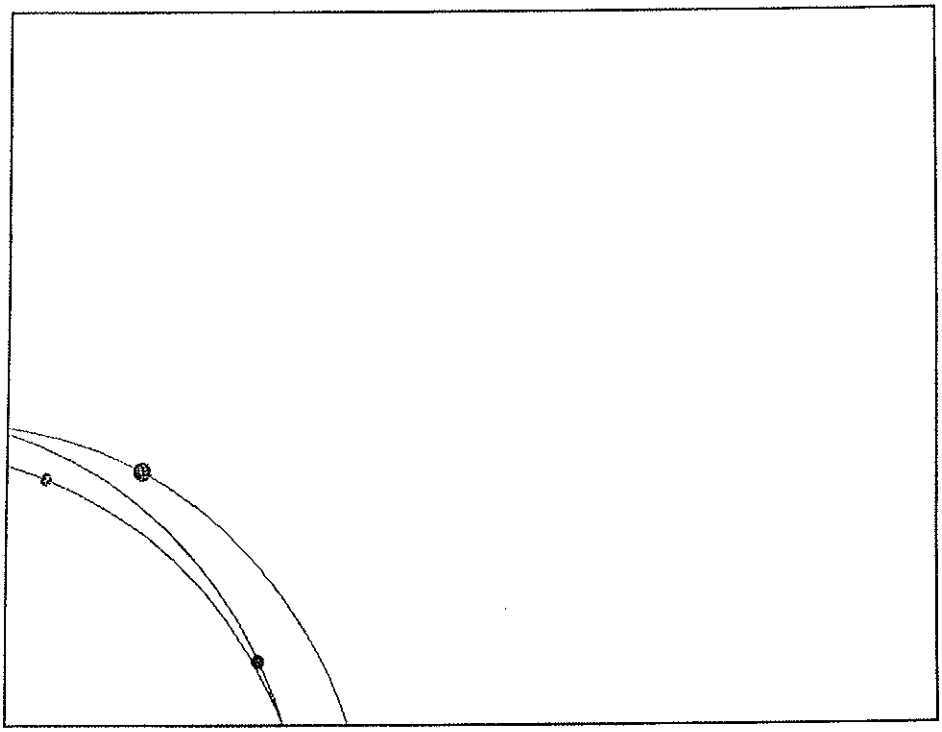
- *Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique*
- *Valve aortique : remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques Présence d'un petit foyer de calcification non spécifique*

Valvulopathies: anatomopathologie (4)

- Cas espagnol publié par Rafel Ribera J (2003)
- *« Fibrose diffuse avec raccourcissement des cordages de la valve mitrale, une valve tricuspide épaissie et des sigmoïdes aortiques rétractées*
- *Les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves »*

H. Conolly : « Valvular heart disease associated with fenfluramine-phentermine».

- Valve mitrale scintillante et épaisse
  - Valve antérieure a une mobilité préservée
  - Valve postérieure est immobile
  - Cordages épaissis et raccourcis
- Valve aortique épaisse
- Histopathologie : plaques de myofibroblastes dans une matrice extracellulaire abondante de collagène
- Semblable à ergotamine et maladie valvulaire carcinoïde



Valvulopathies

- TO060355 : Publication Noize

- F, 48 ans
- BMI = 25
- BPCO
- Tabagisme
- MEDIATOR, 7 ans : intolérance au sucre
- I.M. grade 3 ; I.T. grade 2

Valvulopathies

- BR20080051: publication de Boutet K (n°6)
- F, 50 ans
- BMI = 34
- Insuffisance hypophysaire
- DNID
- Tabagisme
- MEDIATOR, 6 ans
- ISOMERIDE, 1 à 3 mois (20 ans auparavant)
- I.M. grade 3, I.A. grade 3

Valvulopathies

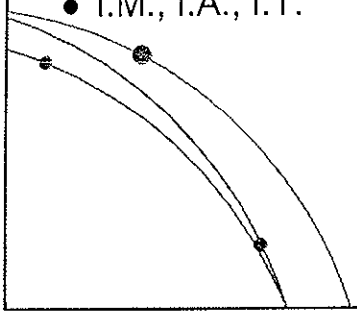
BR20090080 (Brest PMSI)

- F, 54 ans
- BMI = 30
- MEDIATOR, 15 mois
- Cardensiel, Triatec, Lasilix, Hemigoxine, Effexor
- Amphétamines, 7 à 8 ans
- I.M. grade 3, I.A. grade 3, I.T. grade 1
- Début I.M. et I.A. : 3 mois après MEDIATOR

Valvulopathies

- Cas espagnol publié par Rafel Ribera J (2003)

- F, 50 ans
- Benfluorex pendant 12 mois par intermittence
- I.M., I.A., I.T.



Estimation du risque d'HTAP pour les patients exposés au benfluorex
au regard des données présentées lors du CTPV du 5 mai 2009

J'ai donc repris les calculs « d'incidence » d'hypertension artérielle pulmonaire (HTAP) figurant dans le compte-rendu de la réunion du Comité Technique de Pharmacovigilance du 5 mai 2009.
Si l'on s'en tient au nombre de cas retenus (je ne peux me prononcer sur ce point car je n'ai pas les dossiers mais il est évident que dans une stratégie d'enquête à objectif d'alerte il ne faut pas être trop conservateur et plutôt privilégier la sensibilité à la spécificité), on retrouve :

- une estimation de 1 cas d'HTAP pour 8 738 542 boites vendues en 2007 (ce qui correspond donc, sur la base de 3 cas retenus, à 26,2 millions de boites vendues sur la période),
- une estimation de 1 cas d'HTAP pour 9 655 713 boites vendues en 2009 (ce qui, sur la base de 4 cas retenus, correspond, pour la période cumulée, à 38,6 millions de boites vendues).

On peut noter que, sans considérer une très probable sous-notification d'une partie des cas survenus, l'estimation de 2007 dépasse légèrement (sans considérer non plus la fluctuation statistique) la fourchette haute de ce qui est admis comme risque de base de l'HTAP en population générale (2 cas par million et par an, soit 2 cas par million d'année de suivi). En effet, 26,2 millions de boites de 30 comprimés avec une posologie moyenne de 1,6 comprimé par jour (calcul également utilisé par Catherine Hill) aboutit à un temps d'exposition cumulé (en considérant que tout ce qui a été vendu a été consommé) de 1,346 million d'années d'exposition au benfluorex et donc à un « risque » de 3/1,346 million, soit 2,23 cas d'HTAP par million d'année de traitement.
Pour l'estimation 2009, le même calcul amène à une estimation de 2,02 cas par million d'année de traitement.
Il est évident qu'une analyse de sensibilité considérant plusieurs hypothèses de sous-notification aurait été bienvenue ici ; un facteur de sous-notification réaliste de 4 ou 5 (25 à 20% des cas survenus étant notifiés) faisant passer l'estimation à 9 ou 11 par million d'année d'exposition, soit largement au dessus du risque de base.
Le rapporteur écrit par ailleurs que « *le nombre de cas d'HTAP rapportés dans l'enquête ne constitue pas un signal significatif de la toxicité du MEDIATOR°* ». Il est difficile de savoir si « significatif » est utilisé ici dans le sens subjectif de « fort » ou de « statistiquement significatif ». Cette dernière hypothèse serait contestable car de nature à retarder grandement le processus de décision. En effet, un calcul fondé sur la loi de Poisson ou la loi binomiale (seules utilisables ici du fait du faible nombre de cas) montre que pour conclure à un risque significativement différent du risque de base (2 par million), il aurait fallu, sur la base des ventes disponibles en 2009, un nombre de cas d'HTAP retenus de 9 au lieu de 4 pour un test bilatéral (avec une erreur de première espèce de 5%) et de 8 en hypothèse unilatérale, soit le double ou plus du double du nombre de cas retenus jusqu'à lors ce qui, en conservant la même approche, ne serait attendu qu'au bout de plusieurs années supplémentaires.

Fait à Bordeaux, le 6 janvier 2011

Professeur Bernard Bégaud
Université de Bordeaux2
INSERM, Unité 657

Annexe 3-77

Réunion du groupe de travail « PGR et étude pharmaco-épidémiologiques »n°2 3 juin 2009

Mise en place d'une étude pharmaco-épidémiologique afin d'évaluer le risque de valvulopathies associé à la prise de benfluorex
Présentation Martine David-Laroche (CRPV de Besançon), Irène Frachon(hôpital Cavale Blanche/CHU de Brest)
De 1998 à 2009, 19 notifications spontanées de valvulopathies (16 valvulopathies, 3 HTAP post capillaire) ont été enregistrées dans la base nationale de pharmacovigilance. Récemment une requête effectuée via le PMSI dans les services de cardiologie et de chirurgie cardiaque du CHU de Brest a permis de retrouver 14 cas supplémentaires
Le CTPV lors de la séance du 2 mai dernier a conclu que ces données qui constituent un signal de sécurité d'emploi, devaient être explorées et a souhaité que la problématique sot exposée au groupe « PGR-PEPI ».
Il convient de rappeler que l'hypothèse d'une telle association semble cohérente, le benfluorex possédant un métabolite commun avec la fenfluramine (Isoméride) et la dexfenfluramine (Ponderal), substances dont les AMM en 1997 ont été suspendues suite à ces mêmes effets indésirables.
Afin de mesurer l'association entre risque de valvulopathie et prise de benfluorex, les membres du groupe PGR PEPI proposent d'effectuer une étude cas-témoin rétrospective.
Dans la mesure où les cas sont déjà identifiés, restent à définir les témoins

Post meeting notes :
Suite à la réunion, un sous-groupe s'est constitué afin de pouvoir poursuivre la réflexion. Lors d'une réunion téléphonique organisée le 15 juin, il a été décidé de mener une étude cas-témoin :
dans les régions de Brest et d'Amiens, dans lesquelles l'identification des cas est très avancée :
la définition des cas est la suivante : insuffisance mitrale inexpliquée par diagnostic d'exclusion
le choix des témoins a été abordé mais doit être davantage discuté de même que les critères d'appariement (âge, genre). L'appariement des témoins sur le diabète et le surpoids/obésité est remis en question car ils motivent la prescription de benfluorex.

Réunion PGR et étude pharmacoépidémiologiques du 2 décembre 2009

Retour sur la réévaluation du B/R des médicaments contenant du benfluorex
Présentation Carmen Kreft-Jaïs
L'historique du Mediator a été brièvement rappelé ainsi que l'origine de la surveillance des valvulopathies sous benfluorex. Le signal de cardiotoxicité (atteintes valvulaires) détecté par l'analyse de la notification spontanée et des données issues du PMSI du CHU de Brest avait été précédemment abordé lors d'une réunion du groupe et la nécessité de conduire une étude cas-témoin avait alors été exprimée.
Lors de la CNPV de juillet 2009, une nouvelle réévaluation du bénéfice de benfluorex compte tenu des nouvelles données de sécurité a été envisagée mais pour cela la CNPV souhaitait disposer des résultats de 2 études pharmaco épidémiologiques qui étaient en cours :
L'étude du groupe HTAP de Brest

L'étude Regulate, mise en place par les laboratoires Servier dans laquelle des échographies cardiaques étaient réalisées avant et après un an de traitement par Mediator.
D'autres cas de valvulopathies sous benfluorex ont alors été rapportés et les résultats de l'étude cas-témoin conduite par le CHU de brest ont conclu à une augmentation du riqpr

afssaps
Agence française de sécurité sanitaire des produits de santé
Direction de l'Evaluation des Médicaments et des Produits Biologiques
Département de Pharmacovigilance

Saint-Denis, le

COMMISSION NATIONALE DE PHARMACOVIGILANCE

Compte rendu de la réunion du mardi 7 juillet 2009

Etaient présents :

Membres de la Commission nationale de pharmacovigilance :
M. MERLE (président)
Mme LAINE-CESSAC (vice-présidente)
Mme KREFT-JAIS (représentante de la Direction Générale de l'Afssaps)
Mme DELOFFRE (représentant de la Direction Générale de la Santé)
M. MALLARET (Président de la Commission Nationale des Stupéfiants et des Psychotropes)
M. ANDREJAK
Mme AUTRET-LECA
Mme BARBAUD
M. BERNARD
M. BONNETERRE
M. CARON
Mme CARPENTIER
Mme DUGAST (suppléante de M. RATINEY)
M. ESCHALIER
M. FARINOTTI
M. GIROUD
M. JACQUES
M. LARRUMBE
Mme LEMERMALLE
Mme LILLO LE LOUET
M. LIEVRE
Mme PLACE (suppléante de Mme LOBATO DE FARIA)
M. SADEG (suppléant de Mme JOLLIET)
M. SAINT-PIERRE (suppléant de M. SANTINI)
M. SAVIUC
M. WESTPHAL (suppléant de M. PELLETIER)

Annexe 3-78

Département de Pharmacovigilance :
Mme BOULOS
Mme CARDONA
Mme DELEAU
Mme HALLE
Mme OUARET
Mme POROKHOV

Afssaps :
M. FAGOT
Mme LAVERGNE
Mme MONZON
Mme REY-QUINIO
Mme RICHARD
Mme MESSINA

Internes en Pharmacie
Mme CAVEE
Mme RIBEIRO-CRESPEL

Experts présents :
Mme FRACHON
Mme JEAN-PASTOR
M. RICHE
Mme ZENUT

Stagiaire :
Mme PIZZOGLIO

Membres suppléants présents :
M. CHENIQUE
M. GOULLE
M. KANTELIP
Mme PERAULT-POCHAT

Membres excusés :
Mme BOURRET
M. CARLIER
Mme DE LARRE DE LA DORIE
M. DERAY
Mme FOURRIER
Mme JOLLIET
Mme JOUAN-FLAHAULT
Mme LAPEYRE
Mme LOBATO DE FARIA
M. PELLIETIER
M. RATINEY
M. SANTINI
Mme SGRO
M. VIAL

Annexe 3-78

DOSSIERS TRAITES PAR LABORATOIRES

- **SUIVI NATIONAL (PGR) DE LA METHADONE AP-HP® GELULE ET SIROP :**

LABORATOIRE CONCERNE	*REPRESENTANTS*
BOUCHARA RECORDATI	M. DHELLOT Mme MORRIS

- **ENQUETE OFFICIELLE PROPACETAMOL / PARACETAMOL INJECTABLES:**

LABORATOIRES CONCERNES	*REPRESENTANTS*
BMS	Mme PRUVOT
MYLAN SAS	Mme GABRIELLE

- **ENQUETE SUR LES HTAP / VALVULOPATHIES ET BENFLUOREX, MEDIATOR®, BENFLUOREX MYLAN®, BENFLUOREX QUALIMED® :**

LABORATOIRES CONCERNES	*REPRESENTANTS*
MYLAN SAS / QUALIMED	Mme GABRIELLE
SERVIER	M. DUBOIS Mme MAILLERE Mme TUBACH M. WAGNIART

GESTION DES CONFLITS D'INTERETS

Deux situations de conflit d'intérêt majeur concernant deux points à l'ordre du jour (Propacétamol/ paracétamol injectable et benfluorex) ont été déclarées et évaluées préalablement à la séance de la Commission nationale de pharmacovigilance. Le Professeur Eschalier (Responsable du CRPV de Clermont Ferrand) ayant déclaré une activité régulière auprès du laboratoire BMS, et le Professeur Farinotti (Chef de service, Pharmacie, Groupe hospitalier Pitié-Salpêtrière) ayant déclaré une activité régulière auprès des laboratoires Servier, ont quitté la séance lors du traitement des dossiers concernés.

IV – ENQUETE SUR LES HTAP / VALVULOPATHIES ET BENFLUOREX, MEDIATOR®, BENFLUOREX MYLAN®, BENFLUOREX QUALIMED®

Dossier suivi par Béatrice POROKHOV

1 – Introduction :

Nom commercial	MEDIATOR®
DCI	Chlorhydrate de benfluorex
Formes pharmaceutiques	Comprimé pelliculé à 150 mg
Classe pharmacologique	Hypoglycémiant
Procédure d'enregistrement	Procédure nationale
Titulaire de l'AMM	Laboratoires Servier

MEDIATOR® (chlorhydrate de benfluorex) a obtenu une AMM en 1974 par une procédure d'enregistrement nationale. Il est commercialisé en France depuis 1976.
MEDIATOR® est indiqué comme « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ». Il est à noter que l'indication comme « adjuvant du régime adapté dans les hypertriglycéridémies » a été supprimée à la suite de l'avis émis par la Commission Nationale de Pharmacovigilance (CNPV) du 27 mars 2007.

2 – Contexte :

En décembre 2004, la notification de plusieurs cas d'effets indésirables « *amphétamine-like* » sous MEDIATOR® a conduit à une actualisation des données neuropsychiatriques.
Par ailleurs, lors du Comité Technique de pharmacovigilance du 8 mars 2005, la présentation d'un cas d'hypertension artérielle pulmonaire a justifié une extension de l'enquête, incluant alors les hypertensions artérielles pulmonaires (HTAP).
Les résultats de cette enquête officielle ont été présentés par le CRPV de Besançon au Comité Technique de Pharmacovigilance (CTPV) du 7 juin 2005 et à la CNPV du 29 novembre 2005. La CNPV a alors demandé : i) la réévaluation du rapport bénéfice/risque de MEDIATOR®, ii) une étude d'utilisation/prescription, iii) une étude expérimentale sur un modèle animal permettant d'étudier le potentiel du benfluorex à induire des HTAP et iiii) une étude au niveau des Centres d'Evaluation et d'Information sur la Pharmacodépendance (CEIP) afin d'identifier un potentiel d'abus et de pharmacodépendance.

En 2007, suite à la revue des données d'efficacité de Mediator®, le groupe DEUG a proposé la suppression de l'indication «adjuvant du régime adapté dans les hypertriglycéridémies », avec maintien de l'indication chez les diabétiques. Cet avis a été entériné par la Commission Nationale d'AMM en avril 2007.

En mai 2009, le Comité technique de Pharmacovigilance a examiné les résultats actualisés de cette enquête, notamment les données relatives au risque d'HTAP et de valvulopathie cardiaque sous MEDIATOR® ainsi que les données d'une publication[1] récente sur ce sujet.

Depuis le dernier passage en Commission Nationale de Pharmacovigilance du 27 mars 2007, 8 nouveaux cas d'HTAP ont été notifiés, soit un total de 28 cas, parmi lesquels le nombre d'HTAP d'allure idiopathique sous MEDIATOR® non associés à un autre anorexigène, est passé de 3 à 4. Le taux de notification des HTAP imputables au MEDIATOR® reste donc stable par rapport à 2007 (1 cas sur 34 954 169 boîtes vendues, soit 1 cas pour 14 372 602 mois de traitement). De même, la fréquence des cas d'HTAP idiopathiques sous MEDIATOR® est stable par rapport aux données présentées en mars 2007.

Compte tenu de l'incidence des HTAP d'allure idiopathique dans la population générale (1 à 2 cas par millions et par an), le Comité Technique a considéré que le nombre de cas d'HTAP d'allure idiopathique associés à l'utilisation de MEDIATOR® ne semblait pas constituer un signal significatif de la toxicité pulmonaire du Médiator®. Les membres du Comité Technique ont recommandé la poursuite d'une surveillance des notifications spontanées des cas d'HTAP dans la population générale.

Concernant les valvulopathies, nous disposons d'une trentaine de cas entre 1998 et 2009 sous MEDIATOR® ce qui constitue un signal qu'il convient d'explorer.

L'ensemble de ces résultats a également fait l'objet d'une présentation en groupe pharmaco-épidémiologie de l'Afssaps afin de définir un modèle d'étude permettant d'explorer le signal relatif aux valvulopathies. Une étude rétrospective cas-témoins des cas de valvulopathies issus du PMSI a été proposée.

Les conclusions de ce groupe ainsi que les données actualisées de cette enquête sur le risque de valvulopathie cardiaque ont été présentées à la Commission Nationale de Pharmacovigilance du 7 juillet 2009.

3 - Actualisation de l'enquête sur les valvulopathies :

En France, 30 cas sont rapportés entre 1998 et 2009 :

- 19 cas issus de la notification spontanée (NS) dont 3 cas concernant également les HTAP post-capillaires
- 11 cas identifiés par le CRPV de Brest à la suite de l'interrogation du PMSI (Programme de médicalisation des systèmes d'information).

3.1 – Caractéristiques des patients :

	NS : 19	PMSI : 11
Sexe	Femmes : 24, hommes : 6	
Age moyen de survenue (ans) *Femmes* : 54,6 *Hommes* : 62,2	 53,7 54,6	 56,4 69,7
BMI (kg/m^2) *18,5 à 24,9* : 5 cas *25 à 29,9* : 7 cas ≥ *30* : 8 cas	 3 5 4	 ~~3~~ 2 2 4
Durée moyenne de traitement (ans) 5,3	5,6	4,6
Antécédents / Terrain (nombre) *Tabac* : 13 *Hypothyroïdie* : 9 *Diabète* : 9 *Dyslipidémie* : 12 *Polyarthrite rhumatoïde* : 2	 10 7 5 10 1	 3 2 4 2 1
Antécédent/Terrain cardiaque (nombre)	15	
Médicaments associés (nombre) *Levothyroxine* *Antidépresseur IRS*	 9 7	

3.2 – Type et localisation des valvulopathies :

Les 30 valvulopathie rapportées sont monovalvulaires dans 6 cas, bivalvulaires dans 16 cas et trivalvulaires dans 8 cas. Concernant la localisation de ces valvulopathies, 28 cas sont des insuffisances mitrales (sévères dans 17 cas), 24 cas sont des insuffisances aortiques et 11 cas sont des insuffisances tricuspides (sévères dans 4 cas).

3.3 – Aspects anatomo-pathologiques des valvulopathies opérées

Des diagnostics anatomo-pathologiques sont effectués chez 6 patients opérés : 5 patients français et un cas espagnol rapporté dans une publication (Rafel Ribera J.).

a) 4 cas dont l'aspect anatomo-pathologique serait compatible avec celui décrit sous anorexigène :

TO060355 (Noize[1] 2006) : une femme de 48 ans, avec un BMI=25 kg/m^2, sous MEDIATOR® pendant 7 ans pour intolérance aux glucides.

BR20080051 (Boutet[2], cas n°6) : une femme de 50 ans ayant un diabète de type 2, avec un BMI=34 kg/m^2, sous MEDIATOR® de 2001 à 2007 et sous ISOMERIDE® pendant 1 à 3 mois 20 ans auparavant.

BR20090080 (Brest PMSI) : une femme de 54 ans, avec BMI=30 kg/m^2, sous MEDIATOR® de septembre 2007 à décembre 2008, ayant pris des amphétamines 7 à 8 ans jusqu'en 1986.

S03000422 (R. Riber[3] J. 2003) : une femme de 50 ans, sous MEDIATOR® pendant 12 mois par intermittence.

b) Autres cas

Dans 2 cas, l'anatomopathologie n'est pas spécifique.
Dans les autres cas, seules les données échographiques sont disponibles.

4- Conclusions du rapporteur :

Le CRPV de Besançon, rapporteur de cette enquête, a conclu à l'existence d'un signal de cardiotoxicité détecté par la notification spontanée et les données du PMSI. Il convient alors de confirmer ce signal par une étude épidémiologique (cas-témoin).
Le rapporteur souligne que la pharmacologie du benfluorex et de son métabolite, la nor-fenfluramine, devra être prise en compte dans l'analyse du mécanisme de la cardiotoxicité.

Compte tenu de ces nouvelles données de sécurité, le rapporteur propose une réévaluation du bénéfice/risque de benfluorex.

5- Présentation du Dr. Frachon (praticien, CHU de Brest):

Lors de cette réunion, le Docteur Frachon, du groupe HTAP de Bretagne Occidentale (CHU de Brest) a présenté la méthodologie appliquée à Brest pour l'identification des cas de valvulopathies associées au benfluorex.

L'identification des cas de valvulopathies a reposé sur :

i) le signalement spontané de 4 cas par des médecins brestois,
ii) l'interrogation du PMSI en utilisant le codage « valvulopathies et diabète » qui a mis en évidence 240 dossiers dont 3 cas compatibles et le codage « valvulopathies et Médiator® » qui a rapporté 23 dossiers dont 11 compatibles,
iii) une surveillance prospective avec 3 nouveaux cas.

Sur les 15 patients identifiés « compatibles » (dont 11 rapportés par le CRPV de Besançon et 4 très récents à l'étude), 12 étaient des femmes et 3 des hommes. L'âge moyen est de 58 ans (49-78). 6 patients sur 12 étaient diabétiques. La durée moyenne d'exposition est de 53 mois (12-144) avec un délai entre la première prise du médicament et le diagnostic de 97 mois (13-384). L'échographie cardiaque antérieure est normale dans 5 cas sur 7. L'exposition à d'autres anorexigènes concerne 5 patients sur 12, et à un antidépresseur de type inhibiteur de recapture de la sérotonine (IRSI) concerne 8 patients sur 10.
Les valves atteintes sont la valve mitrale et la valve aortique dans 100% des cas, avec une atteinte de la valve tricuspide dans 7 cas et de la valve pulmonaire dans un cas. Une chirurgie de remplacement valvulaire a été effectuée dans 8 cas.

Une analyse systématique de toutes les insuffisances mitrales (IM), isolées ou associées, examinées au CHU de Brest depuis 2003, est actuellement en cours. Plus de 600 dossiers d'IM sont classés en 3 groupes: 1) IM dans un contexte étiologique bien identifié 2) IM inexpliquées 3) IM non classables.
Une recherche de l'exposition au benfluorex sur un modèle de cas témoins est réalisée pour les cas identifiés par le PMSI et par une enquête téléphonique auprès du médecin et du patient.
Les résultats de cette étude sont attendus pour fin juillet 2009.

6- Présentation du laboratoire :

Les représentants des laboratoires Servier, ont présenté lors de la réunion deux propositions d'études à réaliser :

i) une étude anatomopathologique sur un modèle exposé/non-exposé (ce modèle d'étude a été récusé par la commission),
ii) une étude cas-témoin ayant pour objectif de quantifier un éventuel sur-risque de valvulopathie associé au MEDIATOR® chez des patients atteints de valvulopathie idiopathique comparativement à des patients indemnes de valvulopathie. Cette étude se ferait sur une population de patients diabétiques ayant une échographie cardiaque.

Le protocole serait disponible début Septembre et permettrait dans le meilleur des cas d'avoir des résultats dans un an.

Par ailleurs, l'étude, REGULATE, (MEDIATOR® + sulfonylurée versus pioglitazone + sulfonylurée) est actuellement en cours d'analyse. Cette étude incluant 840 patients dont 420 dans chaque bras, comporte une échographie cardiaque à T0 et à la 52ème semaine de traitement. Le laboratoire a informé la Commission que les résultats de cette étude seraient disponibles début 2010.

7- Conclusions de la Commission Nationale de Pharmacovigilance :

Le responsable du CRPV de Brest, présent à la réunion de la CNPV, a informé les membres que les résultats de l'étude brestoise cas-témoin seront disponibles fin Juillet 2009.

Les membres de la CNPV ont également discuté de l'importance des utilisations hors AMM de ce produit, notamment dans la perte de poids, malgré la restriction d'indication.

La commission s'est prononcée en faveur (16 voix pour, 2 voix contre et 2 abstentions) de l'attente des résultats de l'ensemble des études en cours ou planifiées (laboratoires Servier et CRPV de Brest) avant de proposer d'éventuelles mesures.
Elle a toutefois souhaité qu'une communication soit effectuée auprès des professionnels de santé pour leur rappeler le bon usage du Benfluorex dans le cadre de l'AMM.

Les résultats de l'étude Brestoise seront examinés par le groupe «PGR et études pharmaco-épidémiologiques» de l'Afssaps. Ces résultats ainsi que les conclusions du groupe PGR-épi seront ensuite présentés à la Commission Nationale de Pharmacovigilance lors de sa réunion du 29 septembre 2009.

Bibliographie

1- Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C, Carlhant-Kowalski D, Sitbon O, Simoneau G et Humbert M. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 2009; 33 : 684-688

2- Noize P, Sauer M, Bruneval P et al. Valvular heart disease in a patient taking benfluorex. Fundam Clin Pharmacol 2006; 20: 577-578

3- Rafel Ribera J, Casanas Munoz R, Anguera Ferrando N, Batalla Sahun N, Castro Cels A, Pujadas Capmany R. Valvulopatia cardiaca asociada al uso de benfluorex. Rev Esp Cardiol 2003; 56:215-216

7/07/09

Valvulopathies cardiaques et HTAP chez des patients exposés au benfluorex

Méthode de l'enquête brestoise

Irène Frachon, Yannick Jobic, Yves Etienne,
Isabelle Quintin-Roué, Christophe Leroyer
Groupe HTAP de Bretagne Occidentale
CHU de Brest

Patricia Clemot
CIC de Brest

Dominique Carlhant-Kowalski,Christian Riché
Centre de pharmacovigilance de Brest

Identification des HTAP:

CASE STUDY

Fenfluramine-like cardiovascular side-effects of benfluorex

K. Boutet*, I. Frachon#, Y. Jobic#, C. Gut-Gobert#, C. Leroyer#, D. Carlhant-Kowalski#, O. Sitbon*, G. Simonneau* and M. Humbert*

Eur Respir J 2009; 33: 684–688

TABLE 1 Baseline clinical and functional data

	PAH					Valvular heart disease
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	F	F	F	F	F	F
Age at diagnosis yrs	50	54	51	57	55	62
BMI kg·m^{-2}	24.2	32	41.4	49	41	34
Duration of benfluorex exposure months	54	36	3	120	~120	60
Cumulative dosage g	246	328	40	1095	1642	821
Time between start of benfluorex use and symptoms yrs	4	1	<1	Several	Several	5
Time between start of benfluorex use and diagnosis yrs	4.5	3	10	10	11	5
Search for known drug related causes	Negative	Negative	Negative	Negative	Positive (dexfenfluramine <3 months several years ago)	Positive (dexfenfluramine <3 months several years ago)
NYHA functional class	II	III	II	III	II	III

PAH: pulmonary arterial hypertension; BMI: body mass index; NYHA: New York Heart Association; F: female.

Identification des valvulopathies

1. 4 cas signalés spontanément par des collègues brestois (dont le1er cas publié dans l'ERJ)

2. Interrogation du PMSI (données à partir de 2003)
   - Codages "valvulopathies" et "diabète" : 240 dossiers, 3 cas compatibles
   - Codage "valvulopathies" et terme "Médiator®" : 23 dossiers, 11 compatibles

3. Vigilance prospective : 2 nouveaux cas compatibles

Caractéristiques des 15 patients identifiés "compatibles" depuis 2003 au CHU de Brest

(compatibles = la prise de Médiator^{R} précède les symptômes et le diagnostic de valvulopathie fuyante + valvulopathie inexpliquée)

-**12 femmes**, 3 hommes

-Âge moyen au diagnostic = **58 ans** [49-78] (série" fen-phen" du NEJM : 44)

-BMI moyen = **33** [24-52] (38)

-Diabète : **6 / 12**

-Durée exposition moyenne = **53 mois** [12-144] (11)

-Délai entre la première prise et le diagnostic = **97 mois** [13-384]

-Echographie cardiaque antérieure (ex.cardio 1 fois) "normale" : **5 / 7**

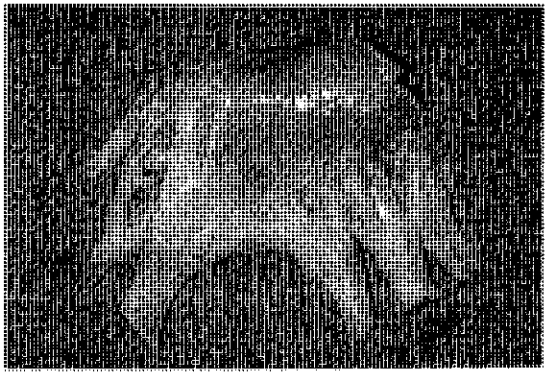
-Exposition à d'autres anorexigènes : **5 / 12**

-Exposition à un ISRS : **8 / 10**

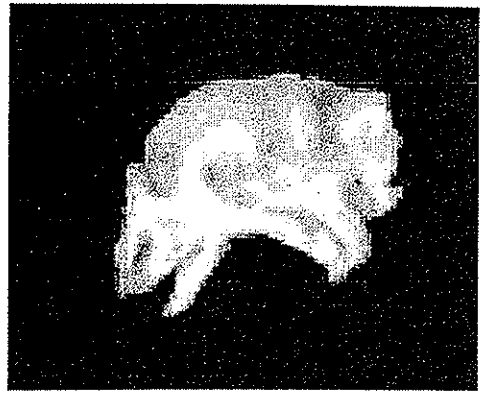
-Valves atteintes : **mitrale 100 %, aortique 100%,** tricuspide 7/15, pulmonaire 1/15

-Chirurgie de remplacement valvulaire : **8 / 15**

Etude macroscopique (3 cas) : comparaison aux photos publiées



Cas brestois : valve mitrale



Valvular Heart Disease Associated with Benfluorex; Riberaa et al, Rev Esp Cardiol 2003

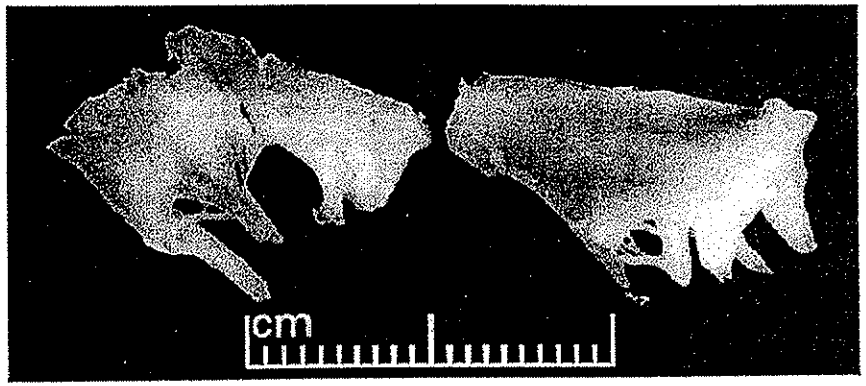
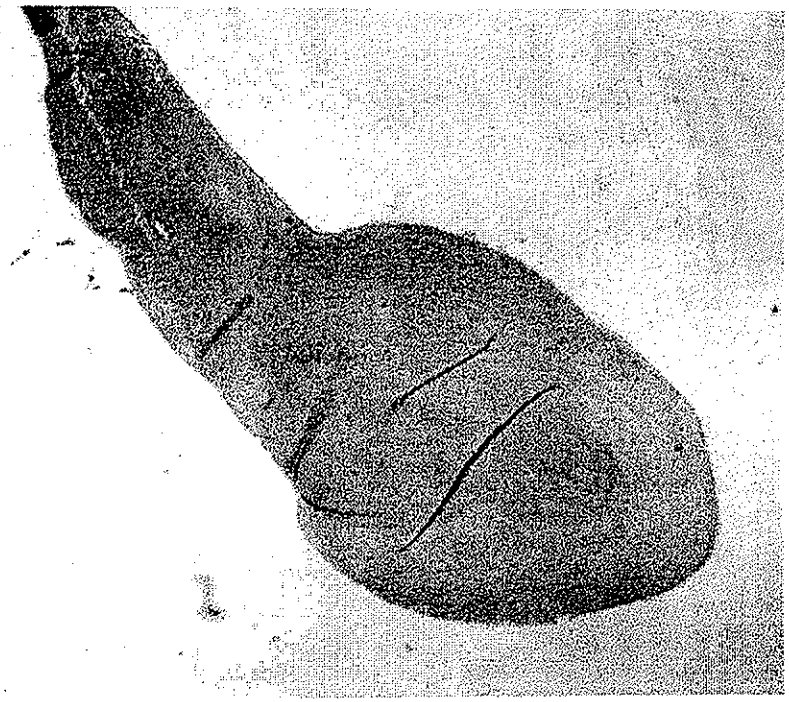
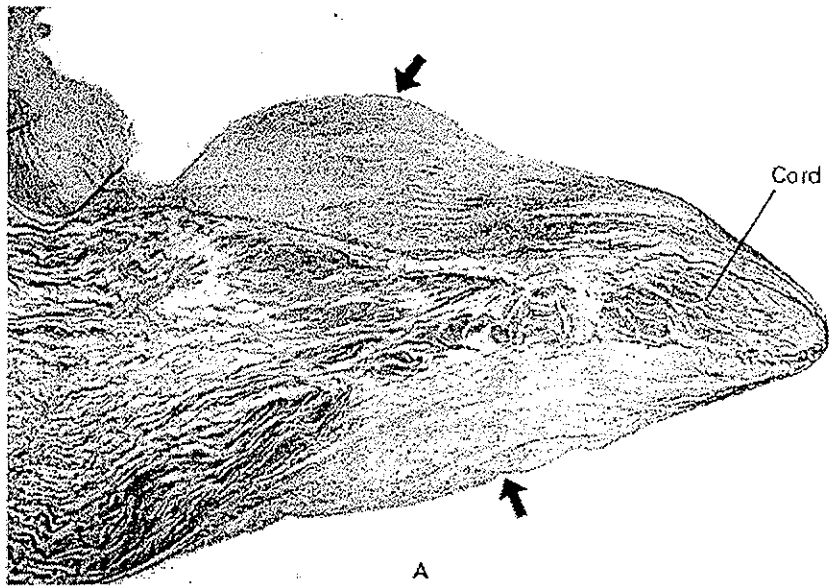


Figure 1. Explanted Mitral Valve from Patient 5, Demonstrating Glistening White Leaflets and Chordae with Mild-to-Moderate Irregular but Diffuse Thickening.

Valvular Heart Disease Associated with Fenfluramine-phentermine; Connoly et al, NEJM 1997

Etude microscopique (3 cas) : Comparaison aux études publiées





In Panel A, a low-power view (elastic–van Gieson stain, ×36) shows intact valve architecture with "stuck-on" plaques (arrows). In Panel B, a high-power view (hematoxylin and eosin, ×360) shows pro-

Cas brestois : dépôts myxoides diffus modérés le long de la face atriale de la sigmoide aortique, se majorant au niveau de son bord libre

Valvular Heart Disease associated with fenfluramine-phentermine; Connoly et al, NEJM 1997

Annexe 3-78

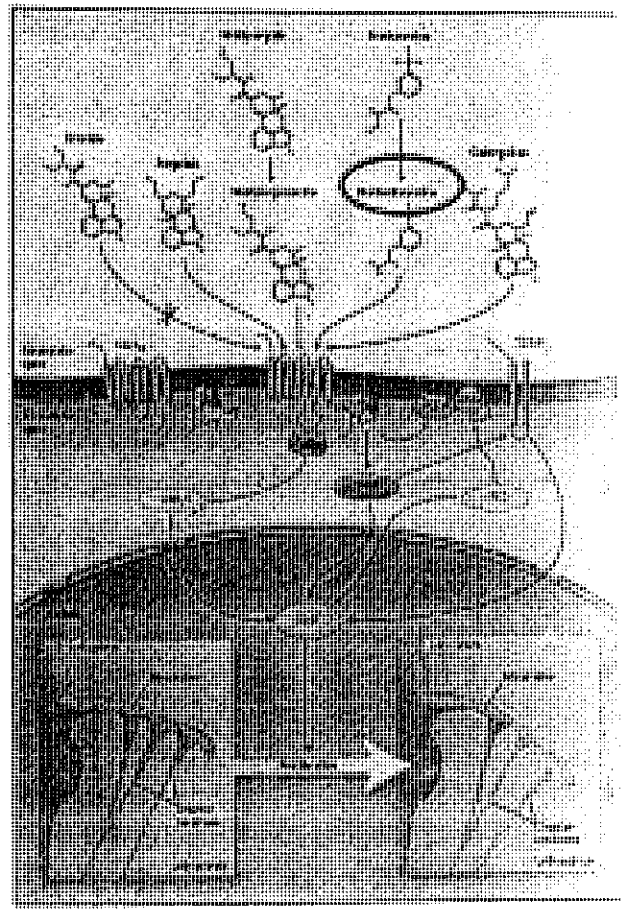
En cours : analyse systématique de toutes les "insuffisances mitrales" isolées ou associées vues au CHU depuis 2003

- 622 dossiers d'insuffisance mitrale triés en 2 groupes :
  - Groupe 1 : IM apparue dans un contexte étiologique bien identifié (RAA, coronaropathie, CMD, Maladie de Barlow avec rupture de cordage, endocardite…)
  - Groupe 2 : IM inexpliquée
  - Comparaison de l'exposition au Médiator à partir des cas identifiés par la requête du PMSI et sur enquête téléphonique (patient + médecin traitant) sur un modèle cas-témoin.

- A partir des 400 dossiers déjà analysés il apparaît qu'une large majorité d'insuffisances mitrales inexpliquées (ou qualifiées "rhumatismales" sans RAA connu) est associée à l'exposition au Médiator^{R}

CONCLUSION

- Notre étude monocentrique retrouve un signal important en faveur d'1 association "Médiator^{R}-valvulopathies cardiaques" :
  - Nombre élevé de cas décrits compatibles (série du NEJM : 24 patientes, 5 cas chirurgicaux)
  - Etude comparative macroscopique et microscopique des valves
  - Revue de dossiers exposés/non exposés (en cours)
- Il existe des arguments théoriques pour suspecter une telle association (schéma)
- Point important : association à risque Médiator^{R} + ISRS ?
- Nos propositions :
  - Collaboration urgente avec un autre centre sur un schéma proche de Brest : proposition d'un travail en commun avec Amiens (C.Tribouilloy, A. Jacques)
  - Retrait de Médiator^{R} ?



Roth et al, NEJM 2007

MEDIATOR : benfluorex

PHARMACOVIGILANCE
Commission nationale:
7 juillet 2009
Rapporteurs JP Kantelip
C Riché

MEDIATOR : historique

- 11 juillet 1995 : mise au point E.I.(CT)
- 30 avril 1998 : enquête officieuse E.I
- 17 décembre 1998 et 20 juillet 1999 : enquête officielle
- 7 décembre 2004 : bouffée délirante aiguë
- 8 mars 2005 : hypertension pulmonaire
- 29 novembre 2005: enquête relative aux hypertension artérielle pulmonaire et aux troubles neuropsychiatriques (CN)
- 27 mars 2007: mise à jour des données de pharmacovigilance et résultats de l'étude d'utilisation (CN)

Chlorhydrate de benfluorex (Médiator)

- La seule indication est :

  «adjuvant du régime adapté chez les diabétiques avec surcharge pondérale »

  L'indication «adjuvant du régime adapté dans les hypertriglycéridémies » a été supprimée.

MEDIATOR: benfluorex et valvulopathies

Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C,Carlhant-Kowalski D, Sitbon O, Simmoneau G et Humbert M;

Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 2009; 33:684-688

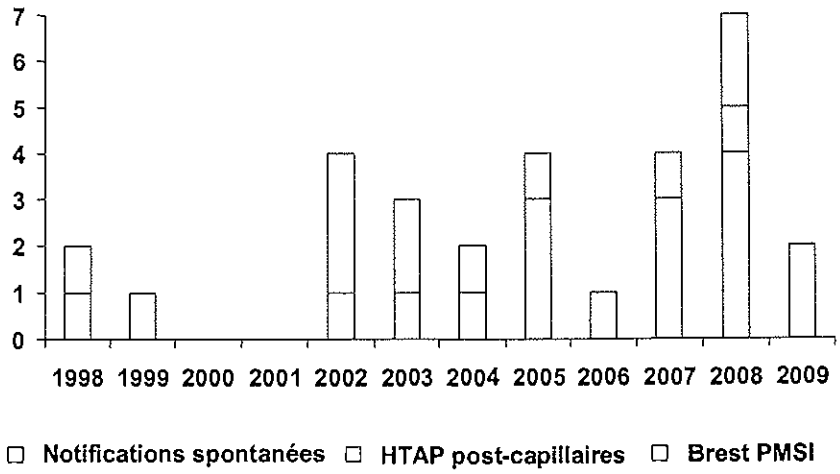
5 cas d'hypertension artérielles pulmonaire et un cas de valvulopathies

Travail de l'équipe de Brest sur les cas extraits du PMSI

Valvulopathies

- 30 valvulopathies : 1998 – 2009
- 19 notifications spontanées :
  - 16 valvulopathies
  - 3 HTAP post-capillaires
- 11 PMSI Brest

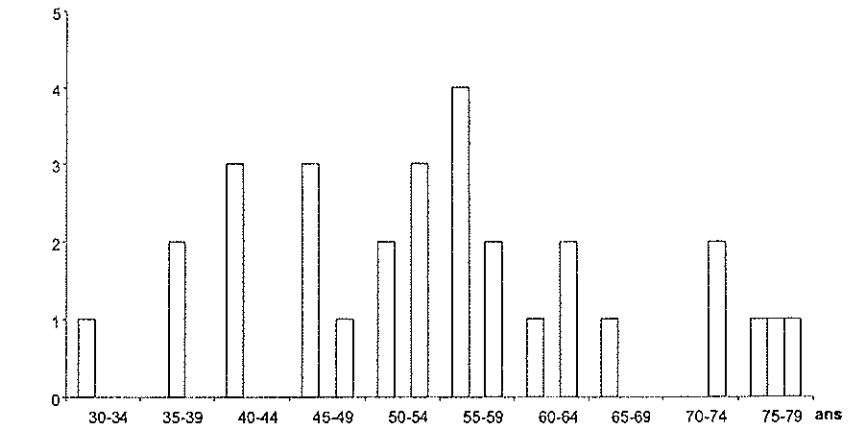
Valvulopathies (années de survenue)



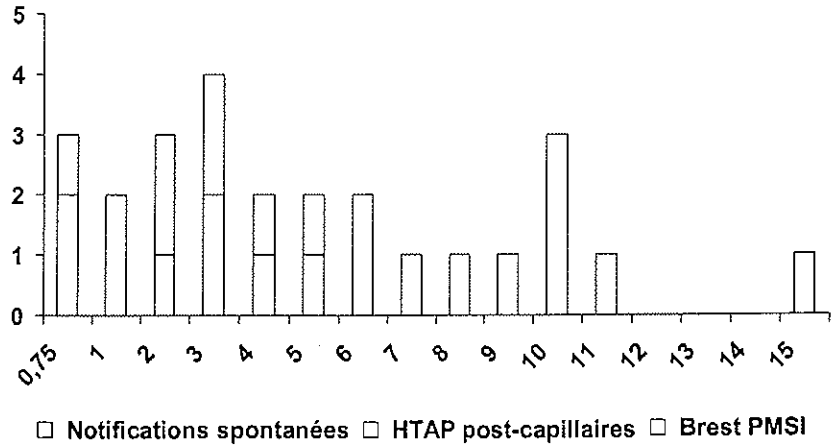
Valvulopathies : sexe/âge/durée TTT

- Femmes: 24
  - 54,6 ans : 53,7 ans (N.S.)
    : 56,4 ans (BR PMSI)
- Hommes: 6
  - 62,2 ans : 54,6 ans (N.S.)
    : 69,7 ans (BR PMSI)
- Durée TTT : 5,3 ans (8 mois à 15 ans)
  - 5,6 ans (N.S.)
  - 4,6 ans (BR PMSI)

Valvulopathies (par âges)

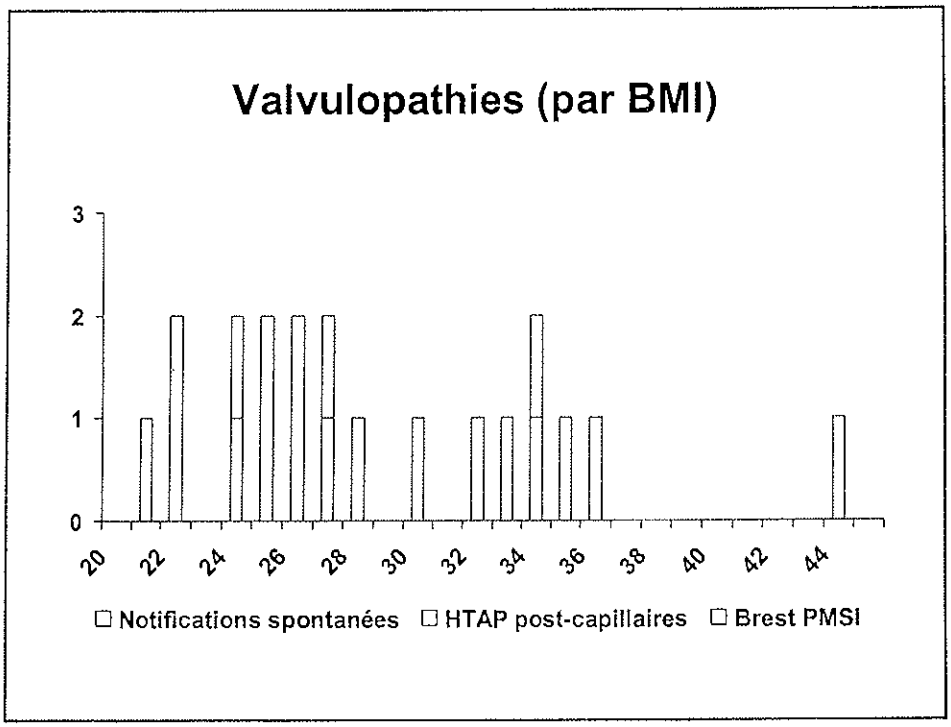


Valvulopathies (durée TTT en années)



Valvulopathies : Antécédents - Terrain

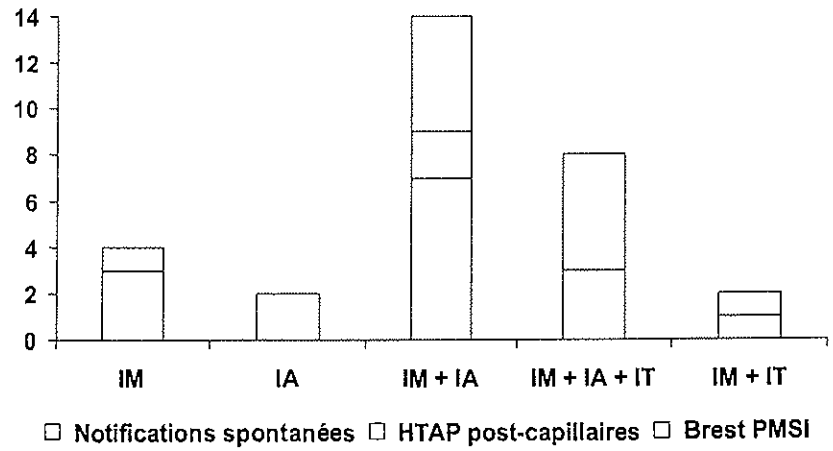
- Hypothyroïdie : 9
- HTA : 9
- Infarctus du myocarde : 2
- Angines dans l'enfance : 4
- BMI : (/20)
  - Surpoids : 7
  - Obésité : 8



Valvulopathies :

	I.M.	I.A.	I.M. + I.A.	I.M. + I.T.	I.M + I.A. + I. T.
N.S.	4	2	9	1	3
Brest PMSI			5	1	5
Total	4	2	14	2	8

Types de valvulopathies



Valvulopathies : gravité

- I.M. : 28/30
  - Grade 2-3 à 3 : 17
- I.A. : 24/30
  - Grade 1 à 2 : 17
- I.T. : 11/28

  Grade 3: 4

Valvulopathies : évolution

- Chirurgie Valvulaire (prévues) : 10 + 2
- Stable : 4
- Stable avec TTT : 5
- Inconnue : 4
- En cours : 5

Valvulopathies opérées

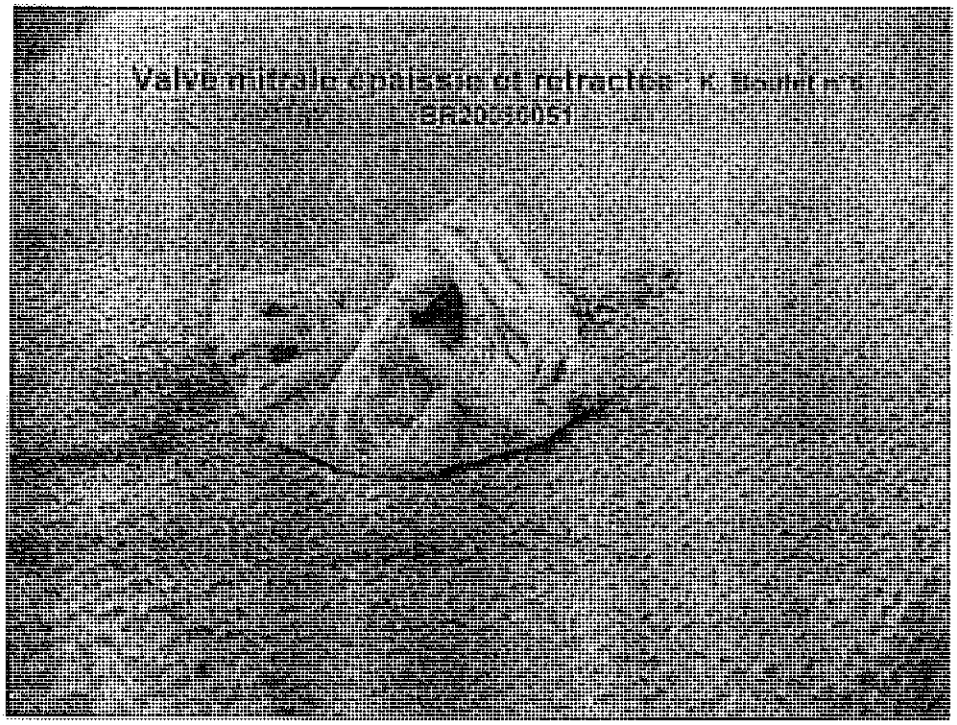
- Anatomopathologie non spécifique:
  - TO (2005)
  - TO (2003) (HTAP)
- Pas d'anatomopathologie
  - BR (1998)
  - BR (2002)
  - BR (2003)
  - BR (2004)
  - GR (2009)

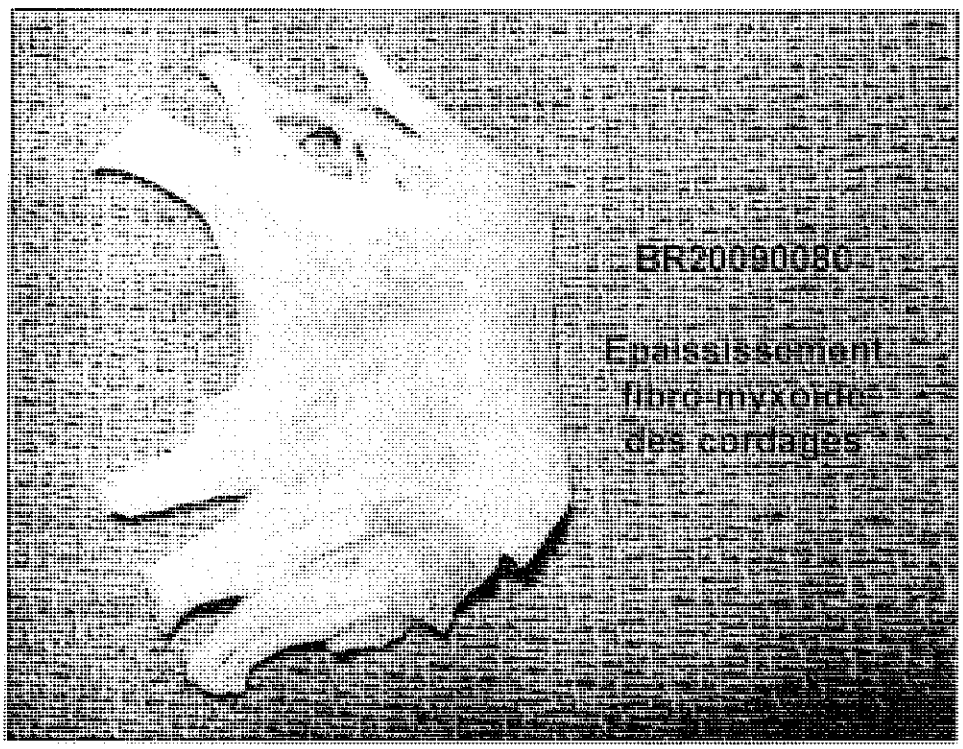
Valvulopathies opérées

- Anapath. compatibles avec anorexigènes!: 4 cas*
  - TO (2005) : Publication Noize
  - BR (2007) : Publication de Boutet
  - BR (2008) : PMSI Brest
  - *2002 ou 2003* : Publication espagnole Rafel Ribera*

Valvulopathies opérées

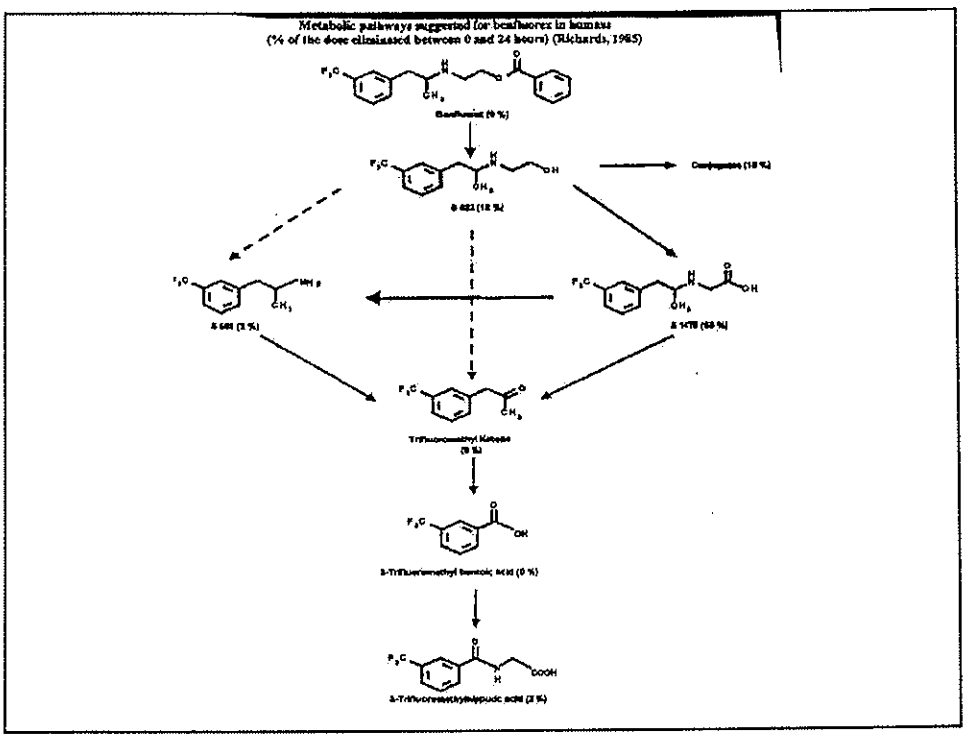
- Noize et al; Fund Clin Pharmacol, 2006: Patient de 48 ans, BMI:25, BPCO et tabagisme, IM grade 3 et IT grade 2
- AP: aspect non spécifique dans l'absolu de la toxicité des anorexigènes mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes


Valve mitrale épaissie et rétractée
BR20090051


BR20090080
Epaississement
fibro-myxoïde
des cordages

Valvulopathies induites par les anorexigènes

- Conolly H et al: Valvular heart desease associated with fenfluramine-phentermine; N Engl J Med; 1997, 28; 337 (9):581-8
- AP: plaques de myofibroblastes dans une matrice extracellulaire abondante de collagène. « aspect semblable aux valvulopathies dues à l'ergotamine et aux maladies valvulaires carcinoïdes »



Cardiotoxicité des anorexigènes

- **Stimulation des récepteurs 5-HT2B**
- **Induction de mitogenèse fibroblastique**
- **Expression du récepteur 5-HT2B dans les valves cardiaques**
- **Benfluorex: N-(benzoyloxy-2- ethyl)norfenfluramine)**

Valvulopathies : publication Nkomo (2006)

- **Prévalence estimée à 2,5%: 12 000 patients**
  - Sexe: pas de ≠
  - Age :
    - < 2 % avant 65 ans
    - 8,5 % entre 65 et 74 ans
    - 13,2 % après 75 ans
    - Lancet; 368; 2006; 1005-1011

Framingham Heart Study 1999: Prévalence des insuffisances valvulaires

- 3589 sujets
- 1991-1995

- 1696 H, 1893 F

- IM : âge, HTA, BMI bas
- IA : âge, sexe masculin
- IT : âge, BMI bas, sexe féminin

Etude Euro Heart Survey: surveillance prospective des patients ayant une valvulopathie en Europe

- 25 pays
- 1 avril au 31 juillet 2001
- 5001 patients : valvulopathie modérée ou sévère
- 14% : polyvalvulopathie
- 28% : valvulopathie déjà opérée
- 58% : monovalvulopathie
  - Dégénératives : 63 %
  - Rhumatismales: 22%
  - Congénitales : 6% (bicuspidies aortiques)
  - Secondaires à une endocardite : 3%
  - Ischémiques : 2%
  - Autres: 4%

Répartition des monovalvulopathies Etude Euro Heart Survey (2001)

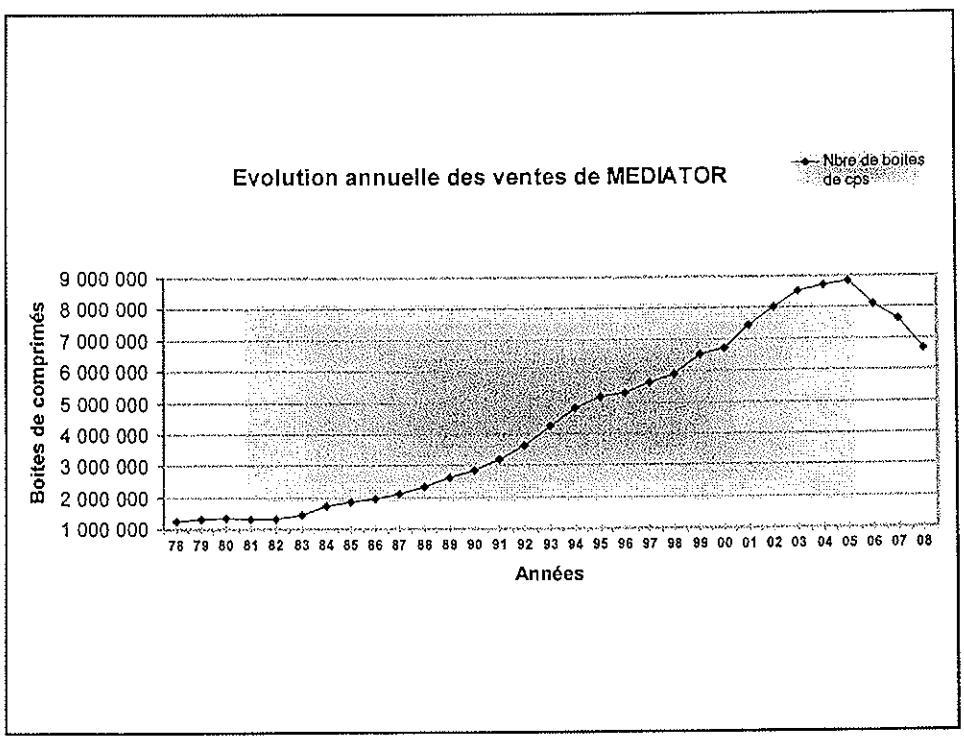
	Rétrécissement aortique	Insuffisance aortique	Rétrécissement mitral	Insuffisance mitrale
N	1197	389	336	877
%	**43**	13	12	**32**
Dégénérative	81,9	50,3	12,5	61,3
Rhumatismale	11,2	15,2	85,4	14,2
Endocardite	0,8	7,5	0,6	3,5
Inflammatoire	0,1	4,1	0	0,8
Congénitale	5,4	15,2	0,6	4,8
Ischémique	0	0	0	7,3
Autres	0,6	7,7	0,9	8,1

Publication Mohaved 2007 : Prévalence des valvulopathies aortiques non rhumatismales chez diabétiques de type 2

- Veterans Health Administration Hospitals:
  - Fichier patient : 1990-2000
- Diabétique type 2 non HTA: 2,5 % (293 000)
- HTA non diabétique : 2 % (552 600)

Valvulopathies

- 139 816 678 boites vendues
- 57 490 410 mois de traitement



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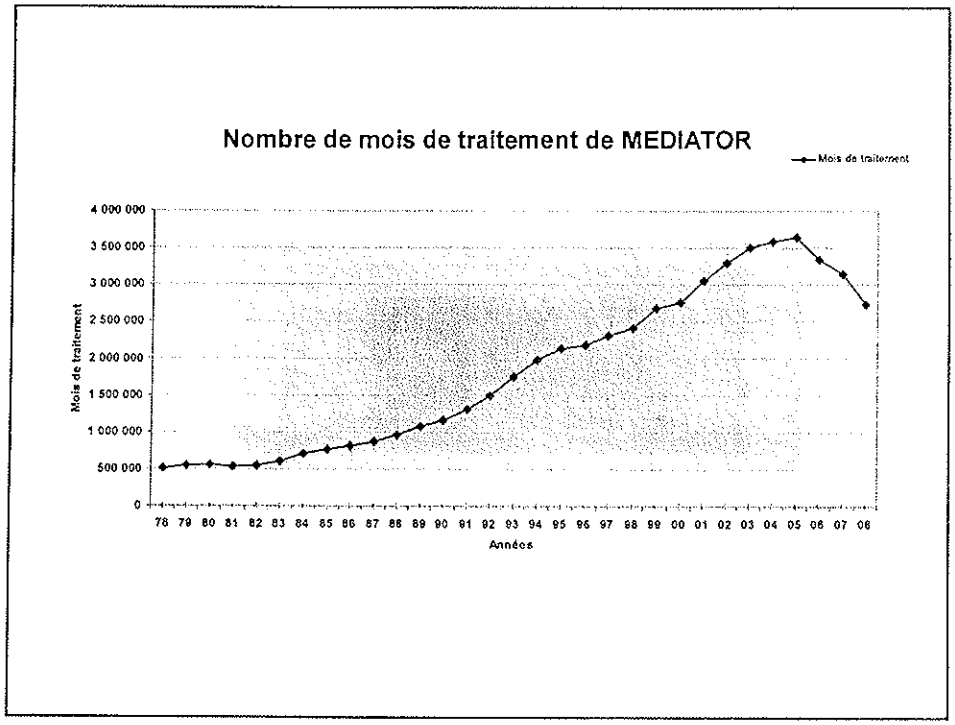
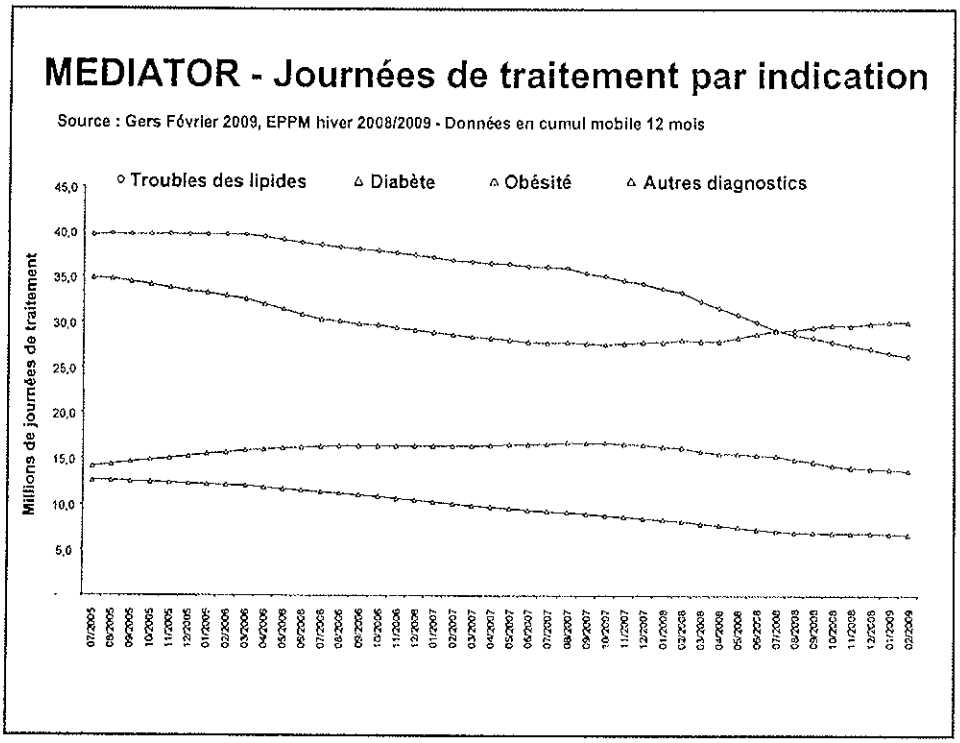

Nombre de mois de traitement de MEDIATOR
Mois de traitement
4 000 000
3 500 000
3 000 000
2 500 000
2 000 000
1 500 000
1 000 000
500 000
0
Mois de traitement
78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08
Années


MEDIATOR - Journées de traitement par indication
Source : Gers Février 2009, EPPM hiver 2008/2009 - Données en cumul mobile 12 mois
Troubles des lipides
Diabète
Obésité
Autres diagnostics
Millions de journées de traitement
45,0
40,0
35,0
30,0
25,0
20,0
15,0
10,0
5,0

CONCLUSIONS

- Un signal de cardiotoxicité (atteintes valvulaires) a été détecté par l'analyse de la notification spontanée et des données issues du PMSI du CHU de Brest.
- Nécessité de confirmer ce signal par une étude rétrospective cas témoins basée sur l'exploitation du codage PMSI effectuée par plusieurs CRPV (AP-HP, Brest, Reims, Grenoble..) selon une méthodologie commune d'après les propositions du groupe PGR-PEPI qui a examiné le sujet le 2 juin 2009
- La pharmacologie du benfluorex et de son métabolite , la nor-fenfluramine doivent être considérés dans le mécanisme de la cardiotoxicité (plausibilité biologique).
- Une nouvelle réèvaluation du bénéfice de benfluorex est à envisager compte tenu des nouvelles données de sécurité.

Annexe 3-78

CENTRE REGIONAL DE PHARMACOVIGILANCE
BESANCON
CHU Saint-Jacques – 25030 BESANCON Cedex

MEDIATOR® (benfluorex)

Enquête officielle

Hypertensions artérielles pulmonaires

Et

Valvulopathies

Commission Nationale du 7 juillet 2009

M. DAVID-LAROCHE
J.P. KANTELIP

Annexe 3-78

Suite à la publication de K. Boutet et coll. « *Fenfluramine-like cardiovascular side-effects of benfluorex* », rapportant 5 cas d'hypertension artérielle pulmonaire (HTAP) et un cas de valvulopathies cardiaques chez des patients ayant été exposés au benfluorex, le Comité Technique a demandé d'actualiser l'enquête officielle sur les HTAP sous benfluorex.
Un cas de valvulopathie étant rapporté dans cet article et suite au travail de l'équipe de Brest sur les cas extraits du PMSI, l'enquête a été étendue aux cas de valvulopathies de patients ayant reçu benfluorex.
Nous y avons ajouté les cas d'HTAP post-capillaires, lorsque la valvulopathie parait être postérieure à la prise de benfluorex.

Le MEDIATOR® (chlorhydrate de benfluorex) est commercialisé en France depuis 1976, par les laboratoires SERVIER (BIOPHARMA), sous forme de comprimés, dosés à 150 mg et par les laboratoires Mylan et Qualimed (Générique).

La seule indication est : « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale », car l'indication, « adjuvant du régime adapté dans les hypertriglycéridémies » a été supprimée, suite aux conclusions de la Commission Nationale de Pharmacovigilance du 27 mars 2007.

Le nombre d'HTAP d'allure idiopathique retrouvé dans l'enquête présentée à cette commission, ne constituait pas un signal significatif de toxicité du MEDIATOR® dans la classe organe cardiovasculaire.

Métabolisme : (rappel)

- In vivo : Chez l'homme, le MEDIATOR® est hydrolysé très rapidement au niveau plasmatique et hépatique par des estérases en S422 (dérivé alcool), puis transformé en 8 métabolites majeurs, par oxydation (S1475, dérivé acide) ou désalkylation (S585, norfenfluramine).
  Le métabolite majoritaire est le dérivé carboxylique : S1475.
  Le métabolite primaire S422 et la norfenfluramine sont retrouvés à des taux très inférieurs.

Après administration de benfluorex radioactif ; 87 à 99% de la radioactivité est présente dans les urines après 72 heures. L'absence de quantité significative dans les fécès montre que le produit est bien absorbé.
Il n'existe pas de phénomène d'accumulation.

L'élimination se fait en 2 phases :
- une première phase rapide (60% en 3 ou 4 heures)
- une seconde phase lente de 36 heures environ.

- In vitro : Après incubation d'hépatocytes frais humains, il a été montré que les principaux cytochromes P450 jouent un rôle très minoritaire dans le métabolisme du benfluorex.

Annexe 3-78

I. Hypertensions Artérielles Pulmonaires

28 notifications ont été rapportées (dont 8 depuis la Commission Nationale du 27 mars 2007) :

1. Notifications MEDIATOR® associé à un anorexigène :

13 notifications d'«Hypertension artérielle pulmonaire » ont été rapportées.

- 11 d'entre elles, expertisées par le Professeur WEITZENBLUM (Strasbourg), faisaient partie de l'enquête «Anorexigènes et hypertensions artérielles pulmonaires» présentée à la Commission Nationale du 27 mars 2007
Par rapport à la prise d'anorexigènes, la prise de MEDIATOR® est :

- antérieure dans 2 cas : 1 HTAP post-capillaire (10052733)
  1 HTAP post-embolique (10840770)

- concomitante dans 5 cas : 5 HTAP d'allure idiopathique (PP890081, NC9300007, 10052455, 10840193, 10840D01)

- inconnue dans 1 cas : 1 HTAP post-capillaire (10840954)

- postérieure dans 3 cas : 2 HTAP d'allure idiopathique (10840255, 10840663)
  1 HTAP post-capillaire (1084B19)

- 2 nouveaux cas ont été rapportés :

BR20080383 : (cas n°5 de la publication de K. Boutet et al)

Femme de 55 ans, obèse (BMI= 41), diabétique et dépressive, prise en charge pour une dyspnée d'effort associée à un syndrome d'obésité/hypoventilation et d'apnée du sommeil, appareillée en avril 2006.
Lors d'une visite de suivi, on découvre à l'échocardiographie une dilatation des cavités droites.
La PAPs est évaluée à 59 mmHg.
Le cathétérisme (janvier 2007) montre une PAPm à 28 mmHg. L'HTAP modérée est prise en charge sans traitement médical.
En 2008, l'état clinique de la patiente est stable.
Le dossier médical retient une prise d'ISOMERIDE®, très ancienne, pendant moins de 3 mois et de MEDIATOR® pendant plusieurs années, arrêté 1 an avant le diagnostic d'HTAP.

PB0700302 :

Ce cas, très succinct, datant de 2002 est rapporté rétrospectivement.
Diagnostic d'HTAP précapillaire, chez une femme de 65 ans, alors qu'elle avait pris de l'ISOMERIDE® de 1992 à 1993 et du MEDIATOR® de 1996 à 1999. Au moment de la notification, la patiente n'était pas rétablie.

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2. Notifications MEDIATOR® non associé à un anorexigène :

15 notifications d'«Hypertension artérielle pulmonaire » ont été rapportées.

- 9 d'entre elles, expertisées par le Professeur WEITZENBLUM (Strasbourg), faisaient partie de l'enquête «Anorexigènes et hypertensions artérielles pulmonaires» présentée à la Commission Nationale du 27 mars 2007.

  - 1 HTAP post-embolique
    - MP0500189 →*Avis de l'expert : « Vraisemblable HTAP post-embolique »*

  - 2 HTAP post-capillaires :

    - TO040278 :

    →*Avis de l'expert: « cardiopathie valvulaire sévère, l'OAP ayant entraîné une HTAP post-capillaire. »*

    - NT0500397 = S05001666 :

    → *Avis de l'expert : « HTAP probablement post-capillaire, peu documentée »*

  - 6 HTAP d'allure idiopathique

    - 2 cas non pris en compte lors de la Commission Nationale (CN) du 27 mars 2007 :

    - S02001046 : dossier trop succinct.
    - BR0700050 (publication K. Boutet, cas n°3) : → *Avis de l'expert : « HTAP idiopathique »*, mais la patiente a été traitée par MEDIATOR® pendant 3 mois, 10 ans auparavant.

    - Les 3 cas retenus lors de la CN du 27 mars 2007 sont :

    - PS9900385 : cas n° 1 de la publication de K. Boutet et coll.
    - S02001877 = PB20090105 : cas n° 2 de la publication de K. Boutet et coll.
    - TO060957

    - Le cas de BR0700051 (publication K. Boutet, cas n°4) était incomplet lors de la CN et l'avis de l'expert *était : « probable HTAP idiopathique mais documentation incomplète » (manque cathétérisme cardiaque)*
    Depuis nous avons reçu, le résultat du cathétérisme cardiaque droit retrouvant une pression artérielle pulmonaire moyenne à 46 mmHg (systolique à 98 mmHg et diastolique à 30 mmHg).
    Il s'agit d'une femme de 58 ans, ayant un DNID, une HTA et une obésité morbide (BMI= 49), qui la fait passer du lit au fauteuil toute la journée et ce depuis plusieurs années.
    Elle a pris du MEDIATOR® pendant 10 ans. Au moment du diagnostic, la patiente prenait LANTUS®, metformine, TEMERIT®, APROVEL® et LASILIX®.
    Elle sort de l'hôpital avec un traitement comportant en plus TRACLEER® et DIAMOX®.

- 6 nouveaux cas notifiés depuis le rapport de mars 2007.

Ces cas n'ont pas été expertisés par le Professeur Weitzenblum, comme les cas antérieurs, mais :

- dans 1 cas, (MA20070346), il s'agit d'une patiente de 52 ans, ayant un BMI = 25,8, traitée pour une hypercholestérolémie par MEDIATOR® depuis 8 ans avec adjonction ensuite de LIPANTHYL®, qui souffre d'une dyspnée d'effort depuis 1 an. L'échocardiographie montre un ventricule droit non dilaté, la pression pulmonaire systolique (PAPs) est estimée à 45 mmHg. Le MEDIATOR® est arrêté. Une échographie cardiaque de contrôle, moins de 3 mois plus tard, montre la normalisation des PAPs, ainsi que l'absence d'insuffisance cardiaque clinique. Un cathétérisme cardiaque n'a pas été effectué.
Il est donc difficile de retenir ce cas comme HTAP d'allure idiopathique.

- dans 1 cas, une HTAP post-embolique est évoquée, (MA20070231) : la patiente âgée de 37 ans est hospitalisée pour péricardite chronique et pneumopathie interstitielle. Elle avait été traitée pendant 1 an par MEDIATOR®, qui a été arrêté 6,5 ans avant la survenue de l'HTAP. La scintigraphie pulmonaire est en faveur d'embolies pulmonaires.

- dans 4 cas, il existe une valvulopathie associée à l'HTAP.

Remarque : parmi ces 4 cas, lorsque le traitement par MEDIATOR semble antérieur à la valvulopathie : MP0700281 et BX20080964, ces cas seront repris dans la partie « II. Valvulopathies » (avec le cas *TO040278 rapporté antérieurement).*

Le nombre d'HTAP d'allure idiopathique passe de 3 à 4, depuis le dernier rapport de mars 2007, en comptant le cas BR0700051.

3. Fréquence :

Depuis le début de la commercialisation de MEDIATOR® à décembre 2008, le nombre de boites de 30 comprimés vendues est de : 139 816 678 correspondant à 57 490 410 mois de traitement*.

En prenant en compte toutes les HTAP, avec ou sans anorexigènes associés, et après élimination des HTAP post-emboliques (3) et post-capillaires (9), il reste 16 cas d'HTAP idiopathique soit :

- 1 cas pour 8 738 542 boites vendues
- ou 1 cas pour 3 593 150 mois de traitement.

Lors du précédent rapport de mars 2007, elle était de :

- 1 cas pour 9 655 713 boites vendues
- ou 1 cas pour 3 970 277 mois de traitement.

(*) Mois de traitement : estimation établie sur la base d'une posologie quotidienne moyenne à 2,4 comprimés (1 mois = 30,4 jours).

Après élimination des 9 HTAP idiopathiques survenues lors de traitement par MEDIATOR® associé à un anorexigène, 3 dossiers succincts ou de chronologie douteuse :S02001046, MA20070346 (évolution favorable en 3 mois) et BR0700050 (3 mois de traitement par MEDIATOR®, 10 ans auparavant), il reste 4 cas d'HTAP d'allure idiopathique (PS9900385, S02001877, TO060957 et BR0700051) soit :

- 1 cas pour 34 954 169 boites vendues
- ou 1 cas pour 14 372 602 mois de traitement.

Lors du précédent rapport de mars 2007, elle était de :

- 1 cas pour 41 841 426 boites vendues
- ou 1 cas pour 17 204 533 mois de traitement.

4. Conclusion :

Compte tenu de l'incidence des HTAP d'allure idiopathique (1 à 2 cas par millions et par an), le nombre de cas d'HTAP d'allure idiopathique rapporté dans l'enquête, ne constitue pas un signal significatif de toxicité du MEDIATOR dans la classe organe cardiovasculaire.

Hypertensions artérielles pulmonaires (1) (avec anorexigènes associés)

HTAP d'allure idiopathique							
N° Année survenue	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
PP890081= 540V06 (1988)	F, 42	1 an	Dinintel Tenuate Dospan Fringanor	5 ans 5 ans 5 ans	Concomitant	U	
NC9300007 = 052454 (1991)	M, 48	4 ans	ISOMERIDE Zyloric Lipanthyl	3 ans 6 ans	Concomitant	D	
10052455 (1993)	F, 46	25 mois	ISOMERIDE Corgard Buspar Veliten Aldactone	580 jours	Concomitant	F	
10840193 (1993)	F, 47	?	ISOMERIDE Coversyl Lasilix Glucophage	730 jours	Concomitant	F	
10840D01 (1995)	F, 59	4 ans	ISOMERIDE PONDERAL Zocor Progestogel Spiroctan	Environ 12 mois Environ 6 mois	Concomitant	D	
10840255 (1993)	F, 57	1 mois! (sept. 1993)	ISOMERIDE (1986) PONDERAL (1978) Stilnox Xanax Veinobiase	? 2 mois	Postérieur	F	Novembre 1993 : PAPs = 73 mmHg Février 1994 : PAPs = 95 mmHg
10840663 (1993)	M, 48	Plusieurs mois (depuis février 1992)	ISOMERIDE (1990-1991) Fludex	210 jours	Postérieur	Décès	Février 1992 : dyspnée d'effort stade 3-4 Mai 1993 : PAPs= 50 mmHg

N° Année survenue	S/Age	Durée TTT	TTT associé	Durée TTT anorexigène	MEDIATOR/anorexigène	Evolution	
HTAP d'allure idiopathique (nouveaux dossiers)							
BR20080383 = S08005656 (2007)	**F, 55 BMI: 41**	**Plusieurs années Arrêté 1 an avant HTAP**	**ISOMERIDE Anafranil Imovane Lysanxia Glucophage**	**Moins de 3 mois Il y a plusieurs années**	**Postérieur**	**B**	**PAPm : 28 mmHg *Public. Boutet n°5***
PB0700302 = S07002196 (2002)	**F, 65 BMI: 39**	**3 ans (1996-1999)**	**ISOMERIDE**	**1 an (1992/93)**	**Postérieur**	**B**	**HTAP (2002)**
HTAP post-embolique							
10840770 (1991)	F,66		ISOMERIDE Fenproporex	1 mois	Antérieur	F	HTAP post-embolique
HTAP post-capillaires							
10840954 (1994)	F,54		ISOMERIDE Stagid Diamicron	1-2 semaines	Inconnu	A	HTAP post-capillaire
10052733 (1993)	F,71	60 mois	ISOMERIDE	45 jours	Antérieur	F	HTAP post-capillaire
10840B19 (1994)	F, 51	5 ans ?	ISOMERIDE Sectral Moduretic Kaleorid Lexomil Raniplex Prepulsid	2 X 3 mois	Postérieur	F	HTAP post-capillaire

*Les nouveaux cas notifiés depuis le rapport de mars 2007 sont inscrits **en gras***

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Hypertensions artérielles pulmonaires (2) (sans anorexigènes retrouvés!)

N° Année suvenue	S/Age	BMI	Durée TTT	ATCD	TTT associé	Evolution	Commentaires
HTAP d'allure idiopathique							
PS9900385 = 126V79 (1998)	F, 50	24	4 à 5 ans	Hypercholestérolémie Diabète HTA	Logirène Triatec Fenofibrate	B	*Pub. Boutet n°1*
S02001877 = PB20090105 (2002)	F,55	32	3 ans	Dyslipidémie Dépression DNID	Teralithe Aldactone Lasilix Lescol Previscan Lipanthyl, Lipur, Glucophage…	B	*Pub. Boutet n°2*
TO060957 = S06002671 (2005)	F,50	38	3 ans	DNID Hypothyroïdie HTA Obésité	Levothyrox	F	
BR0700051 = S07001172 (2006)	F,58	49	10 ans	Diabète HTA Obésité	Lantus Metformine Aprovel Temerit Lasilix	B	*Dossier succinct* *Pub. Boutet n°4*
S02001046 (2002)	F,59	? Poids= 86 Kg	9.5 ans	Hyperlipidémie HTA Dépression	Captea Lopril Humoryl Praxinor Progynova Utrogestan	U	*Dossier succinct*
BR0700050 = S07001089 (2006)	F,51	41	3 mois (il y a 10 ans)	DNID BPCO Thrombose veineuse profonde Synd. d'apnée du sommeil Obésité	Hytacand Novonorm Zyprexa Symbocort Bricanyl	B	*Chronologie!!* *Pub. Boutet n°3*
MA20070346 = S007003637 (2007)	**F, 52**	**26**	**8 ans**	**Hypercholestérolémie**	**Lipanthyl**	**A**	Evolution favorable en 3 mois

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Annexe 3-78

N° Année suvenue	S/Age	BMI	Durée TTT	ATCD	TTT associé	Evolution	Commentaires
HTAP post-emboliques							
MP0500189 = S05000620 (2005)	F,55	35	31 mois	Hypertriglycéridémie Embolie pulmonaire HTA Obésité	Mopral Previscan Cotareg Vioxx	D	HTAP post-embolique
MA20070231 = S08001396 (2007)	**F,37**		**1 an arrêté depuis 6,5 ans**	**DNID Dyslipidémie Péricardite chronique Pneumopathie interstitielle Syndrome dépressif Psychose ! Tabac**	**Glucophage Amarel Paroxétine Abilify Haldol Théralène Lexomil**	F Par poussées	HTAP post-embolique !
HTAP post-capillaires (valvulopathies antérieures à MEDIATOR®)							
NT0500397 = S05001666 (2005)	M, 74	31	9 ans	Dyslipidémie Scléroses valvulaires mitrale et aortique Arythmie HTA	Hytacand Chrono-adalate Kerlone Previscan	B	Valvulopathies évoluant depuis 10 ans avant la prise de MEDIATOR
MP0700282 = S07002383 (2007)	**F,72**	**35**	**?**	**Valvulopathie mitrale**	**Coversyl Lasilix Cordarone Cardensiel Inexium**	**F**	HTAP : 15 mars2007 Embolie pulmonaire : 26 avril 2007 HTAP Post-capillaire (Insuffisance mitrale) Ou post-embolique ?
MP20080211 = S08001458 (2007)	**F, 62**	**Pds= 54 kg**	**Début juillet 2007 Continué pdt 7 mois**	**Dyslipidémie Cardiopathie ischémique Infarctus du myocarde (1999) HTA sévère**	**Ticlid Bitildiem Elisor Clarityne**	F	Insuffisance aortique

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Annexe 3-78

N° Année suvenue	S/Age	BMI	Durée TTT	ATCD	TTT associé	Evolution	Commentaires
HTAP post-capillaires (dossiers classés également en valvulopathies)							
MP0700281 = **S07002370** **(1999)**	**M,67**	35	**5 ans** **Arrêté depuis 2 ans (1997)**	**Infarctus du myocarde (1980) → Insuffisance cardiaque** **Fibrillation auriculaire** **Cirrhose (1981)** **Tabagisme** **Obésité**	**Levothyrox** **Previscan** **Hemigoxine** **Ikorel** **Coversyl** **Lasilix** **Ogast**	**F**	Insuffisance mitrale
BX20080964 = **S08005674** **(2008)**	**F, 78**	**36**	**15 ans**	**Diabète type 2** **Hypertriglycéridémie** **HTA** **Fibrillation auriculaire**	**Aprovel** **Hyperium** **Amlor** **Zocor**	**F**	Insuffisances mitrale et aortique
TO040278 = S04000348 (2003)	F,36	24	8 mois (Continué 2 ans)	Hypothyroïdie HTA Tabac	Levothyrox Prozac Canol Ginkor fort Hept a myl	B	Insuffisances mitrale et aortique

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*Les nouveaux cas notifiés depuis le rapport de mars 2007 sont inscrits **en gras***

Annexe 3-78

II. Valvulopathies

En France, 30 notifications ont été rapportées entre 1998 et 2009:
(Un cas espagnol rapporté par le laboratoire sera pris en compte dans la partie «8. Aspect des valves, page 15»: publication de Rafel Ribera J.)

- 19 notifications spontanées : 16 valvulopathies + 3 HTAP post-capillaires rapportées ci-dessus
- 11 notifications recueillies intensivement par le CRPV de Brest par l'intermédiaire du PMSI.

A. Notifications

1. Sexe/ Age :

Les notifications de valvulopathies concernent 24 femmes et 6 hommes.

a) Femmes :

La moyenne d'âge de survenue des valvulopathies est de 54,6 ans:
- 53,7 ans (de 34 à 78 ans) pour les notifications spontanées
- 56,4 ans (de 49 à 72 ans) pour les cas de Brest (PMSI)

b) Hommes

La moyenne d'âge de survenue des valvulopathies est de 62,2 ans:
- 54,6 ans (43, 54 et 67 ans) pour les notifications spontanées
- 69,7 ans (60, 70 et 79 ans) pour les cas de Brest (PMSI)

2. BMI : connu dans 20 cas

Dans 3/4 des cas, le BMI indique un surpoids ou une obésité.

BMI entre 18,5-24,9 : 5 cas
Notifications spontanées : 3 femmes
Brest PMSI: 2 (1homme, 1 femme)

Entre 25-29,9 (surpoids) : 7 cas
Notifications spontanées : 5 cas (1 homme, 4 femmes)
Brest PMSI: 2 femmes

Supérieur à 30 (obésité) : 8 cas
Notifications spontanées : 4 (1 homme, 3 femmes)
BMI = 33 et 34 concernant 2 valvulopathies
BMI = 35 et 36 concernant 2 HTAP
Brest PMSI: 4 femmes
BMI : 30, 32, 34, 44

3. Durée de traitement : (dates imprécises dans 4 cas)

La moyenne des durées de traitement est de 5,3
- 5,6 ans (8 mois à 15 ans) pour les notifications spontanées
- 4,6 ans (de 1 à 10 ans) pour les cas de Brest (PMSI)

4. Antécédents et terrain:

a) Tabac :

Un tabagisme est connu chez 13 patients :
- 10 fois dans les notifications spontanées. Il concerne 9 femmes et 1homme
- 3 fois dans les cas de Brest PMSI. Il concerne 2 femmes et 1 homme.

b) Hypothyroïdie

Une hypothyroïdie traitée par levothyroxine est connue dans 9 cas:
- 7 cas pour les notifications spontanées
- 2 cas pour les cas de Brest (PMSI)

c) Antécédents ou terrain cardiaque :

- Hypertension artérielle: rapportée 9 fois
- Infarctus du myocarde : 2 cas
- Angine de poitrine : 1 cas
- Thrombo-embolie : 1 cas
- Cardiomyopathie dilatée (avec HTA) : 1 cas
- Décompensation cardiaque sur bronchopathie (avec HTA) : 1 cas
- Insuffisance cardiaque non précisé mais traitement cardiaque connu dans 2 cas

d) divers

- Angines dans l'enfance sans RAA connu : rapportées 4 fois
- Polyarthrite rhumatoïde : 2 cas
- BPCO : 1 cas

5. Médicaments associés :

- Levothyroxine (9 fois : cf. ci-dessus)
- Antidépresseurs inhibiteurs de la recapture de la sérotonine (IRS)
  - Fluoxétine : 3 fois
  - Paroxétine : 2 fois
  - Vinlafaxine : 2 fois

Remarque : un antidépresseur (IRS) est connu dans 5 cas sur 11 pour Brest PMSI.

6. Insuffisances valvulaires :

a) Localisation :

En ce qui concerne les notifications spontanées, sur 19 cas:

- Insuffisance mitrale dans 4 cas
- Insuffisance aortique dans 2 cas
- Insuffisances mitrale + aortique dans 9 cas
- Insuffisances mitrale + tricuspide dans 1 cas
- Insuffisances mitrale + aortique + tricuspide dans 3 cas

En ce qui concerne les cas de Brest PMSI, sur 11 cas :

- Insuffisances mitrale + aortique dans 5 cas
- Insuffisances mitrale + tricuspide dans 1 cas
- Insuffisances mitrale + aortique + tricuspide dans 5 cas

b) Gravité :

- Une insuffisance mitrale (IM) est présente dans 28 cas sur 30.
  Remarque: Une IM sévère de grade 2-3 à 3 est rapportée dans 9 cas sur 15 pour les notifications spontanées et dans 8 cas sur 11 pour Brest (PMSI)
- Une insuffisance aortique (IAO) est présente dans 24 cas sur 30.
  Remarque :
  Une IAO de grade 1 et 2 est rapportée dans 11 cas sur 14 pour les notifications spontanées et dans 6 cas sur 11 pour Brest (PMSI)
  Dans 2 cas, il n'existe qu'une insuffisance aortique isolée, modérée.
- Une insuffisance tricuspide (IT) est présente dans 11 cas sur 28.
  Remarque : Une IT de grade 1 à 2 est rapportée dans 7 cas : (2 cas de valvulopathies et dans 5 cas sur 11 de Brest (PMSI))
  Une IT sévère de grade 3 est rapportée dans 4 cas : (2 cas de valvulopathies et dans 2 cas 11 de Brest PMSI)

7. Evolution des valvulopathies

- 4 valvulopathies sont bien tolérées sans traitement (dont 3/11de Brest PMSI), 5 ont nécessité un traitement médical ou changement du traitement.

- Dans 4 dossiers, l'évolution est inconnue et 5 dossiers sont en cours.

- Une chirurgie valvulaire a été effectuée dans 10 cas (dont 5 cas sur 11 pour les dossiers de Brest PMSI), elle est prévue dans 2 cas (cf. BR20090086 et GR20090107) décrits ici:

GR20090107
Une échographie cardiaque, début décembre 2008, découvre une HTAP de repos à près de 75 mmHG, chez une femme de 57 ans, pesant 105 Kg, qui a une HTA, une hypothyroïdie, une insuffisance mitrale et une fibrillation auriculaire, traitée par cardioversion externe. Son traitement habituel est HEMIGOXINE®, LEVOTHYROX®, LOGIRENE®, CORDARONE®, PREVISCAN® et FLECAINE®.
Elle a pris du MEDIATOR® d'octobre à décembre 2002, de janvier à avril 2004 et en 2008.
Le cathétérisme cardiaque réalisé en janvier 2009 retrouve une PAPs à 60 mmHG. L'insuffisance mitrale de grade 2 est plutôt centrale, la fuite va jusque dans les veines pulmonaires. L'oreillette gauche est dilatée en rythme sinusal. L'insuffisance mitrale sera traitée dans un premier temps avec des IEC et un diurétique en attendant un remplacement valvulaire.

BR20090086 (Brest PMSI)
Il s'agit d'une femme de 60 ans, ayant un BMI=27, qui présente à l'échocardiographie en mars 2008, un rétrécissement mitral avec insuffisance mitrale de grade 3, une insuffisance aortique de grade 1 et une HTAP. La pression artérielle pulmonaire systolique (PAPs) est égale à 44 mmHg). La valve mitrale est notée de mobilité réduite, épaissie et remaniée.
L'examen clinique retrouve un épanchement pleural droit récidivant de type transsudat. Dans ses antécédents, on retrouve des angines fréquentes sans RAA, une hypothyroïdie, une dépression, un alcoolisme sevré et un tabagisme. Son traitement habituel est LEVOTHYROX®, TAHOR®, PROZAC®, NEULEPTIL®, LAROXYL®, NOCTRAN®, ART 50®. Elle a pris du MEDIATOR® pendant une dizaine d'années (jusqu'en 2008)

Le bilan d'auto-immunité retrouve des IgM antihistones positives mais pas d'anticorps antiphospholipides.

La décision opératoire est en attente, elle permettra d'éliminer une maladie rhumatismale.

8. Aspects morphologique, macroscopique et microscopique des valves :

8.1. Valvulopathies opérées:

Nous rapportons ici les 10 cas de patients français ayant subi une chirurgie valvulaire, ainsi que le cas espagnol, publication de Rafel Ribera J, qui est rapporté par le laboratoire (S03000422).

a) cas où l'anatomo-pathologie serait compatible avec les anorexigènes : 4 cas

- TO060355=S06001104: Cas publié par P. Noize (2006)

Femme de 48 ans, dont le BMI est de 25, traitée par MEDIATOR® pendant 7 ans, dans le cadre d'une intolérance au sucre responsable d'hypoglycémies répétées jusqu'à décembre 2005. Dans ces antécédents, on note une BPCO et un tabagisme important depuis l'âge de 19 ans, sevré fin octobre 2005 avec la survenue d'une dyspnée.
L'échodoppler montre une insuffisance mitrale de grade 3, une insuffisance tricuspide de grade 2 et pas d'insuffisance aortique. L'échographie montre un épaississement de la grande valve qui reste bien mobile et rétraction de la valve postérieure.

Anatomopathologie, histologie :
1° avis : *« Sclérose collagénique englobant cordages et pilier*
Lésions histologiques inhabituelles. Sclérose dense, pauci cellulaire, fortement collagénisée, remaniée par des microfissures.
Valve : fibrose associée à de petits territoires d'œdème mixoïde.
Tissu sous-valvulaire : fibrose particulièrement dense qui englobe en monobloc des cordages mal identifiés et le pilier charnu ».

2° avis : « *Valve épaissie par une fibrose constituée d'accumulation de matrice extra-cellulaire avec peu de cellules fusiformes dans le territoire de l'endocarde, sans inflammation, sans néo-vaisseaux, sans calcifications, sans altération des tuniques sous-jacentes :*
Aspect non spécifique dans l'absolu de la toxicité des anorexigènes, mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes ».

- BR20080051= S08002916: Cas n°6 de la publication de Boutet K. (2009)

Femme de 50 ans, avec un BMI = 34, découverte en novembre 2007 d'une valvulopathie fuyante mitro-aortique responsable d'une décompensation cardiaque. Dans ses antécédents, on note une insuffisance hypophysaire, un DNID et un tabagisme. Elle est traitée par levothyroxine, ramipril, somatropine et depuis 6 ans (de 2001 à septembre 2007) par MEDIATOR®. L'insuffisance mitrale est de grade 3 et l'insuffisance aortique de grade 3. Il existe une HTAP (PAPs= 49 mmHg). L'histoire clinique de la patiente retient qu'elle a pris de l'ISOMERIDE® pendant 1 à 3 mois, 20 ans auparavant.

Anatomopathologie, histologie:
« Epaississement et rétraction des valves (particulièrement de la valve mitrale)
Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire ».

BR20090080 (Brest PMSI)

Femme de 54 ans, avec un BMI = 30, traitée pendant 15 mois par MEDIATOR® (de septembre 2007 à décembre 2008) et pour une dépression par LAROXYL® en 2006 et par EFFEXOR® en 2001 et 2008. Le traitement associé est : CARDENSIEL®, TRIATEC®, LASILIX®, HEMIGOXINE® ET ATARAX®.
En octobre 2005, l'échographie cardiaque était normale avec absence de valvulopathie.
En décembre 2007, 3 mois après le début du traitement par MEDIATOR®, l'échocardiographie montre une insuffisance mitrale et une insuffisance aortique de grade 1.
En octobre 2008, une nouvelle échocardiographie conclut à une altération de la fonction ventriculaire gauche (52%), une insuffisance mitrale de grade 3, une insuffisance aortique de grade 3 et une insuffisance tricuspide de grade 1. La PAPs est à 44 mmHg.
En mars 2009, la dyspnée de grade IV entraîne la décision opératoire avec double remplacement valvulaire.
Il est a noté que la patiente avait pris des amphétamines (biphetamine) pour contrôle du poids pendant 7 à 8 ans jusqu'en 1986.

Anatomopathologie, histologie :
Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique.
Valve aortique :remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques. Présence d'un petit foyer de calcification non spécifique.

S03000422 : Cas espagnol publié par Rafel Ribera J (2003)

Ce cas rapporte une atteinte des 3 valves mitrale, aortique et tricuspide, associée à une HTAP (PAPs: 72 mmHg) chez une femme de 50 ans (BMI non précisé) qui a été traitée pendant 12 mois par intermittence par benfluorex.

Anatomopathologie, histologie :
« Fibrose diffuse avec raccourcissement des cordages de la valve mitrale, une valve tricuspide épaissie et des sigmoïdes aortiques rétractées.
Les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves ».

b) 2 cas où l'anatomopathologie n'est pas spécifique :

TO051212=S05002371

Femme de 49 ans, (BMI inconnu), ayant une hypothyroïdie traitée par LEVOTHYROX® ayant débuté un traitement par MEDIATOR® en 2002.
Pendant ses vacances en Egypte apparaît alors une dyspnée.
En août 2005, elle est hospitalisée pour pneumopathie de la base droite.
En octobre 2005, elle présente une insuffisance mitrale de grade 3, sans rupture de cordage, qui est opérée en novembre 2005. La PAPm est à 22 mmHg. MEDIATOR® est alors arrêté.
Conclusion du cardiologue : *« il s'agit vraisemblablement d'une insuffisance mitrale qui a évoluée à bas bruits pendant de nombreuses années et qui devient symptomatique actuellement »*
Une pathologie post-rhumatismale est évoquée.

Anatomopathologie, histologie :
Les valves sont légèrement indurées sans végétations.
Les remaniements tissulaires associent des plages de fibrose cicatricielle dense, fortement collagénisée, à des territoires oedémateux et myxoïdes de caractère dégénératif, occupés par de nombreux fibroblastes.
On observe des micro-fissures et de rares îlots adipocytaires.
Il n'y a ni dépôt calcique, ni infiltrat inflammatoire, ni bourgeonnement capillaire.
Absence de lésions spécifiques.

S04000348= TO0400278 (dossier classé également dans les HTAP post-capillaires)

Il s'agit d'une femme de 36 ans, avec un BMI = 24, des antécédents d'hypothyroïdie traitée par LEVOTHYROX®, d'HTA et de tabagisme. Elle est traitée par MEDIATOR® de 2002 à 2004 et par PROZAC®, CANOL®, GINKOR FORT®, PRAXINOR®, HEPT A MYL®.
8 mois après l'introduction de MEDIATOR® (2003), est découverte une insuffisance aortique de grade 2 avec insuffisance mitrale minime.
La patiente est hospitalisée en décembre 2003 pour décompensation cardiaque avec une double insuffisance mitrale grade 3 et aortique grade 2, qui sera opérée en janvier 2004. La PAPs est à 50 mmHg.

Remarque : la sœur de la patiente est suivie également pour valvulopathie.

Anatomopathologie, histologie :
Lésions dégénératives non spécifiques.

c) 5 cas sans résultat d'anatomopathologie:

GR20090108

Une insuffisance mitrale de grade 3, associée à une HTAP (PAPs évaluée à 70-75 mmHg) est découverte chez une femme de 56 ans, (BMI inconnu) qui a été traitée pendant 14 ans (1994-2009) par MEDIATOR® pour dyslipidémie et diabète de type 2 associé à fenofibrate, GLUCOPHAGE® et CORDARONE®. Dans ses antécédents, on trouve une dépression, un tabagisme actif et des angines à 20 ans traitées par perfusion intraveineuse.

Aspect des valves :
Valve mitrale remaniée, épaissie, non calcifiée
Grande valve mitrale : aspect en crosse de hockey

BR20090084 (Brest PMSI)

Une double valvulopathie (mitrale et aortique) est découverte en 1998, chez une femme de 51 ans, ayant un BMI=32, qui a pris ISOMERIDE® pendant au moins un an en 1989, MEDIATOR® en 1988, 1999, et quelques mois en 2004. Elle a été traitée également pour état dépressif par PROZAC® pendant 4 ou 5 ans jusqu'en 1995.
En août 2004, l'examen cardiologique relève une valve aortique remaniée avec insuffisance aortique de grade 3, une insuffisance mitrale de grade 3 non calcifiée. Une insuffisance tricuspide et une ACFA sont rapportées.
Un double remplacement valvulaire est réalisé en novembre 2004.

BR20090079 (Brest PMSI)

Il s'agit d'un homme de 60 ans, diabétique chez lequel on a découvert une insuffisance mitrale sévère en septembre 2002. Un traitement par CARDENSIEL®, TRIATEC®, DIGOXINE®, LASILIX® et KALEORID® est instauré.
En mars 2003 l'échographie montre une insuffisance mitrale de grade 3 et une insuffisance aortique de grade 2, sans HTAP. Le traitement chirurgical est réalisé en mai 2003.
Le patient aurait pris du MEDIATOR® pendant une dizaine d'années jusqu'en mars 2003.
Il est suivi en 2009 pour insuffisance tricuspide.

Aspect des valves :
Petite valve mitrale rétractée

BR20090087 (Brest PMSI)

Début 2003, chez un homme de 79 ans, ayant un BMI = 24, une coronarographie réalisée dans le cadre d'une angine de poitrine conduit à une angioplastie et pontage de IVA. Ses antécédents sont un diabète, une hypercholestérolémie, une pancréatite et un tabagisme.
Son traitement habituel (durée inconnue) est PLAVIX®, KARDEGIC®, ZYLORIC®, TRIATEC®, LIPANTHYL®, LASILIX®, CARDENSIEL® et MEDIATOR®.

En juin 2003, lors d'un OAP, l'échographie cardiaque montre une insuffisance mitrale de grade 3, une insuffisance aortique de grade 1, une insuffisance tricuspide de grade 1 et une HTAP (PAPs: 77 mmHg). Une hypothèse rhumatismale non ischémique est évoquée.
Une intervention chirurgicale pour plastie et reconstruction valvulaire est réalisée en octobre 2003.
En février 2005, les bons résultats de la plastie sont notés, la valve aortique parait remaniée et une insuffisance tricuspide de grade 2 est rapportée.

Aspect des valves :
2003 : Cordages de la petite valve uniformément rétractées, mais encore souples et bien individualises
Le mécanisme de l'insuffisance mitrale est un basculement de la petite valve dans le VG. Elle est attirée par des cordages raccourcis.

BR20090078 (Brest PMSI)

En 2002, lors d'une consultation pour hypertension artérielle est noté une insuffisance mitrale de grade1 chez une femme de 53 ans, ayant un BMI= 21, traitée par LIPANTHYL® pour une hypercholestérolémie. Un diabète découvert en 2002 est traité par MEDIATOR® et GLUCOPHAGE® ;
En juin 2004, une échocardiographie met en évidence une insuffisance mitrale de grade 3, une insuffisance aortique de grade 2, une insuffisance tricuspide de grade 3 et une HTAP (PAPs: 90 mmHg).
Un double remplacement valvulaire est réalisé en août 2004.
On note dans ses antécédents, une amygdalectomie à l'âge de 18 ans, suite à de nombreuses angines et une dépression. Son traitement habituel comprend également LASILIX®, DIFFU K®, APROVEL®, PREVISCAN®, DIANTALVIC®, XANAX®, IMOVANE®, ELISOR® et DEROXAT®.

Aspect des valves :
Mitrale :
Epaississement fibreux des grandes et petites valves
Soudure de la commissure antérieure
Rétraction importante de l'appareil sous-valvulaire avec des valves et cordages irrécupérables.
Aortique :
Epaississement des sigmoïdes
Athérome minime à la coronarographie

8.2. Valvulopathies non opérées

TO020331 :

Il s'agit d'une femme de 60 ans, avec comme antécédents : diabète de type 2, hypercholestérolémie, macroadénome hypophysaire, hypothyroïdie, syndrome dépressif, obésité ancienne et dipsomanie, traitée par de nombreux médicaments dont MEDIATOR®, depuis 3 ans, LEVOTHYROX® et EFFEXOR®.
Lors de l'exploration d'un souffle cardiaque, est découvert une insuffisance aortique de grade 2, ainsi qu'une insuffisance mitrale de grade 1-2, et une faible insuffisance tricuspide.
L'évolution est inconnue.

Aspect des valves :
Grande valve mitrale légèrement ballonisée
Décalcification des sigmoïdes aortiques avec diminution de leur mobilité
Ouverture sigmoïdienne mesurée à 16 mm
Pas de rétrécissement aortique

TO070121 :

Femme de 44 ans, en surpoids (BMI= 25), tabagique modérée, traitée pour hypercholestérolémie par MEDIATOR® pendant 9 mois, hospitalisée pour décompensation cardiaque gauche. L'échocardiographie permet de découvrir une insuffisance aortique de grade 4 et une insuffisance mitrale de grade 3. Il existe un minime épanchement péricardique sans HTAP. L'angio-scanner élimine une embolie pulmonaire mais note une infiltration des septas pulmonaires. La patiente sort avec un traitement par LASILIX®, COVERSYL®, MOPRAL® et régime peu salé. Le MEDIATOR® est arrêté.

Aspect des valves :
Echocardiographie : Epaississement valvulaire sur la grande valve mitrale avec une image compatible avec une végétation mesurant environ 10 mm.
Echographie trans-oesophagienne : insuffisance mitrale de grade 2, centrale et commissure antérieure sur restriction du jeu valvulaire avec une rigidité du feuillet antérieur et une restriction du feuillet postérieur.
L'appareil sous-valvulaire est d'aspect brillant.
On note une insuffisance aortique centrale sur une valve à trois cuspides de grade 2 sur 4.

MP20080857 :

Patiente de 77 ans, obèse (BMI= 32,9), hypertendue, ayant une hypercholestérolémie et une hypertriglycéridémie, de multiples antécédents chirurgicaux (colectomie partielle, 4 éventrations, cholécystectomie, hernie et prolapsus) hospitalisée en octobre 2008 pour aggravation d'une dyspnée. Son traitement habituel est HYTACAND®, pravastatine, PLAVIX® et MEDIATOR® depuis plusieurs années. L'aortographie trouve une fuite aortique de grade 2-3 et une insuffisance mitrale de grade 2 confirmée par le cathétérisme. Un éventuel remplacement valvulaire est discuté, vu l'âge de la patiente.

Aspect des valves :
Rétraction de la petite valve mitrale
Calcification sur l'anneau

BR20090085 (Brest PMSI)

Femme de 49 ans, (BMI= 28), ayant dans ses antécédents, un AVC, une splénectomie, un tabagisme et un PTI. Son traitement habituel est : LIORESAL®, OGAST®, NEURONTIN®, URBANYL® et CORTANCYL®. Elle a pris du MEDIATOR® en 2002 et en 2003.
En 2002, lors d'une transfusion pour PTI, une suspicion d'OAP entraîne la réalisation d'une échographie cardiaque qui montre une insuffisance mitrale de grade 2 et une insuffisance aortique de grade 2.
En août 2003, suite à un OAP brutal, l'échocardiographie retrouve cette double valvulopathie avec un rétrécissement mitral non serré ainsi qu'une insuffisance tricuspide.

Aspect des valves :
Remaniement valvulaire au niveau des sigmoïdes et de la mitrale
Valve mitrale un peu épaissie et sténosante
Rétrécissement mitral lâche avec petite valve immobile.

BR20090092 (Brest PMSI)

Femme de 55 ans, hospitalisée en urgence en 2001 pour aggravation d'une dyspnée et suspicion d'OAP. Elle a une insuffisance aortique de grade 1. L'évolution est favorable sous diurétiques. Ses antécédents sont une obésité (BMI= 34), une HTA traitée par CELECTOL® et une cholécystectomie.
Un bilan en 2003 trouve une double fuite aortique et mitrale de grade 2.
En mars 2009, l'échocardiographie montre un aspect stable de la double valvulopathie.
La patiente prend du MEDIATOR® depuis au moins 1998 pour contrôler son poids et ne désire pas arrêté.

Aspect des valves :
Remaniement et rétraction de l'appareil sous-valvulaire sans calcification (en 2003)

S06001337 :

Homme, 54 ans traité pour dyslipidémie par MEDIATOR® de mars 2003 à septembre 2005. Le traitement associé est VASTEN®, KARDEGIC® et TENORMINE®. Suite à un épisode de tachycardie avec insuffisance cardiaque en septembre 2005, une coronarographie et une échocardiographie montrent une insuffisance mitrale de grade 2-3, une insuffisance aortique modérée, une sténose de 70% de l'artère coronaire droite et une hypokinésie du ventricule gauche. Le patient subit une angioplastie de l'artère coronaire avec insertion d'un stent.

Aspect des valves :
Pas d'anomalie sur valves à l'échocardiographie.

Remarque : dans 12 cas, nous n'avons aucune information sur les valves

9. Aspects des valves dans la publication de H. Conolly et coll. intitulée « Valvular heart disease associated with fenfluramine-phentermine».

La valve mitrale est scintillante et épaisse. La valve antérieure a une mobilité préservée tandis que la valve postérieure est immobile. Les cordages sont épaissis et raccourcis.
La valve aortique est épaisse.
L'histopathologie montre des plaques de myofibroblastes dans une matrice extracellulaire abondante de collagène.
L'aspect est semblable aux valvulopathies dues ergotamine et aux maladies valvulaires carcinoïdes.

B Propositions/avis :

1- un signal de cardiotoxicité (atteintes valvulaires) a été détecté par l'analyse de la notification spontanée et des données issues du PMSI de CHU de Brest
2- Nécessité de confirmer ce signal par une étude retrospective, cas temoins basée sur l'expoitation du codage PMSI effectuée par plusieurs CRPV (AP-HP, Brest, Reims, Grenoble ...) selon une méthodologie commune selon les propositions du groupe PGR-PEPI qui a examiné le sujet le 2 juin 2009.

3- La pharmacologie du benfluorex et de son metabolite la nor-fenfluramine,douivent être considerés dans le mécanisme de la cardiotoxicité (plausibilité biologique.)
4- Une nouvelle réévaluation du bénéfice de benfluorex est à envisager compte tenu des nouvelles données de sécurité.

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Bibliographie

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Noize P, Sauer M, Bruneval P et al. Valvular heart disease in a patient taking benfluorex. Fundam Clin Pharmacol 2006; 20: 577-578

Rafel Ribera J, Casanas Munoz R, Anguera Ferrando N, Batalla Sahun N, Castro Cels A, Pujadas Capmany R. Valvulopatia cardiaca asociada al uso de benfluorex. Rev Esp Cardiol 2003; 56:215-216

Conolly H et coll. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 28; 337(9):581-8.

Valvulopathies : Aspects morphologique, macroscopique, microscopique

N° Dossiers	Année de survenue		Aspects morphologique, macroscopique, microscopique
MA9900176 = 125P75	1998	I.A I.M. modérée	
TO020331	2002	I.M. grade 1-2 I.A.grade 2 I.T. minime	Grande valve mitrale légèrement ballonisée Décalcification des sigmoïdes aortiques avec diminution de leur mobilité Ouverture sigmoïdienne mesurée à 16 mm Pas de rétrécissement aortique
MP0500087 = S05000405	2004	Aggravation d'1 Valvulopathie (HTAP à Isoméride)	
TO051212 = S05002371	2005	I.M. majeure	Trame valvulaire dégénérative, Absence de lésions spécifiques Les valves sont légèrement indurées sans végétations *Les remaniements tissulaires associent des plages de fibrose cicatricielle dense, fortement collagénisée, à des territoires oedémateux et myxoïdes de caractère dégénératif, occupés par de nombreux fibroblastes.* *On observe des micro-fissures et de rares îlots adipocytaires* *Il n'y a ni dépôt calcique, ni infiltrat inflammatoire, ni bourgeonnement capillaire*
TO060355 = S06001104	2005	I.M.	**Cas publié : Noize P. 2006** 1° avis : Sclérose collagénique englobant cordages et pilier *Lésions histologiques inhabituelles. Sclérose dense, pauci cellulaire, fortement collagénisée, remaniée par des microfissures.* *Niveau valve : fibrose associée à de petits territoires d'œdème mixoïde.* *Tissu sous-valvulaire :fibrose particulièrement dense qui englobe en monobloc des cordages mal identifiés et le pilier charnu* 2° avis : *valve épaissie par une fibrose constituée d'accumulation de matrice extra-cellulaire avec peu de cellules fusiformes dans le territoire de l'endocarde, sans inflammation, sans néo-vaisseaux, sans calcifications, sans altération des tuniques sous-jacentes : aspect non spécifique dans l'absolu de la toxicité des anorexigènes), mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes.*
S06001337	2005	I.M. grade 2-3	Pas d'anomalies sur valves
TO070121 = S07000845	2006	I. M. grade 3 I. A. sévère	Epaississement valvulaire sur la grande valve mitrale avec une image compatible avec une végétation ETO : Commissure antérieure sur restriction du jeu valvulaire avec une rigidité du feuillet antérieur et une restriction du feuillet postérieur. L'appareil sous-valvulaire est d'aspect brillant.
BR20080051 = S08002916	2007	I. M. grade 3 I. A. grade3	**Cas publié : Boutet K. 2009.** Epaississement et rétraction des valves (particulièrement de la valve mitrale) Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire Isoméride 20 ans auparavant
MP20070034 = S07002863	2007	I.A. modérée	Etat stable *Dossier complet mais succinct*
NT20080555 = S09000197	2007	I. M. I. A.	*Dossier complet mais succinct*
CN20080152 =S08002252	2008	I.A. modérée	*Dossier complet mais succinct*
NT20080556 = S09000205	2008	I. M. grade 2 I. A. grade 2 I. Tricuspide grade 3	
MP20080857 =S08006172	2008	IM grade 2 IA grade 2-3	IM: rétraction petite valve Calcification de l'anneau
GR20090107	2008	IM grade 2	
GR20090108	2009	I.M.	Valve mitrale remaniée, épaissie, non calcifiée Grande valve mitrale : aspect en crosse de hockey
GR20090109	2009	I.M. grade 2 IA grade 2	

Dossiers classées également en HTAP post-capillaires			
MP0700281 = S07002370	1999	I.M. 2-3	
S04000348 = TO0400278	2003	I. M. grade 3 I. A. grade 2	Lésions dégénératives non spécifiques Valvulopathie familiale (sœur)
S08005674 = BX20080964	2008	I.M. grade 2 I.A. grade 1	
Valvulopathies : cas CRPV Brest (PMSI)			
BR20090084	1998	I.M. grade 3 I.A. grade 3 I.T.	(Isoméride associé)
BR20090079	2002	I.M. grade 3 I.A. grade 2-3	Petite valve mitrale rétractée
BR20090085	2002	I.M. grade 2 I.A. grade2 I.T.	Remaniement valvulaire au niveau des sigmoïdes et de la mitrale Valve mitrale un peu épaissie et sténosante Rétrécissement mitral lâche avec petite valve immobile
BR20090088	2002	I.M grade 1. I.A. grade 3	
BR20090087	2003	I.M. grade 3 I.A. grade 1 I.T. grade 1	2003 : Cordages de la petite valve uniformément rétractées, mais encore souples et bien individualises Le mécanisme de l'insuffisance mitrale est un basculement de la petite valve dans le VG. Elle est attirée par des cordages raccourcis 2005 : Valve aortique remaniée
BR20090092	2003	I.M. grade 2 I.A. grade 2	Remaniement et rétraction de l'appareil sous-valvulaire sans calcification
BR20090078	2004	I.M. grade 3 I.A. grade 2 I.T. grade 3	Niveau mitral : Epaississement fibreux des grandes et petites valves Soudure de la commissure antérieure Rétraction importante de l'appareil sous-valvulaire avec des valves et cordages irrécupérables. Niveau aortique : Epaississement des sigmoïdes avec défaut de coaptation des sigmoïdes Athérome minime à la coronarographie Pas d'anatomopathologie
BR20090089	2005	I.M. grade 3 I.T. grade 1	
BR20090082	2007	I.M. grade 2-3 I.A. modérée	
BR20090080	2008	I.M. grade 3 I.A. grade 3 I.T. grade I	Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique. Valve aortique :remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques. Présence d'un petit foyer de calcification non spécifique.
BR20090086	2008	I.M. grade 3 I.A. grade 1	Rétrécissement mitral Valve mitrale: mobilité réduite, épaissie et remaniée
Valvulopathies : Cas espagnol publié par Rafel Ribera J			
S03000422	2002 ou 2003	I. M. I. A. I. Tricuspide	Fibrose diffuse avec raccourcissement des cordes mitrales Une valve tricuspide épaissie et des sigmoïdes aortiques rétractées Les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves

VALVULOPATHIES (classées par année de survenue)

Valvulopathies : Notifications spontanées

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
MA9900176 = 125P75 (1998)	M, 43	26	6 ans (1992-1998)	Hypercholestérolémie Surpoids Infarctus du myocarde Insuffisance mitrale minime Tabagisme	Tenormine Vasten Aspirine	I. A. I.M. modérée		IA bien tolérée	ATCD : Infarctus du myocarde
TO020331 (2002)	F, 60	27	3 ans (1998- début 2002)	Diabète type 2 Hypercholestérolémie Obésité ancienne Hypothyroïdie Macroadénome hypophysaire Alcoolisme chronique Syndrome dépressif	Levothyrox Zyrtec Zocor Effexor Stilnox Noctamide	I. M. grade 1-2 I. A. grade 2 I. Tricuspide faible	Pas d'HTAP	U	Décalcification des sigmoïdes aortiques postérieures Grande valve mitrale ballonisée
MP0500087 = S05000405 (2004)	F, 42	22	8 ans (1996-2004)	Hyperlipidémie Hypothyroïdie Tabagisme ancien	Levothyrox Lasilix	Aggravation d'1 Valvulopathie I.M. grade 3 I.A. grade 2 I.T. grade 3	PAPs : 50	TTT médical	ATCD :valvulopathies, HTAP sous ISOMERID
TO051212= S05002371 (2005)	F, 49	?	3 ans (2002-2005)	Hypothyroïdie	Levothyrox	I. M. grade 3	PAPm : 22	Chirurgie	Dyspnée débute en même temps que MEDIATOR (Voyage en Egypte) Pathologie post-rhumatismale évoquée Trame valvulaire dégénérative Absence de lésions spécifiques
TO060355= S06001104 (2005)	F, 48	25	7 ans (fin : 2005)	Intolérance au sucre BPCO Tabagisme		I. M.grade 3 I.T. grade 2	PAPm=24	Chirurgie	Cas publié : P. Noize 2006 Sclérose collagénique englobant cordages et pilier Lésions de fibrose (*)

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Valvulopathies : Notifications spontanées (suite)

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
S06001337 (2005)	M, 54	? P=88 kg	2,5 ans (2003-2005)	Dyslipidémie	Vasten Tenormine Kardegic	I. M.grade 2-3 I. A. modérée		U	Pas d'anomalies sur valves
TO070121 = S07000845 (2006)	F, 44	25	9 mois (2006-2007)	Hypercholestérolémie Surpoids Tabagisme modéré		I. M. grade 3 I. A. grade 4	PAPs= 35	U	Début des symptômes : 8 mois Epaississement de la grande valve mitrale
BR20080051 **= S08002916** **(2007)**	F, 50	34	6 ans (2001-2007)	Hypopituitarisme DNID Obésité Tabagisme	Levothyrox Ramipril Somatropine	I. M. grade 3 I. A. grade 3	PAPs : 49	Chirurgie	Anatomopathologie, histologie (**) Isoméride 20 ans Auparavant *Public Boutet n°6*
MP20070034 **= S07002863** **(2007)**	F, 68	26	5 ans (2001-2007)	HTA Cardiomyopathie dilatée primitive Surpoids	Fludex	I.A. modérée		TTT médical	Etat stable
NT20080555 **= S09000197** **(2007)**	F, 56	?	10 ans (1998-2008)	Hypertriglycéridémie		I. M. I. A.		F	Dossier complet mais succinct
CN20080152 **= S08002252** **(2008)**	F, 34	22	4 ans (2004-2008)	Hyperlipidémie Dépression Tabagisme Alcoolisme	Noctamide Lysanxia	I.A. modérée		F	Automédication abusive Demande en cours pour anorexigènes
NT20080556 **= S09000205** **(2008)**	F, 57	?	3 ans (fin : 2008)	Dyslipidémie HTA Angine dans l'enfance		I. M. grade 2 I. A. grade 2 I. Tricuspide grade 3	PAPs : 55	F	
MP20080857= **S08006172** **(2008)**	F, 77	33	Plusieurs années (fin : 2008)	Hypercholestérolémie Hypertriglycéridémie Obésité HTA Surcharge athéromateuse des axes carotidiens Sténose sous-clavière D	Hytacand Pravastatine Plavix	IM grade 2 IA grade 2-3	PAPs: 60	U	IM: rétraction petite valve Calcification de l'anneau

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Valvulopathies : Notifications spontanées (fin)

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
GR20090107 **(2008)**	F, 57	? P: 105 Kg	2 à 3 mois en 2002, 2004 , 2008	Insuffisance mitrale Fibrillation auriculaire HTA Hypothyroïdie	Hemigoxine Logirène Cordarone Previscan Flecaine Levothyrox	I.M. grade 2	PAPs : 60	Chirurgie prévue	
GR20090108 **(2009)**	F, 56	?	14 ans (1994-2009)	Dyslipidémie Diabète type 2 Dépression Tabagisme actif Angine à 20 ans	Fenofibrate Glucophage Cordarone	I.M. grade 3	PAPs : 70-75	Chirurgie	Valve mitrale remaniée, épaissie, non calcifiée Grande valve mitrale : aspect en crosse de hockey
GR20090109 **(2009)**	F, 48		8 mois (fin : début 2009)	Insuffisance mitrale Polyarthrite rhumatoïde HTA Synd. Gougerot-Sjögren Tabagisme Syndrome dépressif Splénectomie pour PTI		I.M. grade 2 I.A. grade 2	PAPs : 48	En cours	Prise d'Isoméride pendant plusieurs années Consultation prévue en juin 2009 en pneumologie

Dossiers classés également dans HTAP

N° dossier Date de survenue	S, A	BMI	Durée TTT	ATCD	TTT associé		PAP (mmHg) si HTAP connue	Evol°	Commentaires
MP0700281 = **S07002370** **(1999)**	M, 67	35	5 ans (arrêté depuis 2 ans : 1997)	Infarctus du myocarde (1980) → Insuffisance cardiaque Fibrillation auriculaire Hypothyroïdie Cirrhose (1981) Tabagisme sevré (1980) Obésité	Levothyrox Previscan Hemigoxine Ikorel Coversyl Lasilix Ogast	I.M. 2-3	PAPs: 100	F	Non opérable car HTAP trop importante
S04000348 = TO0400278 (2003)	F, 36	24	2 ans (2002-2004) (Début des symptômes à 8 mois : 2003))	Hypothyroïdie HTA Tabagisme	Levothyrox Prozac Canol Ginkor fort Hept a myl	I. M. grade 3 I. A. grade 2	PAPs :50	Chirurgie	Lésions dégénératives non spécifiques) Valvulopathie familiale (sœur)
S08005674 = **BX20080964** **(2008)**	F, 78	36	15 ans (1994-2008)	Décompensation cardiaque sur bronchopathie HTA Diabète type 2 Hypertriglycéridémie Obésité Fibrillation auriculaire	Aprovel Hyperium Amlor Zocor	I.M. grade 2 I.A. grade 1	PAPs : 63	TTT médical	2162

Dossiers PMSI Brest

N° (Année survenue)	S, A	BMI	Durée TTT	ATCD	Méd associés		HTAP	Ev	Commentaires
BR20090084 **(1998)**	F, 51	32	1 an (1988) 1 an (1999) Quelques mois (2004)	Dépression	Prozac	I.M. grade 3 I.A. grade 3 I.T.		Chirurgie	Isoméride (1989) I.M, I.A.: 1998 Aggravation en 2004 : valve aortique remaniée
BR20090079 **(2002)**	M, 60		18 ans ? (1990-2002)	Diabète		I.M. grade 3 I.A. grade 2-3		Chirurgie	Petite valve mitrale rétractée I. Tricuspide en 2009

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Dossiers PMSI Brest (suite)

N° (Année survenue)	S, A	BMI	Durée TTT	ATCD	Méd associés		HTAP	Ev	Commentaires
BR20090085 **(2002)**	F, 49	28	En 2002-2003	Rétrécissement mitral AVC PTI Splénectomie Tabagisme	Neurontin Ogast Lioresal Urbanyl Cortancyl	I.M. grade 2 I.A. grade2 I.T.		Stable	2002 : Valvulopathie Sept 2003 : Remaniement valvulaire au niveau des sigmoïdes et de la mitrale Valve mitrale un peu épaissie et sténosante Rétrécissement mitral lâche avec petite valve immobile
BR20090088 **(2002)**	M, 70		En 1997 En 1998 En 2003			I.M grade 1. I.A. grade 3 (en 2003)		Stable!	En 1999: I.M. grade 1 et HTAP
BR20090087 **(2003)**	M, 79	24	début : non précisé fin : juin 2003	Diabète Hypercholestérolémie Angine de poitrine Pancréatite Tabagisme	Plavix Kardégic Zyloric Triatec Lipanthyl Lasilix Cardensiel	I.M. grade 3 I.A. grade 1 I.T. grade 1	PAPs: 77	Chirurgie	2005: valve aortique remaniée, I.T. grade 2 Etiologie rhumatismale évoquée
BR20090092 **(2003)**	F, 55	34	10 ans (début avant 1998) Non arrêté	Obésité HTA Cholécystectomie	Celectol	I.M. grade 2 I.A. grade 2 (2003)		Stable	2001 : dyspnée, I.A. grade 1 2009: aspect stable Médiator non arrêté
BR20090078 **(2004)**	F, 53	21	3 ans (2002-2005)	Hypercholestérolémie DNID HTA Nombreuses angines Dépression	Glucophage Lasilix Diffu k Aprovel Previscan Diantalvic Xanax Imovane Elisor Deroxat	I.M. grade 3 I.A. grade 2 I.T. grade 3	PAPs: 85	Chirurgie	Epaississement fibreux des valves mitrales avec rétraction de l'appareil sous-valvulaire Epaississement des sigmoïdes aortiques Athérome minime à la coronarographie Pas d'anatomopathologie
BR20090089 **(2005)**	F, 57	44	3 ans (2003-2006)	Diabète Thromboembolie Obésité Dépression	Levothyrox Triatec Lasilix Foradil Paroxétine Xanax Diantalvic Diffu K	I.M. grade 3 I.T. grade 1 (en 2005)	PAPs:53	TTT médical	Début dyspnée: 2004 I.M. fonctionnelle évoquée

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Dossiers PMSI Brest (suite et fin)

N° (Année survenue)	S, A	BMI	Durée TTT	ATCD	Méd associés		HTAP	Ev	Commentaires
BR20090082 **(2007)**	F, 72		4 ans (fin 2003-2008)	Polyarthrite rhumatoïde	Seroplex	I.M. grade 2-3 I.A. modérée	HTAP	TTT médical	2004 : I.A. modérée
BR20090080 **(2008)**	F, 54	30	15 mois	Dépression	Cardensiel Triatec Lasilix Hemigoxine Effexor Atarax	I.M. grade 3 I.A. grade 3 I.T. grade I		Chirurgie	Amphétamine: 7-8 ans (arrêtées en 1986) Début symptômes: 3 mois après benfluorex (I.A. grade 1) Anatomopathologie histologie (***)
BR20090086 **(2008)**	F, 60	27	10 ans	Angines fréquentes sans RAA Dépression Alcoolisme sevré Tabagisme	Levothyrox Tahor Prozac Neuleptil Laroxyl Noctran Art 50	I.M. grade 3 I.A. grade 1	PAPs: 44	Chirurgie prévue	IgM antihistones + Epanchement pleural Rétrécissement mitral

Cas publié espagnol : Rafel Ribera J

S03000422 (2002 ou 2003)	F, 50	?	12 mois TTT intermittent			I. M. I. A. I. Tricuspide	PAPs : 72	Chirurgie	Anatomopathologie, histologie (****)

(*) : aspect non spécifique dans l'absolu de la toxicité des anorexigènes, mais correspondant parfaitement aux lésions décrites dans l'atteinte valvulaire des anorexigènes.

(**) : épaississement et rétraction des valves (particulièrement de la valve mitrale)
Fibrose dense, faite de myofibroblastes dans une matrice de mucopolysaccharides sans infiltration inflammatoire

(***) : Valve mitrale : Lésions valvulaires intéressant essentiellement les cordages sous la forme d'un épaississement fibromyxoïde sans caractère de spécificité mais compatible avec une origine toxique.
Valve aortique :remaniements myxoïdes d'intensité modérée des sigmoïdes aortiques. Présence d'un petit foyer de calcification non spécifique.

(****) :Fibrose diffuse avec raccourcissement des cordes mitrales, une valve tricuspide épaissie et des sigmoïdes aortiques rétractées.
les valves présentent des plaques fibreuses composées de myofibroblastes avec une matrice de mucopolysaccharides et de collagène, causant la rétraction des valves.

Les nouveaux cas notifiés depuis mars 2007 sont inscrits ***en gras***

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Annexe 3-78

afssaps

Agence française de sécurité sanitaire des produits de santé
Direction de l'Evaluation des Médicaments et des Produits Biologiques
Département de Pharmacovigilance

Saint-Denis, le

COMMISSION NATIONALE DE PHARMACOVIGILANCE

Compte rendu de la réunion du mardi 29 septembre 2009

Etaient présents :

Membres de la Commission nationale de pharmacovigilance :
M. MERLE (président)
Mme LAINE-CESSAC (vice-présidente)
Mme CASTOT (représentante de la Direction Générale de l'Afssaps)
Mme BOUXIN-METRO (représentant l'INSERM)
Mme DELOFFRE (représentant de la Direction Générale de la Santé)
M. ANDREJAK
Mme AUTRET-LECA
Mme BAGHERI (suppléante de M. ESCHALIER)
Mme BARBAUD
M. BERNARD
M. BONNETERRE
Mme BOURRET
M. CARLIER
M. CARON
M. GALEZOWSKI
M. GOULLE (suppléant de M. GIROUD)
M. JACQUES
Mme JOLLIET
M. LARRUMBE
Mme LEMERMALLE
M. LIEVRE
Mme LILLO LE LOUET
Mme LOBATO DE FARIA
Mme PAULMIER-BIGOT
M. PELLETIER
M. SAINT-PIERRE (suppléant de M. SANTINI)
M. SAVIUC
Mme SGRO
M. VIAL

Annexe 3-79

Département de Pharmacovigilance :
Mme BOULOS
Mme CHOQUENE
Mme DELEAU
Mme GRENE
Mme KREFT-JAIS
M. MENDOZA
Mme OUARET
Mme PAGE
Mme PHAM
Mme PIZZOGLIO
Mme POINSARD
Mme POROKHOV
Mme ROBINE
Mme SANCTUSSY
Mme VERMILLARD
Mme VITORES
Mme TONNAY

Interne en Pharmacie
Mme CAVEE

Membres suppléants présents :
M. DRICI
M. KANTELIP
Mme PERAULT-POCHAT
M. TRENQUE
M. VAN AMERONGEN
M. WESTPHAL

Afssaps :
M. BOUCAUD-MAITRE
Mme THOMASSIN

Experts présents :
Mme DE LA GASTINE
M. ETIENNE
Mme FRACHON
M. LE GAL
M. LEROYER
M. RICHE

Membres excusés :
M. GIROUD
M. MUNERA
M. RATINEY
M. SANTINI
M. SMADJA

Annexe 3-79

DOSSIERS TRAITES PAR LABORATOIRES

- **SUIVI NATIONAL DE PHARMACOVIGILANCE CONCERNANT LA DESMOPRESSINE ET LE RISQUE D'INTOXICATION PAR L'EAU : MARS 2008 A MARS 2009 :**

LABORATOIRE CONCERNE	*REPRESENTANTS*
FERRING	Mme DENDEN Mme HUSSON Mme KRAUSE Mme MONDIET

- **MISE AU POINT DE L'ENQUETE ET RESULTATS DE L'ETUDE BRESTOISE : HTAP / VALVULOPATHIES ET BENFLUOREX :**

LABORATOIRES CONCERNES	*REPRESENTANTS*
MYLAN SAS / QUALIMED	Mme GABRIELLE
SERVIER	M. DERUMEAUX M. DUBOIS Mme LAUBIGNAT Mme MAHLBERG-GAUDIN Mme RAVAUD Mme TUPINON-MATHIEU M. WAGNIART

GESTION DES CONFLITS D'INTERETS

Aucune situation de conflit d'intérêt n'a été retenue ni déclarée au cours de la séance de la Commission Nationale de pharmacovigilance du 29 septembre 2009.

Annexe 3-79

III- ENQUETE DE PHARMACOVIGILANCE ET RESULTATS DE L'ETUDE BRESTOISE : HTAP / VALVULOPATHIES ET BENFLUROREX

Dossier suivi par Béatrice Porokhov

1. Introduction

Nom commercial	MEDIATOR®
DCI	Chlorhydrate de benfluorex
Formes pharmaceutiques	Comprimé pelliculé à 150 mg
Classe pharmacologique	Antidiabétique
Procédure d'enregistrement	Procédure nationale
Titulaire de l'AMM	Laboratoires Servier

MEDIATOR® (chlorhydrate de benfluorex) a obtenu une AMM en 1974 par une procédure d'enregistrement nationale. Il est commercialisé en France depuis 1976.
MEDIATOR® est indiqué comme « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ». Il est à noter que l'indication comme « adjuvant du régime adapté dans les hypertriglycéridémies » a été supprimée à la suite de l'avis émis par la Commission Nationale de Pharmacovigilance (CNPV) du 27 mars 2007.

Les résultats actualisés de l'enquête officielle relative au « benfluorex et hypertension artérielle pulmonaire », étendue aux valvulopathies en mai 2009, ainsi que les résultats préliminaires de la série des cas brestoise issus du PMSI ont été présentés à la CNPV du 7 juillet 2009.
Une actualisation de cette enquête et les résultats définitifs de l'étude brestoise ont été présentés à la CNPV du 29 septembre.

2. Commission nationale de pharmacovigilance du 7 juillet 2009 :

Lors de la réunion de la CNPV du 7 juillet 2009, le CRPV de Besançon, rapporteur de cette enquête, avait conclu à l'existence d'un signal de toxicité valvulaire détecté par la notification spontanée et les données issues du PMSI. Il convient alors de confirmer ce signal par une étude épidémiologique (cas-témoin).
Le rapporteur a également souligné que la pharmacologie du benfluorex et de son métabolite, la nor-fenfluramine, devra être prise en compte dans l'analyse du mécanisme de la toxicité valvulaire. Compte tenu de ces nouvelles données de sécurité, le rapporteur a proposé une réévaluation du bénéfice/risque de benfluorex.

De même, les données du PMSI de Brest ont permis d'identifier 15 cas dont 11 pris en compte dans le bilan effectué par le CRPV de Besançon et 4 cas très récents à l'étude. Il s'agit de 12 femmes et de 3 hommes. L'âge moyen est de 58 ans (49-78). 6 patients sur 12 sont diabétiques. La durée moyenne d'exposition est de 53 mois (12-144) avec un délai moyen de 97 mois (13-384) entre la première prise du médicament et le diagnostic. L'échographie cardiaque antérieure est normale dans 5 cas sur 7. L'exposition à d'autres anorexigènes concerne 5 patients sur 12 et à un antidépresseur de type inhibiteur de recapture de la sérotonine (IRSI) 8 patients sur 10.
Les valves atteintes sont la valve mitrale ou la valve aortique dans 100% des cas, avec une atteinte de la valve tricuspide dans 7 cas et de la valve pulmonaire dans un cas. Une chirurgie de remplacement valvulaire a été effectuée dans 8 cas.

Par ailleurs, une analyse systématique de toutes les insuffisances mitrales (IM), isolées ou associées, examinées au CHU de Brest depuis 2003, était en cours. Plus de 600 dossiers d'IM sont classés en 3 groupes: 1) IM dans un contexte étiologique bien identifié 2) IM inexpliquées 3) IM non classables.
Une recherche de l'exposition au benfluorex sur un modèle d'étude cas témoins est réalisée pour les cas identifiés par le PMSI et par une enquête téléphonique auprès du médecin et du patient.
Les résultats de cette étude étaient attendus pour fin juillet 2009.

A l'issue de la présentation de ces données, les laboratoires Servier ont proposé deux modèles d'études:
i) une étude anatomopathologique sur un modèle exposé/non-exposé (ce modèle a été récusé par la commission),

ii) une étude cas-témoins ayant pour objectif de quantifier un éventuel sur-risque de valvulopathie associé au Médiator® chez des patients atteints de valvulopathie idiopathique comparativement à des patients indemnes de valvulopathie. Cette étude se ferait sur une population de patients diabétiques ayant une échographie cardiaque. Le protocole serait disponible début Septembre 2009 et permettrait dans les meilleurs des cas d'avoir des résultats dans un an.

Par ailleurs, le laboratoire a informé la commission que l'étude « REGULATE », (Médiator®+sulfonylurée versus pioglitazone+ sulfonylurée) est en cours d'analyse. Cette étude incluant 840 patients dont 420 dans chaque bras, comporte une échographie cardiaque au début et à la fin (52ème semaine) de la période de traitement. Les résultats d'efficacité et de tolérance sont attendus pour la fin du premier trimestre 2010.

3. Conclusions de la CNPV du 7 juillet 2009 :

Les membres de la commission nationale avaient alors souhaité disposer des résultats de l'ensemble des études en cours ou planifiées (l'étude cas-témoins brestoise et les études des laboratoires Servier) avant de proposer d'éventuelles mesures.

4. Commission nationale de pharmacovigilance du 29 septembre 2009 :

Données de la pharmacovigilance :

Une mise à jour des données de pharmacovigilance a été effectuée par le CRPV de Besançon. 11 nouveaux cas de valvulopathie associés au benfluorex sont rapportés dont 3 issus de la notification spontanée et 8 notifications sont des cas recherchés dans une base de données d'échographie cardiaque et provenant d'Amiens. L'analyse de ces 11 nouveaux cas montre une prédominance féminine, une durée moyenne de traitement de 3 ans et un âge de survenue le plus fréquemment identifié de 55 ans. Sur les 11 cas de valvulopathies, un cas était associé à une hypertension artérielle pulmonaire, un cas correspondait à une insuffisance mitrale et aortique et un cas était associé à une atteinte mitrale+aortique+tricuspide. Pour ces cas documentés sur le plan échographique, les données anatomopathologiques restent peu informatives.

Certains membres de la CNPV ont souligné qu'en cas de notification « recherchée » dans d'autres bassins de population, de nombreux autres cas de valvulopathie associés au benfluorex pourraient vraisemblablement être mis en évidence.

Données de l'étude Brestoise :

L'étude cas-témoin rétrospective menée par le CHU de Brest, a pour objectif la recherche d'une association entre l'exposition au benfluorex et la survenue de cas d'insuffisance mitrale (IM) inexpliquée. La population source est constituée de tous les patients hospitalisés entre 2003 et 2009 dans le département de cardiologie ou le service de chirurgie cardiaque au CHU de Brest, et ayant un diagnostic d'IM. Les patients ayant une IM inexpliquée constituent les cas (n=27) et les patients ayant une IM expliquée constituent les témoins (n=54). Deux témoins ont été appariés à chaque cas sur les critères d'âge et de genre. L'appariement ne concernait pas le diagnostic de diabète ou l'Indice de Masse Corporelle (IMC). L'exposition au benfluorex est recherchée auprès du patient, de sa famille et de ses médecins, par téléphone, sur la base d'un questionnaire semi-structuré et à l'aveugle du statut cas ou témoin.

Sur les 27 cas, 19 avaient été exposés au benfluorex contre 3 témoins sur 54 ($p<0.001$ soit un odds-ratio (OR) = 40,4 (9,7- 168,3, IC à 95%)), soit un risque relatif très important d'IM en cas d'exposition au benfluorex. L'ajustement à différentes variables telles que le poids, le diabète ou l'exposition à la dexfenfluramine, ne modifie pas la significativité du résultat. En effet, l'ajustement sur diabète et l'Indice de Masse Corporelle est associé à un OR de 27,6 (6,1-124,6), l'ajustement sur le diabète et l'obésité est associé à un OR de 35,2 (6,8-182) et l'ajustement à une exposition préalable à la dexfenfluramine est associé à un OR de 31,1 (7,2-134,1). Les résultats de cette étude confortent donc le signal de risque de valvulopathie associé au benfluorex.

Données de l'étude « REGULATE » :

Les résultats préliminaires de l'étude REGULATE ont été présentés par les laboratoires Servier. Il s'agit d'une étude multicentrique, en double aveugle, comparant pendant 52 semaines chez 840 diabétiques l'efficacité et la sécurité de 2 traitements, benfluorex et sulphonylurée versus pioglitazone et sulphonylurée. Deux échographies cardiaques ont été réalisées : avant exposition (T0) et à la 52ème semaine. La non-infériorité de l'association benfluorex + sulphonylurée par rapport à l'association pioglitazone + sulphonylurée sur la réduction de l'hémoglobine glycosylée n'a pas été démontrée. La baisse du LDL-cholestérol a été plus importante sous benfluorex que sous pioglitazone.

Concernant le profil de tolérance, dans cette étude, ont été observés :
- 115 patients avec anomalie fonctionnelle détectée : 82 (26,5%) sous benfluorex versus 33 (10,9%) sous pioglitazone (p<0,0001).
- 12 patients avec anomalie morphologique détectée : 8 (2,6%) sous benfluorex versus 4 (1,3%) sous pioglitazone (p=0,264).
- 5 patients avec anomalie fonctionnelle de grade ≥ à 2 : 2 sous benfluorex versus 3 sous pioglitazone.

Il est à souligner que les anomalies fonctionnelles apparues sous benfluorex n'ont pas de traduction clinique.

A l'issue de cette présentation, les laboratoires Servier ont proposé les modifications suivantes du Résumé des Caractéristiques du Produit de Médiator®:
- rubrique 4.2 « Indication » : *Restriction aux diabétiques en échec de traitement après les anti-diabétiques oraux*
-conditions de prescription et de délivrance : *Prescription réservée aux spécialistes tels que diabétologues/endocrinologues.*
- rubriques 4.3 « Contre-indications » : valvulopathie cardiaque et 4.8 « Effets indésirables »: valvulopathie cardiaque
- rubrique 4.4 « Mises en garde spéciales et précautions d'emploi » : mise en place d'un suivi écho cardiographique avant et pendant le traitement.

5. Discussion :

Les résultats de l'étude cas-témoin de Brest ont été largement débattus par l'Afssaps, les membres de la commission, les experts externes sollicités par l'Afssaps, les investigateurs et les laboratoires Servier.
Les experts ont regretté ne pas disposer du protocole de l'étude. Plusieurs biais ont cependant été identifiés:

- le choix des témoins : si la question posée est de savoir si le benfluorex peut ou non être responsable de valvulopathies, les témoins ne devraient alors pas présenter de valvulopathie,
- le choix des valvulopathies inexpliquées : il est difficile d'être absolument sûr que le diagnostic ne soit pas biaisé,
- les cas et les témoins ont des caractéristiques très différentes. Une confusion par indication (lien entre caractéristiques des patients témoins et l'absence de traitement par benfluorex) ne peut être exclue. Les témoins ont très peu de chance d'être exposés au benfluorex,
- le faible nombre de patients exposés,
- le choix de l'anomalie valvulaire (limité à la valve mitrale).

Toutefois, malgré certaines limites méthodologiques de cette l'étude, les experts et les membres de la commission considèrent que le signal d'une relation entre l'exposition au benfluorex et la survenue de valvulopathies se confirme. Ce signal est d'autant plus préoccupant que dans l'étude « REGULATE » une émergence d'anomalies morphologiques et fonctionnelles valvulaires a été observée à la suite d'une exposition d'environ un an au benfluorex (328 jours en moyenne). De plus, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne peut être exclue, notamment en raison des données d'utilisation du produit qui montrent une durée moyenne d'exposition d'environ 3 ans.

6. Conclusions de la CNPV du 29 septembre 2009 :

Les membres de la Commission Nationale de Pharmacovigilance considèrent (25 voix pour et 1 abstention), que les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex et ce, malgré certaines limites méthodologiques. De même, ils considèrent (25 voix pour et 1 abstention) que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

Il est à noter que le dépôt par le laboratoire du protocole de l'étude cas-témoin, prévu initialement pour début septembre 2009 n'a pas encore été effectué.

La CNPV a été informée de la transmission de ces données à la Commission d'AMM au plus tard le 23 octobre 2009, afin qu'elle puisse se prononcer sur la balance bénéfice- risque du produit.

REGULATE STUDY - CL3 - 00780 - 148

Mediator versus pioglitazone in association with sulfonylureas :

"A one-year multicentre, international, Randomised, double-blind study with comparison of bEnfluorex (150 mg bid or 150 mg tid) versus pioGlitazone (30 mg od or 45 mg od) in combination with sULfonylurea administered orAlly for the Treatment of type 2 diabEtes"

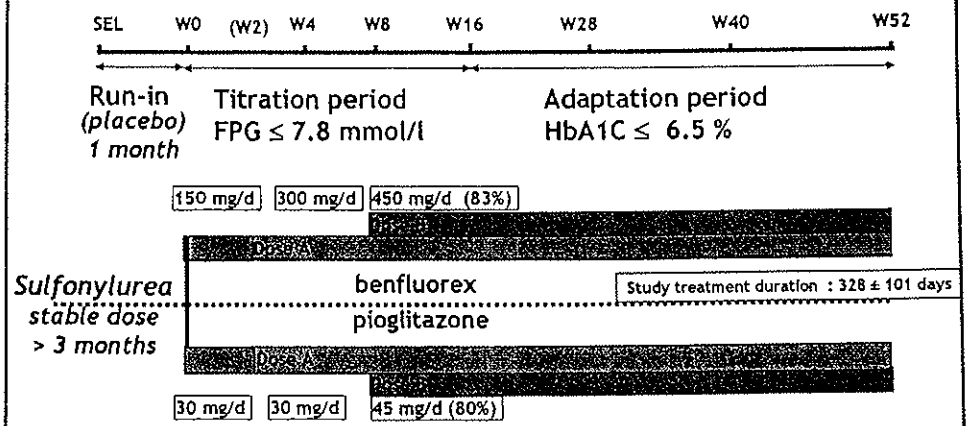
National & International Coordinator
Chairman of Scientific Committee

Pr Philippe MOULIN
Fédération d'Endocrinologie
Diabétologie Nutrition
Hôpital Cardio-vasculaire et
Pneumologique Louis Pradel
69677 BRON - Cedex

Chairman of Adjudication Committee
Member of Scientific Committee

Pr Geneviève DERUMEAUX
Service Explorations Fonctionnelles
Cardiovasculaires
Hôpital Cardio-vasculaire et
Pneumologique Louis Pradel
69677 BRON - Cedex

STUDY PLAN



8 countries - 245 centres - 847 included patients :

30 % France ; 16 % Germany ; 15 % India ; 12 % Argentina ;
9 % South Africa ; 7 % Czech Rep. ; 7 % Tunisia ; 4 % Romania

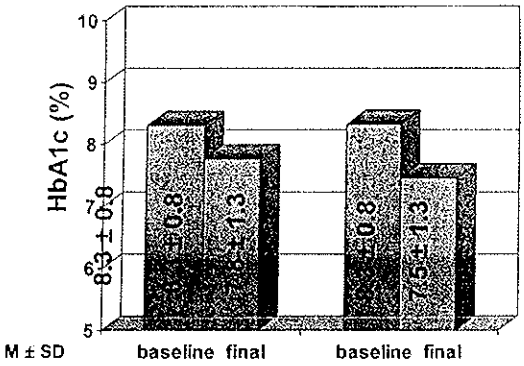
First selection 24/01/06 ; End of inclusion 01/08 ; Last visit 15/01/09

EFFICACY on HbA1c (FAS)

benfluorex n=413
- 0.54 % ±1.12***

pioglitazone n=417
- 0.88% ± 1.24***

*** *p<0.001 vs baseline*



Responders (HbA1c ≤ 7%)
BEN = 32%
PIO = 48%

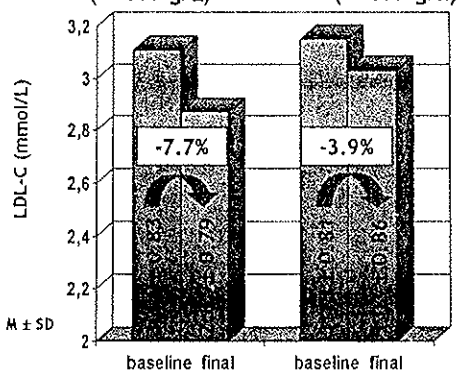
Mean difference between group adjusted on baseline and country : 0.33 %
95% CI [0.17 ; 0.49] - non inferiority test: p = 0.18

EFFICACY on LDL-cholesterol (FAS) (1-13)

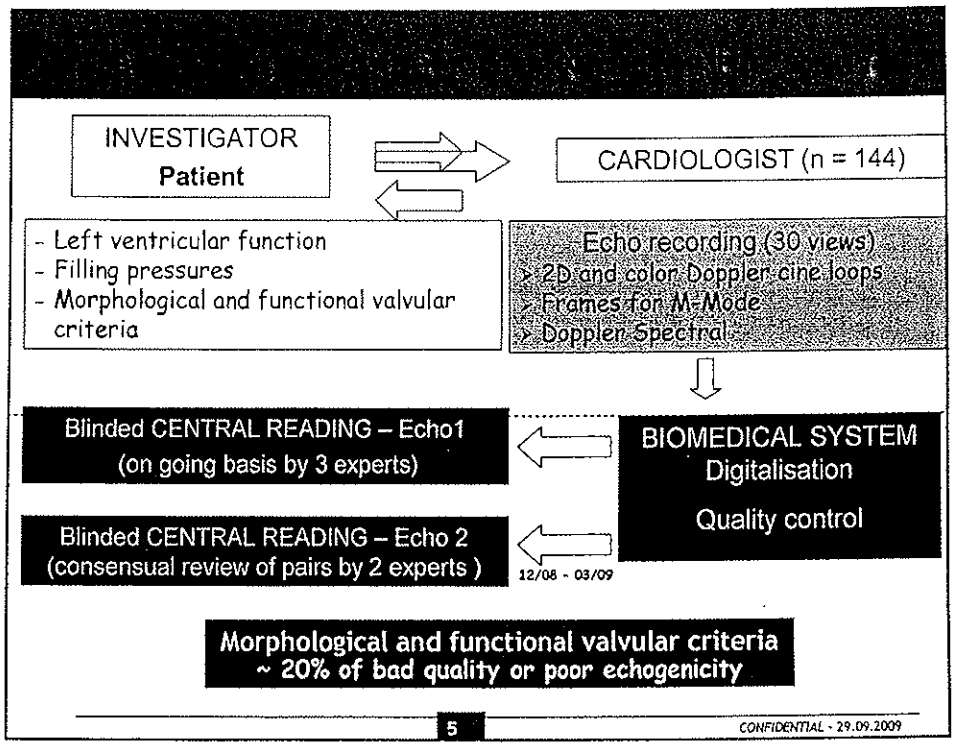
FAS

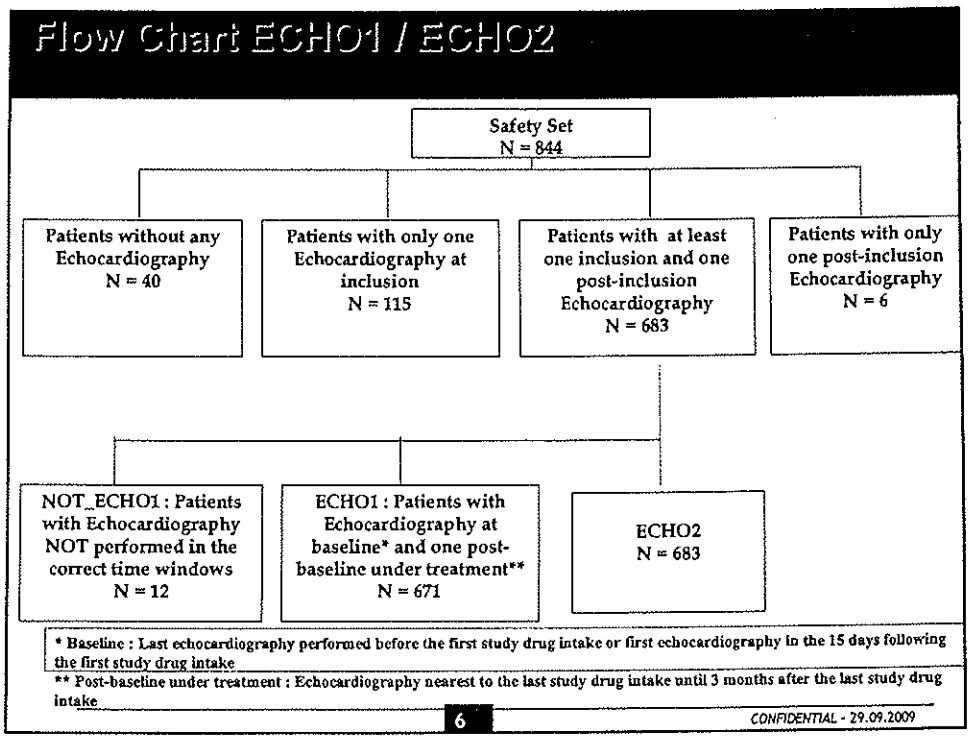
benfluorex n=396
- 0.24 ± 0.03 mmol/L
(- 0.09 g/L)

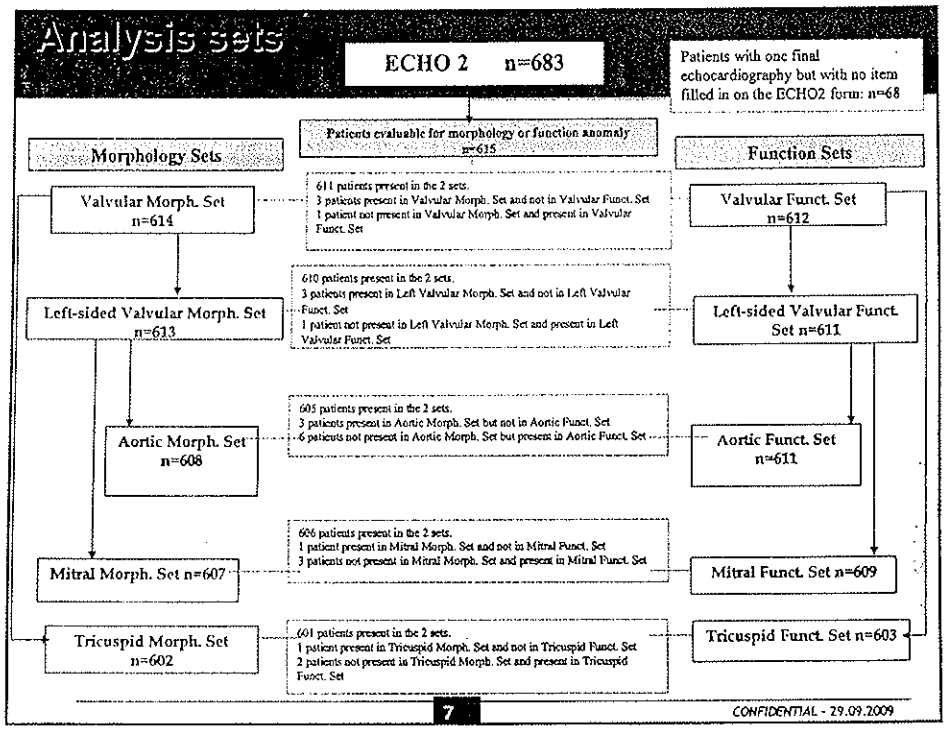
pioglitazone n=396
- 0.12 ± 0.04 mmol/L
(- 0.05 g/L)



Mean difference between groups adjusted on baseline and country :
Δ = - 0.13 / 95% CI [- 0.22 ; - 0.04] / p = 0.0047


INVESTIGATOR
Patient
CARDIOLOGIST (n = 144)
- Left ventricular function
- Filling pressures
- Morphological and functional valvular criteria
Echo recording (30 views)
> 2D and color Doppler cine loops
> Frames for M-Mode
> Doppler Spectral
Blinded CENTRAL READING – Echo1
(on going basis by 3 experts)
BIOMEDICAL SYSTEM
Digitalisation
Quality control
Blinded CENTRAL READING – Echo 2
(consensual review of pairs by 2 experts)
12/08 - 03/09
Morphological and functional valvular criteria
~ 20% of bad quality or poor echogenicity
5
CONFIDENTIAL - 29.09.2009


Flow Chart ECHO1 / ECHO2
Safety Set
N = 844
Patients without any Echocardiography
N = 40
Patients with only one Echocardiography at inclusion
N = 115
Patients with at least one inclusion and one post-inclusion Echocardiography
N = 683
Patients with only one post-inclusion Echocardiography
N = 6
NOT_ECHO1 : Patients with Echocardiography NOT performed in the correct time windows
N = 12
ECHO1 : Patients with Echocardiography at baseline* and one post-baseline under treatment**
N = 671
ECHO2
N = 683
* Baseline : Last echocardiography performed before the first study drug intake or first echocardiography in the 15 days following the first study drug intake
** Post-baseline under treatment : Echocardiography nearest to the last study drug intake until 3 months after the last study drug intake
6
CONFIDENTIAL - 29.09.2009



Morphological valvular abnormalities at baseline

	ALL	BEN	PIO
■ At least 1 abnormality on either valve :	614 314 (51.1%)	309 154 (49.8%)	305 160 (52.5%)
■ Aortic (N) :	608	306	302
Abnormal (%)	33.1	33.0	33.1
– Thickness (%)	31.1	31.1	31.1
– calcification (%)	9.5	10.8	8.3
■ Mitral (N) :	607	307	300
Abnormal (%)	41.5	40.7	42.3
– Thickness (%)	38.6	37.1	40.0
– calcification (%)	7.6	8.5%	6.7
■ Tricuspid (N) :	602	302	300
Abnormal (%)	3.5	3.3	3.7
– Thickness (%)	3.5	3.3	3.7
– calcification (%)	0	0	0

Valvular morphology - emergence

	ALL	BEN	PIO
N	614	309	305
- Emergent	12 (2.0%)	8 (2.6%)	4 (1.3%)

OR = 2.0, 95%CI [0.59 ; 6.69], *p = 0.264*

Details on emergent abnormalities *(n patients)*

Thickness	11	7	4
- Aortic	6	6	0
- Mitral	5	1	4
- Tricuspid	0	0	0
Calcification	1	1	0
- Aortic	1	1	0
- Mitral	0	0	0
- Tricuspid	0	0	0

Functional valvular abnormalities at baseline

		ALL	BEN	PIO
■ **Either valve**		612	309	303
At least 1 abnormality (%) :		**84.2**	**84.1**	**84.2**
■ **Aortic (N) :**		611	309	302
– Regurgitation	- Trivial (%)	14.9	15.9	13.9
	- Mild (%)	0.7	0	1.3
– Stenosis (%)		1.8	2.3	1.3
■ **Mitral (N) :**		609	309	300
– Regurgitation	- Trivial (%)	59.3	60.2	58.3
	- Mild (%)	1.3	1.0	1.7
	- Moderate (%)	0.2	0.3	0
– Stenosis (%)		0.5	0.3	0.2
■ **Tricuspide (N) :**		603	304	299
– Regurgitation	- Trivial (%)	71.8	68.4	75.3
	- Mild (%)	0.5	0	1.0
– Stenosis (%)		0	0	0

Valvular Functional - emergence

	ALL 612	BEN 309	PIO 303
– Emergent	115 (18.8%)	82 (26.5%)	33 (10.9%)

OR = 2.97, 95%CI [1.91 ; 4.63], *p<0.0001*

Details on emergent abnormalities

Aortic Regurgitation	45 (7.4%)	42 (13.6%)	3 (1.0%)
Mitral Regurgitation	36 (5.9%	22 (7.1%)	14 (4.7%)
Tricuspid Regurgitation	50 (8.3%)	33 (10.9%)	17 (5.7%)
Stenosis	0	0	0

Clinically relevant regurgitations grade > 1

	Aortic		Mitral		Tricuspid	
BASELINE (n)	**Ben**	**Pio**	**Ben**	**Pio**	**Ben**	**Pio**
Grade 2 - mild	0	4	3	5	0	3
Grade 3 - moderate	0	0	1	0	0	0
EMERGENCE (n)						
Grade 2 - mild	2	0	1	1	0	2
Grade 3 - moderate	0	0	0	0	0	0

OR = 0.65, 95%CI [0.11 ; 3.94], *p=0.642*

Annexe 3-79

Proposition de RCP

- Modification du libellé de l' indication:
  - Restriction aux diabétiques en échec après les antidiabétiques oraux.
  - Prescription par un spécialiste (diabétologue, endocrinologue)
- Ajout de contre-indications (4.3) :
  - Valvulopathie cardiaque
- Ajout en section 4.8 Effets indésirables :
  - Valvulopathie cardiaque

Proposition de RCP

- Ajout de mises en gardes spéciales et précautions d'emploi (4.4) :

  - ***Avant de commencer le traitement*** :

  Évaluation cardiovasculaire par échocardiographie, afin d'évaluer la présence potentielle d'une pathologie valvulaire asymptomatique.

  - ***Pendant le traitement*** :

  Surveillance des signes et symptômes d'une atteinte valvulaire cardiaque

  Suivi échocardiographique

Pr Ravaud
Département d'épidémiologie,
biostatistique et recherche clinique
GH Bichat- Claude Bernard

1

Etude cas-témoins Brest

- Difficile de « critiquer » une étude sans connaître très précisément la méthodologie utilisée
- Protocole « sommaire », 1 page recto-verso
- Peu d'informations disponibles :
  - Cas : recensement des insuffisances mitrales vues au CHU de Brest en cardiologie et chirurgie cardiaque depuis 2003 et **TRI** des observations entre insuffisances mitrales « expliquées » et « inexpliquées », cette dernière catégorie constitue les cas.
  - Témoins : appariement des cas (âge, sexe, période et unité d'hospitalisation) avec des témoins sélectionnés parmi les insuffisances mitrales « expliquées ».

2

Classification des valvulopathies et donc classification des cas et des témoins

- Réalisé par une infirmière de recherche clinique formée en fonction de mots clés
  - Compte-rendus de séjour
  - Dossier médical
  - Compte-rendu opératoire

3

Classement des cas

- Identification du signal à l'aide d'une recherche à partir de mots clés dans les compte-rendus

« atteintes valvulaires » comme code PMSI et « Benfluorex ou Médiator» dans le résumé de sortie

- Introduction du protocole de l'étude : mise en évidence rétrospectivement et prospectivement à partir de 2003 de 18 cas de valvulopathies cardiaques à type d'insuffisances multiples chez des patients exposés au Benfluorex et hospitalisés au CHU de Brest

4

Annexe 3-79

MEDIATOR : benfluorex

PHARMACOVIGILANCE
Commission nationale:
29 septembre 2009
Rapporteurs JP Kantelip
C Riché

MEDIATOR : historique

- 11 juillet 1995 : mise au point E.I.(CT)
- 30 avril 1998 : enquête officieuse E.I
- 17 décembre 1998 et 20 juillet 1999: enquête officielle
- 29 novembre 2005: enquête relative aux hypertensions artérielles pulmonaires et aux troubles neuropsychiatriques (CN)
- 27 mars 2007: mise à jour des données de pharmacovigilance et résultats de l'étude d'utilisation (CN)
- 7 juillet 2009: enquête officielle relative aux valvulopathies observées avec MEDIATOR

Valvulopathies

- 45 valvulopathies : 1998 – 2009

- 19 notifications spontanées
- 18 PMSI (Brest)
- 8 notifications sollicitées (Amiens)

Benfluorex: notifications récentes spontanées

-3 femmes de 33, 56 et 59 ans
- Durées de traitement: 6 à 12 mois, 15 ans et 6 ans
- Antécédents: HTA (2), dépression (2), angines dans l'enfance (1), surpoids (1), obésité (2), diabète type II (2), cardiopathie ischémique (1).
- HTAP sévères (2)
- Maladie mitrale(2), IA (1)
- Chirurgie (2) .

Notifications sollicitées

- 5 femmes âgées de 43 à 71 ans (52,4 ans)
- 3 hommes âgés de 53, 69 et 73 ans
- Durée du traitement de 2 à 10 ans: (3. 5 ans)
- Antécédents: HTA (4), diabète type II (4), cardiomyopathie dilatée (1), cardiopathies ischémiques (3), surpoids (2), obésité (4)
- HTAP (5)
- IM grade II-III (6), IM grade III-IV (3)
- IA grade II-III (3).
- Chirurgie: 2

Mise à jour des données de PV

- Prédominance féminine
- Durée moyenne des traitements: 3 ans
- Ages de survenue les plus fréquents: 55
- HTAP: 2
- IM+IA: 6.
- Echographies documentées
- Anatomie Pathologique peu informative
- Amplification du signal du risque de toxicité cardiaque (atteintes valvulaires) par les notifications sollicités (études en cours).

Annexe 3-80

Sécurité sociale
L'Assurance Maladie
Caisse Nationale

Le Médecin Conseil National
Adjoint au Directeur Général

Monsieur Jean MARIMBERT
Directeur général
AFSSAPS
143/147, bd Anatole France
93285 SAINT DENIS CEDEX

Date : 27 OCT. 2009

Monsieur le Professeur Didier HOUSSIN
Directeur Général de la Santé
Ministère de la Santé, de la Jeunesse, des Sports et de la Vie Associative
14, avenue Duquesne
75350 PARIS CEDEX 07 SP

N/réf. : DIR/CABMCN-D-2009-D-10139

Monsieur le Directeur général,
Monsieur le Directeur général de la santé, cher collègue,

Nous avons été informés, en marge d'un colloque sur l'épidémiologie du cancer le 12 octobre dernier, d'une relation de causalité possible entre la consommation de benfluorex (Médiator®) et certaines valvulopathies cardiaques. Après une revue rapide de la littérature sur le sujet, nous avons pris l'initiative de réaliser une enquête de cohorte exposé-non exposé dans une population de personnes diabétiques âgées de 40 à 69 ans, à partir des données chaînées du SNIIRAM et du PMSI.

Nous constatons que l'usage du benfluorex chez les malades diabétiques est associé significativement dans les deux années qui suivent à des valvulopathies de régurgitation mitrales, aortiques et tricuspidiennes, ainsi qu'à des actes chirurgicaux de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.

Nous tenions à vous informer très rapidement des conclusions de cette étude qui suggèrent fortement l'existence d'un effet indésirable sévère lié à l'utilisation de ce médicament, comme en attestent notamment les risques relatifs très élevés que nous avons calculés. Un rapport préliminaire détaillé est joint en annexe.

Je vous prie de croire, Monsieur le Directeur général, Monsieur le Directeur général de la santé, cher collègue, à l'assurance de mes sentiments les meilleurs.

Professeur Hubert ALLEMAND

PJ : Benfluorex et valvulopathies cardiaques : une étude de cohorte sur 1 092 858 personnes traitées pour diabète. Caisse nationale d'assurance maladie des travailleurs salariés, Paris, octobre 2009 ; 10 pages.

Copie : Monsieur van Roekeghem Directeur général de la CNAMTS

Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés
50, avenue du Professeur André Lemierre - 75986 Paris Cedex 20
Tél. : 01 72 60 10 00 - Fax : 01 72 60 10 10 - www.ameli.fr

Annexe 3-80

Benfluorex et valvulopathies cardiaques : une étude de cohorte sur 1 092 858 personnes traitées pour diabète

Alain Weill (alain.weill@cnamts.fr), Michel Païta, Philippe Tuppin, Philippe Ricordeau, Hubert Allemand

Caisse nationale de l'assurance maladie, Paris, France.

Rapport préliminaire du 27/10/2009

Résumé

Contexte : Plusieurs cas cliniques rapportés dans la littérature suggèrent que le benfluorex commercialisé en France depuis 1976 et dérivé de la fenfluramine pourrait être associé avec des cardiopathies valvulaires de régurgitation. Depuis le 5 avril 2007 la commission d'autorisation sur le marché a limité la prescription du benfluorex à l'indication « *adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* ». L'objectif de ce travail était de préciser, chez les personnes diabétiques, un lien éventuel entre une exposition au benfluorex et une valvulopathie cardiaque de régurgitation et de tester dans l'affirmative un effet dose.

Méthode : étude de cohorte de type exposé-non exposé à partir des données du système national inter-régime de l'assurance maladie (SNIIRAM). Etaient éligibles les patients diabétiques traités (antidiabétiques oraux et/ou insuline) en 2006 et âgés de 40 à 69 ans. Les cas exposés étaient enregistrés de façon passive et définis par la délivrance et le remboursement en 2006 de benfluorex. Après chaînage des données les événements recherchés à l'année n+1 et n+2 dans le PMSI 2007 et 2008 étaient une hospitalisation pour une insuffisance valvulaire toutes causes confondues, une hospitalisation pour une insuffisance mitrale et chirurgie de remplacement valvulaire sous circulation extra-corporelle pour une insuffisance valvulaire toutes causes confondues.

Résultats : les résultats portaient sur 1 092 858 diabétiques de 40 à 69 ans dont 43 208 exposés au benfluorex en 2006. Le risque d'hospitalisation en 2007 pour insuffisance valvulaire cardiaque était de 81 pour 100 000 dans le groupe exposé vs 29 pour 100 000 dans le groupe non exposé RR = 2,77 IC 95[1,95 ;3,93]. Le risque d'hospitalisation pour insuffisance mitrale était de 53 pour 100 000 dans le groupe exposé vs 20 pour 100 000 dans le groupe non exposé RR = 2,66 IC 95[1,7 ;4,1]. Le risque de chirurgie en 2007 avec un remplacement valvulaire sous circulation extracorporelle (CEC) pour une insuffisance

valvulaire toutes causes confondues était de 30 pour 100 000 dans le groupe exposé au benfluorex vs 9 pour 100 000 dans le groupe non exposé RR =3,4 [1,9 ; 6,1]. Parmi les 13 personnes diabétiques exposées et ayant subi un remplacement valvulaire sous CEC en 2007 une était décédée en milieu d'année 2008. Pour les exposés au benfluorex en 2006 les risques absolus et les risques relatifs étaient en 2008 très proches de ceux observés en 2007. Le risque relatif des exposés au benfluorex de chirurgie valvulaire sous CEC était identique (3,4).

Conclusion :

1. L'usage du Benfluorex chez les diabétiques est associé significativement dans les deux années qui suivent à des valvulopathies de régurgitation mitrales, aortiques et tricuspidiennes et à des chirurgies de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.
2. Transmission du dossier en urgence le 27/10/2009 à l'Agence française de sécurité sanitaire des produits de santé et à la Direction générale de la santé
3. Le SNIIRAM avec le chainage PMSI peut contribuer à montrer, en condition réelle d'utilisation pour des médicaments, des effets indésirables sévères mais restés longtemps méconnus ou mal évalués.

Mots clés : benfluorex, valvulopathie, insuffisance mitrale, effets indésirables, bases de données, SNIIRAM, PMSI

Le travail a été débuté le 13/10/2009 et le rapport préliminaire a été adressé le 27/10/2009 à l'Agence française de sécurité sanitaire des produits de santé et à la Direction générale de la santé.

Introduction

Aux Etats-Unis et en Europe la plupart des anorexigènes fenfluraminiques ont été retirés du marché et interdits en 1977 après la constatation d'effets indésirables rares mais graves : l'hypertension artérielle pulmonaire et les insuffisances valvulaires cardiaques[1,2,3].

Plusieurs cas cliniques rapportés dans la littérature suggèrent que le benfluorex commercialisé en France depuis 1976 et dérivé de la fenfluramine pourrait être également associé avec des cardiopathies valvulaires de régurgitation[4,5,6]. Depuis le 5 avril 2007 la commission d'autorisation sur le marché a limité en France la prescription du benfluorex à l'indication « *adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* »[7].

L'objectif de ce travail était de préciser, chez les personnes diabétiques, un lien éventuel entre une exposition au benfluorex et la survenue d'une valvulopathie cardiaque de régurgitation. En cas de liaison significative l'objectif secondaire était de vérifier s'il existait une relation dose-effets.

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[1] Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997 Aug 28;337(9):581-8. Erratum in: N Engl J Med 1997 Dec 11;337(24):1783.

[2] Le 15 septembre 1997 les laboratoires Servier annoncent cesser la commercialisation de l'anorexigène dexfenfluramine (Redux® au USA et Isoméride® en France). Les laboratoires anticipaient ainsi de quelques heures la décision des autorités sanitaires FDA de suspendre les autorisations de mise sur le marché

[3] Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Bégaud B. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996 Aug 29;335(9):609-16.

[4] Noize P, Sauer M, Bruneval P, Moreau M, Pathak A, Bagheri H, Montastruc JL. Valvular heart disease in a patient taking benfluorex. Fundam Clin Pharmacol. 2006 Dec;20(6):577-8.Click here to read Links.

[5] Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C, Carlhant-Kowalski D, Sitbon O, Simonneau G, Humbert M. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J. 2009 Mar;33(3):684-8.

[6] En juin 2005 l'agence espagnole du médicament a retiré de la commercialisation le benfluorex pour trouble cardiaque grave.

[7] Commission nationale de pharmacovigilance. Compte rendu de la réunion du mardi 27 mars 2007. http://www.afssaps.fr/var/afssaps_site/storage/original/application/df5625a7bf8b9ebd4eec8f0f54e34315.pdf (consulté le 26/10/2009)

Méthode

Etude de cohorte de type exposé-non exposé à partir des données anonymes du système national inter-régime de l'assurance maladie (SNIIRAM)[8,9,10].

Etaient éligibles les patients diabétiques traités en 2006 et âgés de 40 à 69 ans en 2006. Le diabète traité était défini par le remboursement à au moins trois dates différentes en 2006 d'antidiabétiques oraux et/ou insuline appartenant à la classe ATC A10. Cette définition est similaire à celle utilisée pour estimer la prévalence du diabète traité en France [11] et à celle de l'étude Entred 2007[12] (tableau 1). La classe d'âge 40-69 ans a été choisie afin d'assurer une homogénéité de la population étudiée et de tenir compte de l'âge des cas ponctuels rapportés[13,14].

Les cas exposés enregistrés de façon passive étaient définis par la délivrance et le remboursement en 2006 de benfluorex, quelque soit la dose et la forme et le nombre de délivrance. Les cas non exposés étaient définis par l'absence de remboursement de benfluorex en 2006 (tableau 1). Après chaînage des données les événements recherchés à l'année n+1 et n+2 dans le PMSI 2007 et 2008 étaient une hospitalisation pour une insuffisance valvulaire toutes valves et toutes causes confondues, une hospitalisation pour une insuffisance mitrale et un remplacement valvulaire pour une insuffisance valvulaire toutes causes confondues (tableau 2).

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[8] Lenormand F. Le système d'information de l'assurance maladie, le SNIIRAM et les échantillons de bénéficiaires. Journal de la Société française de statistique. 2005; 146(3):47-73.

[9] de Roquefeuil L, Studer A, Neumann A, Mérlière Y. L'échantillon généraliste de bénéficiaires : représentativité, portée et limites. Prat Organ Soins 2009;40(3):213-223.

[10] Fender P, Weill A. [Epidemiology, public health and medical rates databases]. Rev Epidemiol Sante Publique. 2004 Apr;52(2):113-7.

[11] Kusnik-Joinville O, Weill A, Ricordeau P, Allemand H. Diabète traité en France en 2007 : un taux de prévalence proche de 4% et des disparités géographiques croissantes. Bulletin épidémiologique hebdomadaire 2008;43-:409-413.

[12] Protocole de l'étude Entred 2007-2010.
http://www.invs.sante.fr/publications/entred/entred%5F2007%5F2010/protocole.htm

[13] Noize P, Sauer M, Bruneval P, Moreau M, Pathak A, Bagheri H, Montastruc JL. Valvular heart disease in a patient taking benfluorex. Fundam Clin Pharmacol. 2006 Dec;20(6):577-8.Click here to read Links.

[14] Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C, Carlhant-Kowalski D, Sitbon O, Simonneau G, Humbert M. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J. 2009 Mar;33(3):684-8.

L'utilisation du SNIIRAM par les agents habilités de la Cnamts a fait l'objet d'un avis favorable de la Cnil en novembre 2001 et d'un arrêté ministériel du 11 avril 2002 relatif à sa mise en œuvre. En octobre 2007, un second arrêté a permis l'utilisation de la variable décès avec la date exacte issue des données de statut vital de l'Insee et de la Cnav.

Table 1 : critères utilisés pour l'inclusion des personnes dans la cohorte de diabétiques et pour définir l'exposition au benfluorex

patients de la cohorte	au moins 3 dates de remboursement différentes en 2006 de médicaments antidiabétiques (classe ATC A10) âge compris entre 40 et 69 ans en 2006
exposés	au moins un remboursement de benfluorex en 2006 cip = 3175579 (mediator® 150 mg boite de 30) cip = 3175591 (mediator® 150 mg boite de 100)
non exposés	pas de remboursement de benfluorex en 2006

Table 2 : critères utilisés pour définir la maladie valvulaire cardiaque de régurgitation

hospitalisation pour insuffisance valvulaire	PMSI MCO avec un diagnostic principal ou relié = I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale I351 Insuffisance (de la valvule) aortique non rhumatismale I061 Insuffisance (de la valvule) aortique rhumatismale I361 Insuffisance (de la valvule) tricuspide non rhumatismale I071 Insuffisance (de la valvule) tricuspide rhumatismale
hospitalisation pour insuffisance mitrale	PMSI MCO avec un diagnostic principal ou relié = I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale
Chirurgie de remplacement valvulaire avec circulation extra corporelle pour insuffisance valvulaire	PMSI MCO avec un des 3 GHM suivants GHM 05C02Z Chirurgie de remplacement valvulaire avec circulation extracorporelle et avec cathétérisme cardiaque ou coronarographie GHM 05C03V Chirurgie de remplacement valvulaire avec circulation extracorporelle, sans cathétérisme cardiaque, ni coronarographie, sans CMA GHM 05C03W Chirurgie de remplacement valvulaire avec circulation extracorporelle, sans cathétérisme cardiaque, ni coronarographie, avec CMA et un diagnostic principal ou relié parmi les six suivants I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale I351 Insuffisance (de la valvule) aortique non rhumatismale I061 Insuffisance (de la valvule) aortique rhumatismale I361 Insuffisance (de la valvule) tricuspide non rhumatismale I071 Insuffisance (de la valvule) tricuspide rhumatismale

Résultats :

Les résultats portaient sur 1 092 860 diabétiques de 40 à 69 ans dont 43 208 exposés au benfluorex en 2006.

Table 3 : caractéristiques des diabétiques exposés et de non-exposés

	exposés	non-exposés
effectifs	43 208	1 049 650
âge (moyenne)	57,24	58,15
%femme	56,38	42,39
%homme	43,62	57,61

Le risque d'hospitalisation en 2007 pour insuffisance valvulaire cardiaque était de 81 pour 100 000 dans le groupe exposé vs 29 pour 100 000 dans le groupe non exposé RR = 2,77 IC 95[1,95 ;3,92]. Le risque d'hospitalisation pour insuffisance mitrale rhumatismale et non rhumatismale était de 53 pour 100 000 dans le groupe exposé vs 20 pour 100 000 dans le groupe non exposé RR = 2,66 IC 95[1,73 ;4,09]. Le risque de chirurgie en 2007 avec un remplacement valvulaire pour une insuffisance valvulaire toutes causes confondues était de 30 pour 100 000 dans groupe exposé au benfluorex vs 9 pour 100 000 dans le groupe non exposé RR =3,4 [1,90 ; 6,06]. Parmi les 13 personnes diabétiques de 40 à 69 ans exposées au benfluorex et ayant subi un remplacement valvulaire en 2007 une était décédée en milieu d'année 2008.

Pour la même population exposé en 2006 le risque d'hospitalisation en 2008 pour insuffisance valvulaire cardiaque était de 74 pour 100 000 dans le groupe exposé vs 27 pour 100 000 dans le groupe non exposé RR = 2,66 IC 95[1,84-3,83]. Le risque d'hospitalisation pour insuffisance mitrale rhumatismale et non rhumatismale était de 37 pour 100 000 dans le groupe exposé vs 17 pour 100 000 dans le groupe non exposé RR = 2,13 [1,28-3,56]. Le risque de chirurgie en 2008 avec un remplacement valvulaire pour une insuffisance valvulaire toutes causes confondues était de 25,4 pour 100 000 dans groupe exposé au benfluorex vs 7,5 pour 100 000 dans le groupe non exposé RR =3,4 [1,80-6,35]. Parmi les 11 personnes diabétiques exposées au benfluorex et ayant subi un remplacement valvulaire sous circulation extracorporelle en 2008 aucune n'était décédée à la date du 30 juin 2009.

La relation dose-effet a été testée pour le risque d'hospitalisation pour insuffisance valvulaire en 2007

Table 4 : relation entre la dose de benfluorex délivrée en 2006 et le risque d'hospitalisation en 2007 pour insuffisance valvulaire pour des personnes diabétiques de 40 à 69 ans.

dose cumulée de benfluorex* remboursée en 2006	effectif	Risque absolu d'hospitalisation pour insuffisance valvulaire en 2007 pour 100 000 personnes	risque relatif
0 gr	1 049 650	29,2	1.00
13,5gr à 40,5 gr	17 603	51,1	1.75
41 gr à 175,5 gr	25 605	101,6	3.47
41gr à 90 gr	*8 832*	*101,9*	*3.48*
91gr à 135 gr	*8 101*	*111,9*	*3.80*
136gr à 175,5 gr	*8 672*	*92,2*	*3.15*

* un comprimé de benfluorex est dosé à 150 mg

Les premiers constats montrent que les personnes ayant eu des doses cumulées plus faibles en 2006 ont eu de moindre risque de développer une insuffisance valvulaire avec une hospitalisation. A partir de 41 grs, soit environ 240 comprimés dosés à 150 mg en 2006, il n'apparaissait pas de dose effet.

Discussion

Ce travail conforte l'hypothèse de départ, à savoir l'existence d'un lien entre benfluorex et valvulopathie de régurgitation.

Il existait une relation positive entre le fait d'avoir fait l'usage (ou plus exactement d'avoir été remboursé) de benfluorex en 2006 et le fait d'avoir été hospitalisé en 2007 et en 2008 pour une insuffisance valvulaire cardiaque (risque relatif 2007 = 2.8 ; RR 2008 = 2.7), une insuffisance mitrale (RR 2007 = 2.8 ; RR 2008 = 2.1), une chirurgie de remplacement valvulaire avec circulation extracorporelle pour insuffisance valvulaire (RR 2007= 3.4 ; RR 2008 = 3.4).

Le choix d'un protocole d'étude observationnelle de type cohorte exposés-non exposés est réputé plus proche de l'approche expérimentale[15] et permet de calculer un risque absolu et relatif. L'estimation d'un risque absolu est importante pour une décision de santé publique. De plus ce choix s'est imposé en raison de l'impossibilité de disposer d'un codage

[15] Boyer J, Hemon D,... Chapitre 8 in Epidémiologie : principes et méthodes quantitatives. Les ed. INSERM, 1995.

étiologique des valvulopathies de régurgitation dans le PMSI (valvulopathies dégénératives, rhumatismales, post endocardite infectieuse, congénitale, ischémique, secondaire à un dysfonctionnement ventriculaire gauche, post radique, tumorale..). Il n'existait par exemple que deux codes de la classification internationale des maladies (CIM-10) pour l'insuffisance mitrale et les experts interrogés s'accordent sur le caractère très imprécis de l'utilisation d'un code ou de l'autre. En testant l'hypothèse « valvulopathie de régurgitation tous types confondus, les biais de classement potentiels étaient plus limités, mais la puissance de l'étude en était affectée.

Un élément positif est d'utiliser pour le suivi de cohorte l'enregistrement passif des expositions par la télétransmission par les pharmaciens d'officine aux CPAM pour obtenir le remboursement du benfluorex, données qui enrichissent de façon exhaustive le SNIIRAM ; l'enregistrement des maladies était également passif par les médecins qui complètent dans les résumés de sortie standardisés (RSS puis RSA) les diagnostics principaux et reliés[16] et les actes médicaux principaux, dit classant. Ces données sont enregistrées dans le PMSI MCO. Le chaînage de deux sources d'information totalement indépendantes permet d'éliminer en principe les biais de classement différentiels sur l'exposition comme sur la maladie.

Plusieurs facteurs peuvent contribuent à minimiser les risques relatifs obtenus.

1. L'exposition évaluée de façon dichotomique est sensiblement surestimée. Une personne ayant eu un remboursement d'une seule boite de benfluorex est présumée exposée, alors même, quelle n'a peut-être absorbé aucun comprimé. Les erreurs d'attribution de bénéficiaires sont en principe rares mais toujours possibles et contribuent également à sous estimer le risque. L'enquête « instauration des traitements médicaments hypolipémiants » menées en 2002 avait retrouvé parmi les nouveaux consommants ayant une seule délivrance ponctuelle jusqu'à 5% d'erreur de bénéficiaires [17]. Nous ne sommes pas dans cette situation car il ne s'agit pas d'une population débutant un traitement, mais des erreurs d'attribution de bénéficiaires entre conjoints notamment dans le cas présent sont toujours possibles.
2. Les non-exposés pourraient avoir été exposés en 2005 ou antérieurement ou à partir de 2007 ; ce dernier point pourrait être corrigé en introduisant dans l'algorithme des

[16] Le diagnostic principal est le motif qui a mobilisé l'essentiel de l'effort médical et soignant au cours de l'hospitalisation dans l'unité médicale. Le diagnostic relié est renseigné lorsque le diagnostic principal est insuffisant. Il rend compte de la prise en charge du patient en termes médico-économiques. C'est une maladie chronique ou de longue durée, ou un état permanent, présent au moment du séjour en hôpital.

[17] Saba G, Weill A, Païta M, Ricordeau Ph, Bourrel R, Nouailher-Lagarde M, Dematons MN, Crochet B, Guilhot J, Fender P, Allemand H et le groupe Dyslipidémie. Instauration des traitements médicamenteux hypolipémiants en France en 2002. Rev Med Ass Maladie 2003;34,4:221-231. Rapport complet http://fulltext.bdsp.ehesp.fr/Cnamts/Etudes/2003/traitementshypolipemiants.pdf?1M4M8-44714-XK96X-D1KX6-81X49

non-exposés le fait de n'avoir pas eu de remboursement en 2006 mais aussi en 2007 et 2008 ou encore avant l'effet indésirable recherchés.

3. Tous les patients diabétiques traités ne sont pas en théorie concernés par une éventuelle indication du benfluorex « *AMM limitée aux diabétiques avec surcharge pondérale* ». Un IMC < à 25 n'était retrouvé en 2007 que chez 20 % des diabétiques de type 2 et 80% était en surpoids ou obèse[18]. Encore faut-il se souvenir qu'en 2006 le benfluorex bénéficiait également de l'indication « adjuvant au régime adapté dans les hypertriglycéridémie ». En revanche l'inclusion de diabétique de type 1 dans l'enquête (5,6%) d'après l'étude entred[19] dans le groupe non exposé contribue à diminuer le risque relatif calculé.
4. Le caractère non spécifique « des insuffisances valvulaires tous types confondus » avec notamment des insuffisances dégénératives ou rhumatismales (principales causes habituelles dans cette tranche d'âge de l'insuffisance mitrale) qui ne peuvent être causées par le benfluorex diminue fortement le risque relatif calculé.
5. Un suivi limité à deux années immédiatement après l'année où l'exposition est enregistrée pourrait également diminuer le risque relatif.

Dans ces conditions le fait d'observer un risque relatif de près de 3 renforce d'autant l'hypothèse d'un lien très fort avec un risque relatif possiblement beaucoup plus élevé (plus de 10 selon toute vraisemblance).

Le jugement de causalité : plusieurs arguments peuvent militer en faveur d'une possible relation de cause à effet.

1. La connaissance d'un mécanisme d'action décrit antérieurement à cette étude pour les fenfluraminiques sérotoninergiques. Des études physiopathologiques ont expliqué les mécanismes en cause : activation des récepteurs sérotoninergiques présents à la surface des vaisseaux pulmonaires et des valves cardiaques par le métabolite toxique norfenfluramine.
2. Une relation dose effet qui semble se dessiner. Il faudrait pour démonter formellement cette relation connaître la totalité de la consommation dans les années antérieures.
3. Les résultats d'une étude cas-témoins menée par des cliniciens qui conclurait à une association benfluorex et valvulopathie spécifique serait un argument décisif en faveur de la relation de cause à effet.

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[18] Anne Fagot-Campagna , Sandrine Fosse, Candice Roudier, Isabelle Romon, Freddy Penfornis, Pierre Lecomte, Isabelle Bourdel-Marchasson, Michèle Chantry, Jean Deligne, Cécile Fournier, Nathalie Poutignat, Alain Weill, Alain Paumier, Eveline Eschwège, pour le comité scientifique d'Entred*Caractéristiques, risque vasculaire et complications chez les personnes diabétiques en France métropolitaine : d'importantes évolutions entre Entred 2001 et Entred 2007. BEH 2D09 ; 42-43,450-54 (sous presse).

[19] Cf réf 18.

Il convient toutefois d'indiquer que nos conclusions ne sont généralisables que dans la population de diabétiques de 40 à 59 ans. Si d'autres études s'avéraient nécessaire il serait toutefois prudent de suspendre temporairement le médicament. La limitation à une population homogène diabétique de 40-69 ans a permis de limiter certains facteurs de confusion. Les personnes traitées par médiator n'étaient en 2006 que dans 17% des cas diabétiques traités par hypoglycémiants oraux et/ou insuline. Des résultats non présentés dans ce rapport préliminaire sont également en faveur d'un risque relatif élevé et significatif de valvulopathie de régurgitation pour les non-diabétques.

Les traditionnelles limites des enquêtes de cohorte longue et coûteuses ont pu être surmontées. Cette enquête a pu être menée en moins de deux semaines par des personnes de l'assurance maladie expérimentées sur les analyses de données issues du SNIIRAM. Ceci conforte l'intérêt des bases de données médico-administratives chaînant SNIIRAM, PMSI, statut vital issu des données de l'Insee et de la Cnav et leur utilisation par des personnes en maitrisant la complexité.

L'ensemble des résultats présentés nous conduisent à suggérer à la tutelle un retrait immédiat de la commercialisation et un arrêt du remboursement de benfluorex dont l'effet est « modeste et mal évalué » et les effets indésirables potentiellement très sévères. Dans ce contexte la balance bénéfice-risque ne parait pouvoir être analysée que défavorablement. Selon les données de la cnamts il y avait en 2006 pour le seul régime général 340 000 personnes traitées en 2006, 320 000 en 2007 et 275 000 en 2008.

Conclusion :

1. L'usage du Benfluorex chez les diabétiques est associé significativement dans les deux années qui suivent à des valvulopathies de régurgitation mitrales, aortiques et tricuspidiennes et à des chirurgies de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.
2. Transmission du dossier en urgence le 27/10/2009 à l'Agence française de sécurité sanitaire des produits de santé et à la Direction générale de la santé
3. Le SNIIRAM avec le chainage PMSI et statut vital peut contribuer à montrer, en condition réelle d'utilisation pour des médicaments, des effets indésirables sévères mais restés longtemps mal évalués ou méconnus parfois depuis plusieurs dizaines d'années.

Benfluorex et valvulopathies cardiaques : une étude de cohorte sur 1 048 173 personnes traitées pour diabète

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Rapport final du 09/11/2009

Résumé

Contexte : Plusieurs cas cliniques rapportés dans la littérature suggèrent que le benfluorex commercialisé en France depuis 1976 et dérivé de la fenfluramine pourrait être associé avec des cardiopathies valvulaires de régurgitation. Depuis le 5 avril 2007 la commission d'autorisation sur le marché a limité la prescription du benfluorex à l'indication « *adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* ». L'objectif de ce travail était de préciser, chez les personnes diabétiques, un lien éventuel entre une exposition au benfluorex et une valvulopathie cardiaque de régurgitation et de tester dans l'affirmative un effet dose.

Méthode : étude de cohorte de type exposé-non exposé à partir des données du système national inter-régime de l'assurance maladie (SNIIRAM). Etaient éligibles les patients diabétiques traités (antidiabétiques oraux et/ou insuline) en 2006 et âgés de 40 à 69 ans. Les cas exposés étaient enregistrés de façon passive et définis par la délivrance et le remboursement en 2006 de benfluorex. Après chaînage des données les événements recherchés à l'année n+1 et n+2 dans le PMSI 2007 et 2008 étaient une hospitalisation pour une insuffisance valvulaire toutes causes confondues, une hospitalisation pour une insuffisance mitrale, une hospitalisation pour une insuffisance aortique et une hospitalisation avec chirurgie de remplacement valvulaire sous circulation extra-corporelle pour une insuffisance valvulaire toutes causes confondues. Les risques relatifs sont présentés bruts et ajustés sur l'âge, le sexe et la présence d'une ALD cardio-vasculaire.

Résultats : les résultats portaient sur 1 048 173 diabétiques de 40 à 69 ans dont 43 044 exposés au benfluorex en 2006. Le risque d'hospitalisation en 2007 pour insuffisance valvulaire cardiaque était de 81 pour 100 000 dans le groupe exposé au benfluorex en 2006 vs 28 pour 100 000 dans le groupe non exposé, soit un risque relatif de 2,9 [2,0 ;4,1] et un RR ajusté de 3,1 [2,2 ;4,5]. Les risques relatifs ajustés d'hospitalisation pour insuffisance mitrale

et insuffisance aortique étaient respectivement de 3,0 [1,9 ;4,7] et de 4,1[2,3 ;7,4]. Le risque de chirurgie en 2007 avec un remplacement valvulaire pour une insuffisance valvulaire toutes causes confondues était de 30 pour 100 000 dans groupe exposé au benfluorex vs 8 pour 100 000 dans le groupe non exposé, soit un RR ajusté de 3,7[2,1 ;6,8]. Parmi les 13 personnes diabétiques de 40 à 69 ans exposées au benfluorex et ayant subi un remplacement valvulaire en 2007 une était décédée en milieu d'année 2008. Pour les exposés au benfluorex en 2006 les risques absolus et les risques relatifs étaient en 2008 très proches de ceux observés en 2007. Ainsi, le risque relatif ajusté des exposés au benfluorex en 2006 de chirurgie valvulaire sous CEC en 2008 était de 4,2 [2,2 ;8,1].

Par ailleurs, les personnes ayant eu des doses cumulées plus faibles en 2006 ont eu de moindre risque de développer une insuffisance valvulaire avec une hospitalisation en 2007.

Conclusion :

1. L'usage du Benfluorex chez les diabétiques en 2006 était associé significativement dans les deux années qui suivaient à des valvulopathies de régurgitation mitrales et aortiques et à des chirurgies de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.
2. Transmission en urgence le 27/10/2009 du rapport préliminaire à l'Agence française de sécurité sanitaire des produits de santé et à la Direction générale de la santé.
3. Le SNIIRAM avec le chainage PMSI peut contribuer à montrer, en condition réelle d'utilisation pour des médicaments, des effets indésirables sévères mais restés longtemps méconnus ou mal évalués.

Mots clés : benfluorex, valvulopathie, insuffisance mitrale, effets indésirables, bases de données, SNIIRAM, PMSI

Le travail a été débuté le 13/10/2009 et le rapport préliminaire a été adressé le 27/10/2009 à l'Agence française de sécurité sanitaire des produits de santé (Afssaps) et à la Direction générale de la santé. Le rapport final a été adressé à l'Afssaps le 9/11/2009.

1. Introduction

Aux Etats-Unis et en Europe la plupart des anorexigènes fenfluraminiques ont été retirés du marché et interdits en 1997 après la constatation d'effets indésirables rares mais graves : l'hypertension artérielle pulmonaire et les insuffisances valvulaires cardiaques[1,2,3].

Plusieurs cas cliniques rapportés dans la littérature suggèrent que le benfluorex commercialisé en France depuis 1976 et dérivé de la fenfluramine pourrait être également associé avec des cardiopathies valvulaires de régurgitation[4,5,6]. Depuis le 5 avril 2007 la commission d'autorisation sur le marché a limité en France la prescription du benfluorex à l'indication « *adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* »[7].

L'objectif de ce travail était de préciser, chez les personnes diabétiques, un lien éventuel entre une exposition au benfluorex et la survenue d'une valvulopathie cardiaque de régurgitation. En cas de liaison significative l'objectif secondaire était de vérifier s'il existait une relation dose-effets.

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[2] Le 15 septembre 1997 les laboratoires Servier annoncent cesser la commercialisation de l'anorexigène dexfenfluramine (Redux® au USA et Isoméride® en France). Les laboratoires anticipaient ainsi de quelques heures la décision des autorités sanitaires FDA de suspendre les autorisations de mise sur le marché

[3] Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Bégaud B. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996 Aug 29;335(9):609-16.

[4] Noize P, Sauer M, Bruneval P, Moreau M, Pathak A, Bagheri H, Montastruc JL. Valvular heart disease in a patient taking benfluorex. Fundam Clin Pharmacol. 2006 Dec;20(6):577-8.Click here to read Links.

[5] Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C, Carlhant-Kowalski D, Sitbon O, Simonneau G, Humbert M. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J. 2009 Mar;33(3):684-8.

[6] Rafel Ribera J, Casañas Muñoz R, Anguera Ferrando N, Batalla Sahún N, Castro Cels A, Pujadas Capmany R. Valvular heart disease associated with benfluorex. Rev Esp Cardiol. 2003 Feb;56(2):215-6.

En juin 2005 l'agence espagnole du médicament a retiré de la commercialisation le benfluorex pour trouble cardiaque grave.

[7] Commission nationale de pharmacovigilance. Compte rendu de la réunion du mardi 27 mars 2007. http://www.afssaps.fr/var/afssaps_site/storage/original/application/df5625a7bf8b9ebd4eec8f0f54e34315.pdf (consulté le 26/10/2009)

2. Méthode

Etude de cohorte de type exposé-non exposé à partir des données anonymes du système national inter-régime de l'assurance maladie (SNIIRAM)[8,9,10].

Etaient éligibles les patients diabétiques traités en 2006, âgés de 40 à 69 ans en 2006 et non décédés au 31/12/2006. Le diabète traité était défini par le remboursement à au moins trois dates différentes en 2006 d'antidiabétiques oraux et/ou insuline appartenant à la classe ATC A10. Cette définition est similaire à celle utilisée pour estimer la prévalence du diabète traité en France [11] et à celle de l'étude Entred 2007[12] (tableau 1). La classe d'âge 40-69 ans a été choisie afin d'assurer une homogénéité de la population étudiée et de tenir compte de l'âge des cas ponctuels rapportés[13,14].

Les cas exposés enregistrés de façon passive étaient définis par la délivrance et le remboursement en 2006 de benfluorex, quelque soit la dose, la forme et le nombre de délivrance. Les cas non exposés étaient définis par l'absence de remboursement de benfluorex en 2006, en 2007 et en 2008 (tableau 1). Après chaînage des données les événements recherchés à l'année n+1 et n+2 dans le PMSI 2007 et 2008 étaient une hospitalisation pour une insuffisance valvulaire toutes valves et toutes causes confondues, une hospitalisation pour une insuffisance mitrale, une insuffisance aortique et une hospitalisation avec remplacement valvulaire pour une insuffisance valvulaire toutes causes confondues (tableau 2). Les risques relatifs (nombre de personnes malades chez les exposés/

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[8] Lenormand F. Le système d'information de l'assurance maladie, le SNIIRAM et les échantillons de bénéficiaires. Journal de la Société française de statistique. 2005; 146(3):47-73.

[9] de Roquefeuil L, Studer A, Neumann A, Merlière Y. L'échantillon généraliste de bénéficiaires : représentativité, portée et limites. Prat Organ Soins 2009;40(3):213-223.

[10] Fender P, Weill A. [Epidemiology, public health and medical rates databases]. Rev Epidemiol Sante Publique. 2004 Apr;52(2):113-7.

[11] Kusnik-Joinville O, Weill A, Ricordeau P, Allemand H. Diabète traité en France en 2007 : un taux de prévalence proche de 4% et des disparités géographiques croissantes. Bulletin épidémiologique hebdomadaire 2008;43-:409-413.

[12] Protocole de l'étude Entred 2007-2010.
http://www.invs.sante.fr/publications/entred/entred%5F2007%5F2010/protocole.htm

[13] Noize P, Sauer M, Bruneval P, Moreau M, Pathak A, Bagheri H, Montastruc JL. Valvular heart disease in a patient taking benfluorex. Fundam Clin Pharmacol. 2006 Dec;20(6):577-8.

[14] Boutet K, Frachon I, Jobic Y, Gut-Gobert C, Leroyer C, Carlhant-Kowalski D, Sitbon O, Simonneau G, Humbert M. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J. 2009 Mar;33(3):684-8.

nombre de personnes malades chez les non-exposés) sont présentés bruts et ajustés sur l'âge, le sexe et le statut d'ALD cardiovasculaire en 2006.

L'utilisation du SNIIRAM par les agents habilités de la Cnamts a fait l'objet d'un avis favorable de la Cnil en novembre 2001 et d'un arrêté ministériel du 11 avril 2002 relatif à sa mise en œuvre. En octobre 2007, un second arrêté a permis l'utilisation de la variable décès avec la date exacte issue des données de statut vital de l'Insee et de la Caisse ationale de l'assurance vieillesse.

Table 1 : critères utilisés pour l'inclusion des personnes dans la cohorte de diabétiques et pour définir l'exposition au benfluorex

patients de la cohorte	au moins 3 dates de remboursement différentes en 2006 de médicaments antidiabétiques (classe ATC A10) âge compris entre 40 et 69 ans en 2006
exposés	au moins un remboursement de benfluorex en 2006 cip = 3175579 (mediator® 150 mg boite de 30) cip = 3175591 (mediator® 150 mg boite de 100)
non exposés	pas de remboursement de benfluorex en 2006, en 2007 et 2008

Table 2 : critères utilisés pour définir la maladie valvulaire cardiaque de régurgitation

hospitalisation pour insuffisance valvulaire	PMSI MCO avec un diagnostic principal ou relié = I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale I351 Insuffisance (de la valvule) aortique non rhumatismale I061 Insuffisance (de la valvule) aortique rhumatismale I361 Insuffisance (de la valvule) tricuspide non rhumatismale I071 Insuffisance (de la valvule) tricuspide rhumatismale
hospitalisation pour insuffisance mitrale	PMSI MCO avec un diagnostic principal ou relié = I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale
hospitalisation pour insuffisance aortique	PMSI MCO avec un diagnostic principal ou relié = I351 Insuffisance (de la valvule) aortique non rhumatismale I061 Insuffisance (de la valvule) aortique rhumatismale

Chirurgie de remplacement valvulaire avec circulation extra corporelle pour insuffisance valvulaire	PMSI MCO avec un des 3 GHM suivants GHM 05C02Z Chirurgie de remplacement valvulaire avec circulation extracorporelle et avec cathétérisme cardiaque ou coronarographie GHM 05C03V Chirurgie de remplacement valvulaire avec circulation extracorporelle, sans cathétérisme cardiaque, ni coronarographie, sans CMA GHM 05C03W Chirurgie de remplacement valvulaire avec circulation extracorporelle, sans cathétérisme cardiaque, ni coronarographie, avec CMA et un diagnostic principal ou relié parmi les six suivants I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale I351 Insuffisance (de la valvule) aortique non rhumatismale I061 Insuffisance (de la valvule) aortique rhumatismale I361 Insuffisance (de la valvule) tricuspide non rhumatismale I071 Insuffisance (de la valvule) tricuspide rhumatismale

Les traitements des données ont été réalisés avec le logiciel SAS version 9.01

3. Résultats

3.1. Description de la population de la population de la cohorte

L'étude portait sur 1 048 173 diabétiques de 40 à 69 ans dont 43 044 exposés au benfluorex en 2006.

Les personnes diabétiques traitées exposées au benfluorex étaient significativement plus jeunes que les non-exposés (57,3 ans vs 58,3 ans), plus souvent des femmes (56,4 % vs 42,0 %), et moins souvent en ALD 76,3% vs 81,1% (tableau 3).

Dans la cohorte des 1 048 173 diabétiques suivis l'exposition au benfluorex était maximale pour les femmes de 45 à 49 ans (6,5%) et minimale pour les hommes de 65 à 69 ans (2,6%) (tableau 4). En 2006 le taux d'ALD cardiovasculaire des personnes de la cohorte augmentait avec l'âge de 2,9% pour les, 40-44 ans à plus de 11% pour les 65-69 ans (tableau 5).

Table 3 : caractéristiques des diabétiques exposés et de non-exposés

	exposés	non-exposés	significativité
effectifs	43 044	1 005 129	
âge (moyenne)	57,3	58,3	***
âge (écart type)	7,2	7,3	
%femme	56.4	42,0	***
%homme	43,6	58,0	***
% ALD	76,3	81,1	***

*< 0.05, **< 0.01, ***< 0.001.

Table 4 : Taux de diabétiques exposés au benfluorex en 2006 par classe d'âge et par sexe

classe d'âge	Hommes	femmes
40 à 44	3.3%	6.1%
45 à 49	3.6%	6.5%
50 à 54	3.5%	6.2%
55 à 59	3.3%	5.9%
60 à 64	3.0%	5.2%
65 à 69	2.6%	4.2%

Table 5 Taux de diabétiques de la cohorte en ALD en 2006 toutes causes confondues et en ALD cardiovasculaires (1, 3, 5, 13)*

	toutes ALD		ALD* 1, 3, 5, 13	
classe d'âge	Hommes	femmes	Hommes	femmes
40 à 44	81.1%	68.3%	2.9%	2.9%
45 à 49	80.0%	73.1%	5.1%	5.5%
50 à 54	79.8%	73.9%	7.2%	6.9%
55 à 59	80.2%	75.6%	9.0%	8.4%
60 à 64	81.6%	78.8%	10.3%	9.4%
65 à 69	82.7%	80.4%	11.6%	10.8%

*ALD 1 = Accident vasculaire cérébral invalidant, ALD 3 = Artériopathies chroniques avec manifestations ischémiques, ALD 5 = Insuffisance cardiaque grave, troubles du rythme graves, cardiopathies valvulaires graves, cardiopathies congénitales graves, ALD 13 = Maladie coronaire

Les hospitalisations en 2007 pour insuffisance valvulaire cardiaque par régurgitation augmentaient fortement avec l'âge de 4 pour 100 000 pour les 40-44 ans à plus de 40 pour 100 000 pour les 65-69 ans (tableau 6).

Table 6 Taux de diabétiques hospitalisés en 2007 pour insuffisance valvulaire cardiaque par régurgitation (pour 100 000 patients diabétiques)

classe d'âge	Hommes	femmes
40 à 44	3.6	4.1
45 à 49	11.8	19.2
50 à 54	36.2	15.8
55 à 59	21.9	29.9
60 à 64	39.1	28.2
65 à 69	48.0	38.2

3.2. Relation entre l'exposition au benfluorex et hospitalisation pour valvulopathie par régurgitation

Le risque d'hospitalisation en 2007 pour insuffisance valvulaire cardiaque était de 81 pour 100 000 dans le groupe exposé au benfluorex en 2006 vs 28 pour 100 000 dans le groupe non exposé, soit un risque relatif de 2,9 [2,0 ;4,1] et un RR_a de 3,1 [2,2 ;4,5]. Les risques relatifs ajustés d'hospitalisation pour insuffisance mitrale et insuffisance aortique était respectivement de 3,0 [1,9 ;4,7] et de 4,1 [2,3 ;7,4]. Le risque de chirurgie en 2007 avec un remplacement valvulaire pour une insuffisance valvulaire toutes causes confondues était de 30 pour 100 000 dans groupe exposé au benfluorex vs 8 pour 100 000 dans le groupe non exposé, soit un RR ajusté de 3,7 [2,1 ;6,8]. Parmi les 13 personnes diabétiques de 40 à 69 ans exposées au benfluorex et ayant subi un remplacement valvulaire en 2007 une était décédée en milieu d'année 2008. (tableau 7).

En 2008 les risques relatifs ajustés d'hospitalisation pour des valvulapthies des exposés en 2006 comparés au non exposés étaient semblables à ceux de 2007. Ils étaient compris entre 2,4 et 4,5 : 3,0 [2,1 ;4,4] pour une hospitalisation pour insuffisance valvulaire, 2,4 [1,4 ;4,1] pour une hospitalisation pour insuffisance mitrale, 4,1 [2,3 ;7,4] pour une hospitalisation pour insuffisance aortique et 4,5 [2,6 ;7,6] pour un remplacement valvulaire pour insuffisance valvulaire. (tableau 8). Parmi les 11 personnes diabétiques exposées au benfluorex en 2006 et ayant subi un remplacement valvulaire sous circulation extracorporelle en 2008 aucune n'était décédée à la date du 30 juin 2009.

Tableau 7 : risque d'hospitalisation en 2007 pour valvulopathie de régurgitation selon l'exposition ou non au benfluorex en 2006 dans une cohorte de diabétiques – données SNIIRAM assurance maladie

	RA pour 100 000 personnes non-exposées	RA pour 100 000 personnes exposées	RR brut (IC 95%)	RR ajusté [1] (IC 95%)
hospitalisation pour insuffisance valvulaire	28	81	2,9 [2,0 ;4,1]	3,1 [2,2 ;4,5]
hospitalisation pour insuffisance mitrale	19	53	2,8 [1,8 ;4,3]	3,0 [1,9 ;4,7]
hospitalisation pour insuffisance aortique	8	30	3,7 [2,0 ;6,6]	4,1 [2,3 ;7,4]
remplacement valvulaire pour insuffisance valvulaire	8	30	3,6 [2,0 ;6,4]	3,7 [2,1 ;6,8]

[1] ajustement sur âge, sexe et ALD cardiovasculaire

Tableau 8 : risque d'hospitalisation en 2008 pour valvulopathie de régurgitation selon l'exposition ou non au benfluorex en 2006 dans une cohorte de diabétiques – données SNIIRAM assurance maladie

	RA pour 100 000 personnes non-exposées	RA pour 100 000 personnes exposées	RR brut (IC 95%)	RR ajusté [1] (IC 95%)
hospitalisation pour insuffisance valvulaire	26	74	2,8 [2,0 ;4,1]	3,0 [2,1 ;4,4]
hospitalisation pour insuffisance mitrale	17	37	2,3 [1,3 ;3,8]	2,4 [1,4 ;4,1]
hospitalisation pour insuffisance aortique	9	37	4,1 [2,4 ;7,0]	4,5 [2,6 ;7,6]
remplacement valvulaire pour insuffisance valvulaire	7	26	3,8 [2,0 ;7,1]	4,2 [2,2 ;8,1]

[1] ajustement sur âge, sexe et ALD cardiovasculaire

La relation dose-effet a été testée pour le risque d'hospitalisation pour insuffisance valvulaire en 2007.

Table 10 : relation entre la dose de benfluorex délivrée en 2006 et le risque d'hospitalisation en 2007 pour insuffisance valvulaire pour des personnes diabétiques de 40 à 69 ans.

dose cumulée de benfluorex* remboursée en 2006	effectif	Risque absolu d'hospitalisation pour insuffisance valvulaire en 2007 pour 100 000 personnes	risque relatif
0 gr	1 005 129	28,0	1.0
13,5grs à 40,5 grs	17 516	51,4	1.9
41 grs à 175,5 grs	25 528	105,8	3.8
41gr à 90 gr	*8 790*	*102,49*	*3.7*
91gr à 135 gr	*8 081*	*111,4*	*4.0*
136gr à 175,5 gr	*8 657*	*92,4*	*3.3*

* un comprimé de benfluorex est dosé à 150 mg

Les premiers constats montrent que les personnes ayant eu des doses cumulées plus faibles en 2006 ont eu de moindre risque de développer une insuffisance valvulaire avec une hospitalisation. A partir de 41 grammes par an, soit environ 270 comprimés dosés à 150 mg en 2006, il n'apparaissait pas de dose effet.

4. Discussion

Ce travail conforte l'hypothèse de départ, à savoir l'existence d'un lien entre benfluorex et valvulopathie de régurgitation. Il existait une relation positive entre le fait d'avoir fait l'usage (ou plus exactement d'avoir été remboursé) de benfluorex en 2006 et le fait d'avoir été hospitalisé en 2007 et en 2008 pour une insuffisance valvulaire cardiaque (risque relatif ajusté RR_a 2007 = 3,1 ; RR_a 2008 = 3,0), une insuffisance mitrale (RR_a 2007 = 3,0 ; RR_a 2008 = 2,4), une insuffisance aortique (RR_a 2007 = 4,1 ; RR_a 2008 = 4,5), une chirurgie de remplacement valvulaire sous circulation extracorporelle pour insuffisance valvulaire (RR_a 2007= 3,7 ; RR_a 2008 = 4,2).

Le choix d'un protocole d'étude observationnelle de type cohorte exposés-non exposés est réputé plus proche de l'approche expérimentale[15] et permet de calculer un risque absolu et relatif. L'estimation d'un risque absolu est importante pour une décision de santé publique. De plus ce choix s'est imposé en raison de l'impossibilité de disposer d'un codage étiologique des valvulopathies de régurgitation dans le PMSI (valvulopathies dégénératives, rhumatismales, post endocardite infectieuse, congénitale, ischémique, secondaire à un dysfonctionnement ventriculaire gauche, post radique, tumorale..). Il n'existait par exemple que deux codes de la classification internationale des maladies (CIM-10) pour l'insuffisance mitrale et les experts interrogés s'accordent sur le caractère très imprécis de l'utilisation d'un code ou de l'autre. En testant l'hypothèse « valvulopathie de régurgitation tous types confondus », les biais de classement potentiels étaient plus limités, mais la puissance de l'étude en était affectée.

Un élément positif était d'utiliser pour le suivi de cohorte l'enregistrement passif des expositions par la télétransmission par les pharmaciens d'officine aux CPAM pour obtenir le remboursement du benfluorex, données qui enrichissent de façon exhaustive le SNIIRAM ; l'enregistrement des maladies était également passif par les médecins qui complètent dans les résumés de sortie standardisés (RSS puis RSA) les diagnostics principaux et reliés[16] et les actes médicaux principaux, dit classant. Ces données sont enregistrées dans le PMSI MCO. Le chaînage de deux sources d'information totalement indépendantes permet d'éliminer en principe les biais de classement différentiels sur l'exposition comme sur la maladie.

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[15] Bouyer J, Hemon D, Cordier et al. Chapitre 8 in Epidémiologie : principes et méthodes quantitatives. Les ed. INSERM, 1995.

[16] Le diagnostic principal est le motif qui a mobilisé l'essentiel de l'effort médical et soignant au cours de l'hospitalisation dans l'unité médicale. Le diagnostic relié est renseigné lorsque le diagnostic principal est insuffisant. Il rend compte de la prise en charge du patient en termes médico-économiques. C'est une maladie chronique ou de longue durée, ou un état permanent, présent au moment du séjour en hôpital.

Plusieurs facteurs peuvent contribuent à minimiser les risques relatifs obtenus.

1. L'exposition évaluée de façon dichotomique est sensiblement surestimée. Une personne ayant eu un remboursement d'une seule boite de benfluorex est présumée exposée, alors même, quelle n'a peut-être absorbé aucun comprimé. Les erreurs d'attribution de bénéficiaires sont en principe rares mais toujours possibles et contribuent également à sous estimer le risque. L'enquête « instauration des traitements médicaments hypolipémiants » menées en 2002 avait retrouvé parmi les nouveaux consommants ayant une seule délivrance ponctuelle jusqu'à 5% d'erreur de bénéficiaires [17]. Nous ne sommes pas dans cette situation car il ne s'agit pas d'une population débutant un traitement, mais des erreurs d'attribution de bénéficiaires entre conjoints notamment dans le cas présent sont toujours possibles.
2. Les non-exposés pourraient avoir été exposés en 2005 ou antérieurement.
3. Tous les patients diabétiques traités ne sont pas en théorie concernés par une éventuelle indication du benfluorex « *AMM limitée aux diabétiques avec surcharge pondérale* ». Un indice de masse corporelle (IMC) inférieur à 25 n'était retrouvé en 2007 que chez 20 % des diabétiques de type 2 et 80% était en surpoids ou obèse[18]. Encore faut-il rappeler qu'en 2006 le benfluorex bénéficiait également de l'indication « *adjuvant au régime adapté dans les hypertriglycéridémies* ». En revanche l'inclusion de diabétiques de type 1 dans l'enquête, 5,6% d'après l'étude Entred[19], dans le groupe non exposé contribue à diminuer le risque relatif calculé.
4. Le caractère non spécifique « des insuffisances valvulaires tous types confondus » avec notamment des insuffisances dégénératives ou rhumatismales (principales causes habituelles dans cette tranche d'âge de l'insuffisance mitrale) qui ne peuvent être causées par le benfluorex diminue fortement le risque relatif calculé.
5. Un suivi limité à deux années immédiatement après l'année où l'exposition est enregistrée pourrait également diminuer les risques relatifs.

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[17] Saba G, Weill A, Païta M, Ricordeau Ph, Bourrel R, Nouailher-Lagarde M, Dematons MN, Crochet B, Guilhot J, Fender P, Allemand H et le groupe Dyslipidémie. Instauration des traitements médicamenteux hypolipémiants en France en 2002. Rev Med Ass Maladie 2003;34,4:221-231. Rapport complet http://fulltext.bdsp.ehesp.fr/Cnamts/Etudes/2003/traitementshypolipemiants.pdf?1M4M8-44714-XK96X-D1KX6-81X49

[18] Fagot-Campagna A, Fosse S, Roudier C, Romon I, Penfornis F, Lecomte P, Bourdel-Marchasson I, Chantry M, Deligne J, Fournier C, Poutignat N, Weill A, Paumier A, Eschwège E, pour le comité scientifique d'Entred. Caractéristiques, risque vasculaire et complications chez les personnes diabétiques en France métropolitaine : d'importantes évolutions entre Entred 2001 et Entred 2007. Bulletin épidémiologique hebdomadaire 2009 ; 42-43,450-54 (sous presse-publication prévue le 10 novembre 2009).

[19] Cf réf 18.

Dans ces conditions le fait d'observer des risques relatifs bruts et ajustés de près de trois renforce d'autant l'hypothèse d'un lien fort avec un risque relatif possiblement plus élevé.

Le jugement de causalité : plusieurs arguments peuvent militer en faveur d'une possible relation de cause à effet.

1. La connaissance d'un mécanisme d'action décrit antérieurement à cette étude pour les fenfluraminiques sérotoninergiques. Des études physiopathologiques ont expliqué les mécanismes en cause : activation des récepteurs sérotoninergiques présents à la surface des vaisseaux pulmonaires et des valves cardiaques par le métabolite toxique norfenfluramine.
2. Une relation dose effet qui semble se dessiner. Il faudrait pour démontrer formellement cette relation connaître la totalité de la consommation dans les années antérieures.
3. Les résultats d'une étude cas-témoins menée par des cliniciens [20] qui conclurait à une association entre benfluorex et valvulopathie spécifique seraient un argument supplémentaire en faveur de la relation entre le benfluorex et les valvulopathies.

Il convient toutefois d'indiquer que nos conclusions ne sont généralisables que dans la population de diabétiques de 40 à 69 ans. La limitation à une population homogène diabétique de 40-69 ans et l'ajustement sur l'âge, le sexe et les ALD cardiovasculaires ont permis de limiter le risque de facteurs de confusion. Toutefois, les personnes traitées par du benfluorex n'étaient en 2006 que dans 17% des cas des diabétiques traités par hypoglycémiants oraux et/ou insuline. Des résultats non présentés dans ce rapport étaient également en faveur d'un risque relatif élevé et significatif de valvulopathies de régurgitation pour les non-diabétiques exposés comparés aux diabétiques non-exposés.

Les traditionnelles limites des enquêtes de cohorte « longue et coûteuses »[21] ont pu être surmontées. Cette enquête a pu être menée en moins de quatre semaines par des personnes de l'assurance maladie expérimentées sur les analyses de données issues du SNIIRAM. Ceci conforte l'intérêt des bases de données médico-administratives chaînant SNIIRAM, PMSI, statut vital issu des données de l'Insee et de la Cnav et leur utilisation par des personnes en maitrisant la complexité.

L'effet du benfluorex est modeste et mal évalué. Il est notable que dans les recommandations publiées par l'Afssaps et la Haute autorité de santé en novembre 2006 sur

[20] Commission nationale de pharmacovigilance : Compte rendu de la réunion du mardi 7 juillet 2009 http://www.afssaps.fr/var/afssaps_site/storage/original/application/83e6e90a48d5beba0556099fa00be94d.pdf (consulté le 5/11/2009).

[21] Bouyer J, Hemon D, Cordier et al. Chapitre 8 in Epidémiologie : principes et méthodes quantitatives. Les ed. INSERM, 1995.

le traitement médicamenteux du diabète de type 2[22] le benfluorex n'est jamais cité. Les effets indésirables observés dans cette étude sont peu fréquents mais potentiellement très sévères. Dans ce contexte la balance bénéfice-risque ne parait pouvoir être analysée que défavorablement. Selon les données de la Cnamts il y avait en 2006 pour le seul régime général 340 000 personnes traitées par benfluorex, 320 000 en 2007 et 275 000 en 2008.

5. Conclusion :

1. L'usage du Benfluorex chez les diabétiques en 2006 était associé significativement dans les deux années qui suivaient à des valvulopathies de régurgitation mitrales et aortiques et à des chirurgies de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.
2. Transmission du dossier en urgence du rapport préliminaire le 27/10/2009 à l'Agence française de sécurité sanitaire des produits de santé et à la Direction générale de la santé
3. Le SNIIRAM avec le chainage PMSI et statut vital peut contribuer à montrer, en condition réelle d'utilisation pour des médicaments, des effets indésirables sévères mais restés longtemps mal évalués ou méconnus parfois depuis plusieurs dizaines d'années.

[22] Afssaps et la Haute autorité de santé. Traitement diabète de type 2 - synthèse des recommandations (13 pages) ; Traitement diabète type 2 -recommandations (45 pages) ; Traitement diabète type 2 - argumentaire (158 pages).

http://www.has-sante.fr/portail/jcms/c_459270/traitement-medicamenteux-du-diabete-de-type-2 (consulté le 9/11/2009

Analyse de cas de valvulopathies observées chez des patients traités par benfluorex.

Pr Bernard Iung, Département de Cardiologie, Hôpital Bichat, Paris, 5 octobre 2009

Ce rapport analyse 45 cas de valvulopathies mises en évidence chez des patients traités par benfluorex. Il s'agit de cas spontanément rapportés par différents centres dans le cadre de la pharmacovigilance et de cas issus d'une recherche rétrospective spécifique effectuée au CHU de Brest à partir des données du PMSI et de cas issus du CHU d'Amiens.

1. Valvulopathies en population générale et valvulopathies médicamenteuses

1.1. Prévalence des valvulopathies en population générale

Les valvulopathies demeurent fréquentes dans les pays occidentaux, avec une prévalence estimée à 2,5 % dans une étude américaine récente qui est la seule étude de grande ampleur basée sur des diagnostics échocardiographiques en population représentative (1). La prévalence des valvulopathies augmente nettement avec l'âge : elle est inférieure à 2% avant 65 ans puis augmente à 8,5% entre 65 et 74 ans et à 13,2% après 75 ans.

La prévalence est encore plus importante lorsque sont prises en compte des valvulopathies minimes, notamment des fuites de grade 1/4 d'après l'échocardiographie Doppler (2).

Parmi les mono-valvulopathies significatives, c'est-à-dire les sténoses au moins modérées ou les régurgitations de grade ≥ 2/4, la valvulopathie la plus fréquente est la sténose aortique, suivie par l'insuffisance mitrale, l'insuffisance aortique puis le rétrécissement mitral (3). Les polyvalvulopathies représentent 20% des valvulopathies natives (4). Malgré la prédominance des valvulopathies dégénératives, les valvulopathies rhumatismales représentent encore la seconde étiologie des valvulopathies en Europe, soit 22% des valvulopathies natives dans l'Euro Heart Survey et 51% parmi les polyvalvulopathies (3,4).

Compte-tenu de leur fréquence en population générale, la simple constatation d'une valvulopathie ne permet donc pas d'imputer celle-ci à un traitement médicamenteux.

1.2. Caractéristiques des valvulopathies médicamenteuses précédemment rapportées

Les premiers cas de valvulopathies susceptibles d'être imputées à des médicaments ont été rapportés dans les années 1970 avec l'observation d'épaississements valvulaires correspondant histologiquement à une fibrose chez des patients traités par un anti-migraineux, le méthysergide (5). Dans les années 1990, d'autres cas analogues ont été rapportés avec des dérivés de l'ergotamine, également prescrits

en tant qu'anti-migraineux (6). Les lésions macroscopiques et histologiques étaient voisines de celles observées dans les valvulopathies des tumeurs carcinoïdes.

La possibilité de survenue de valvulopathies induites par des traitements médicamenteux a surtout été documentée avec l'association de différentes classes d'anorexigènes combinant des dérivés amphétaminiques (fenfluramine et dexfenfluramine) et la phentermine (inhibiteur de la mono-amino-oxydase et agoniste dopaminergique). Après une première description de 24 cas dont les lésions macroscopiques et histologiques s'apparentaient aux valvulopathies des tumeurs carcinoïdes (7), l'imputabilité de ces drogues est devenue hautement plausible après la publication de plusieurs études cas-témoin (8-11). Une méta-analyse de 9 études cas-témoin comportant une confirmation échocardiographique a mis en évidence une association significative entre la survenue de régurgitations valvulaires au moins modérées (critères FDA : IM de grade ≥ 3 ou IA de grade ≥ 2) et la prise d'anorexigènes durant au moins 90 jours, l'association n'étant pas significative pour une durée de traitement inférieure à 90 jours (12).
La possibilité d'une régression des lésions après arrêt du traitement médicamenteux à été décrite, mais avec des données contradictoires (13,14).

La troisième classe de traitement imputée dans la survenue de valvulopathies est celle des antiparkinsoniens agonistes dopaminergiques représentés par le pergolide et la cabergoline. Comme dans le cas des anorexigènes, des cas isolés rapportés ont été suivis par des études cas-témoin concluant à une association statistiquement significative (15,16). Une méta-analyse de 8 études cas-témoin confirmait la significativité de l'association et mettait en évidence une corrélation avec la dose cumulée mais pas avec la durée du traitement (17).

Bien que faisant intervenir des classes pharmacologiques différentes, le point commun de ces valvulopathies médicamenteuses est l'aspect voisin des lésions observées dans les tumeurs carcinoïdes :
- épaississement valvulaire et restriction de la cinétique valvulaire, principalement à l'origine de régurgitations en echocardiographie-Doppler,
- épaississement valvulaire avec présence de plaques de fibrose lisse et blanchâtre à l'examen macroscopique des valves chez les patients opérés,
- apparition d'une fibrose dense en surface de valves dont l'architecture était par ailleurs peu modifiée en histologie.

Sur le plan physiopathologique, la sérotonine est apparue comme un médiateur potentiel commun à ces différentes classes médicamenteuses dans la mesure où toutes ces drogues ont des propriétés agonistes sérotoninergiques et où les lésions ont un aspect échocardiographique, macroscopique et surtout histologique voisin des valvulopathies observées dans les tumeurs carcinoïdes qui sont caractérisées par une hypersécrétion de médiateurs sérotoninergiques (18). Les conceptions physiopathologique actuelles ne privilégient pas le rôle de la sérotonine elle-même, mais plutôt celui des récepteurs sérotoninergiques 5HT2B. Ces récepteurs, présents dans le tissu valvulaire, stimulent la mitogénèse et ont une forte affinité pour toutes les classes médicamenteuses à l'origine de valvulopathies médicamenteuses (19-20). En revanche, d'autres classes médicamenteuses agissant sur le métabolisme de la sérotonine, en particulier les antidépresseurs inhibant la recapture de la sérotonine, ont une faible affinité pour les récepteurs 5HT2B, ce qui est corroboré au

fait que ces drogues n'ont pas été imputées dans la survenue de valvulopathies médicamenteuses (21).
Par ailleurs, des lésions valvulaires identiques ont pu être reproduites dans des modèles animaux par injection de sérotonine (22) ou de pergolide (23).
La forte présomption de l'imputabilité des récepteurs 5HT2B dans la genèse des valvulopathies médicamenteuses a conduit certains auteurs à proposer un screening de leur affinité aux drogues susceptibles d'être imputées dans des valvulopathies médicamenteuses (19).

1.3. Critères d'imputabilité d'une valvulopathie à un traitement médicamenteux

Les connaissances issues des données épidémiologiques contemporaines concernant les valvulopathies et celles issues des études portant sur les valvulopathies médicamenteuses conduisent à retenir un certain nombre de critères permettant de suspecter la responsabilité de drogues dans la survenue de lésions valvulaires :

- interférence de la drogue avec le métabolisme de la sérotonine,
- observation de valvulopathies plutôt régurgitantes que sténosantes, caractérisées par un épaississement valvulaire et une restriction de la cinétique valvulaire en échocardiographie (24),
- présence d'une régurgitation valvulaire au moins modérée, correspondant approximativement à un grade ≥ 2/4 (compte-tenu de la fréquence des valvulopathies de grade 1/4 en population générale) (24),
- épaississement valvulaire avec présence de plaques de fibrose blanchâtre sur les observations macroscopiques,
- présence d'une fibrose dense en surface des valves avec une architecture par ailleurs peu modifiée sur l'examen histologique des valves explantées lorsque les patients ont été opérés.

L'aspect échocardiographique et macroscopique diffère des valvulopathies dégénératives, qui sont les plus fréquentes dans les pays occidentaux, mais peut poser des problèmes diagnostiques différentiels à l'échocardiographie avec une valvulopathie rhumatismale. En revanche l'aspect histologique est plus spécifique car les valvulopathies rhumatismales s'associent à des anomalies histologiques différentes, plus diffuses, du tissu valvulaire.

2. Analyse des cas rapportés chez les patients traités par benfluorex

Les 45 cas rapportés ont été analysés selon l'existence d'une chirurgie valvulaire et, pour les patients non opérés, en fonction de la documentation échocardiographique.

Parmi les 17 cas de valvulopathies opérées (Tableau 1) :

- 6 cas sont fortement évocateurs d'une valvulopathie médicamenteuse liée au benfluorex. Ces 5 cas se caractérisent par des constatations histologiques correspondant aux descriptions de valvulopathies médicamenteuses et pour lesquels il n'existe pas d'autre prise médicamenteuse imputable. A noter que 2

de ces 5 patients avaient également reçu des anorexigènes mais ne présentaient pas de lésion valvulaire significative (régurgitation de grade ≥ 2/4) sur des échocardiographies effectuées plusieurs années après la prise des anorexigènes.

- 6 cas sont possiblement liés au benfluorex en raison de constatations échocardiographiques ou macoscopiques compatibles, mais sans confirmation histologique. Dans ces 6 cas, l'alternative d'une étiologie rhumatismale ne peut être formellement écartée.
- Pour les 5 derniers cas, l'imputabilité du benfluorex semble faible ou très faible. Dans 3 cas, l'absence de toute documentation échocardiographique ou macroscopique ne permet pas d'exclure une autre étiologie de valvulopathie. Dans 2 de ces cas, la description des lésions évoque une autre étiologie (une dégénérative et une insuffisance mitrale fonctionnelle) et l'imputabilité est donc très faible.

Parmi les 15 patients n'ayant pas été opérés mais pour lesquels l'échocardiographie décrit les lésions valvulaires (Tableau 2) :

- L'imputabilité du benfluorex est possible dans 10 cas dont les lésions valvulaires sont compatibles. L'alternative d'une étiologie rhumatismale ne peut cependant pas être écartée.
- Dans les 5 autres cas, l'imputabilité du benfluorex semble très faible car les données anamnestiques ou les descriptions échocardiographiques suggèrent une valvulopathie dégénérative dans 3 cas, une insuffisance mitrale fonctionnelle dans un cas, et une valvulopathie préexistante, possiblement rhumatismale, dans un cas.

Enfin, dans 13 cas, aucune documentation échocardiographique des lésions valvulaires n'est disponible et il n'est donc pas possible de conclure sur le degré d'imputabilité du benfluorex (Tableau 3).

En résumé, l'imputabilité du benfluorex paraît probable dans 6 cas et possible dans 16 cas, la principale alternative étant une valvulopathie rhumatismale. L'imputabilité est faible dans 16 cas où la présence de régurgitations valvulaires est difficile à interpréter en l'absence de tout détail concernant l'anatomie valvulaire. Enfin l'imputabilité est très faible dans 7 cas pour lesquels une autre étiologie paraît plus probable.

3. Perspectives d'analyses ultérieures

3.1. À partir des données existantes

Dans un premier temps, l'amélioration de la qualité des données collectées permettrait de confirmer les 6 cas dans lesquels l'imputabilité du benfluorex est forte est de mieux évaluer l'imputabilité dans les 16 cas où elle est possible.

3.1.1. Données anatomopathologiques

La relecture centralisée des lames d'histologie des valves explantées chez les patients opérés est souhaitable. En effet, les valvulopathies médicamenteuses sont

rares et la description des lésions n'est pas homogène. Le caractère normal ou anormal de l'architecture valvulaire sous-jacente à la fibrose et l'absence d'infiltrats inflammatoires ne sont notamment pas précisés de façon systématique. Une nouvelle analyse effectuée par un centre de référence à partir de critères standardisés permettrait d'améliorer le caractère informatif de l'analyse anatomopathologique, qui est essentielle au diagnostic.
Cette analyse devrait aux nouveaux cas documentés ou aux cas déjà documentés qui seraient opérés ultérieurement.

3.1.2. Données cliniques et échocardiographiques
Pour les patients qui n'ont pas été opérés, le diagnostic de valvulopathie médicamenteuse nécessite aussi d'éliminer d'autres étiologies plus fréquentes.

L'analyse des données échocardiographiques est souvent suffisante pour éliminer le diagnostic de valvulopathie dégénérative. Lorsque les lésions échocardiographiques sont suspectes d'une valvulopathie médicamenteuse, la principale alternative diagnostique est celle d'une valvulopathie rhumatismale.
L'analyse échocardiographique des lésions anatomiques manque parfois de précision. Une relecture centralisée des enregistrements échocardiographiques dynamiques (si elle est disponible) permettrait de mieux identifier les cas suspects. La seule mise en évidence d'une régurgitation valvulaire est moins évocatrice que l'analyse anatomique. La transposition des critères de la FDA, utilisés notamment dans des études sur les anorexigènes, peut poser des problèmes d'application en France car la cotation anglo-saxonne des régurgitations comprend 3 grades alors qu'il est usuel de coter les régurgitations en 4 grades en France (25).

Pour les cas suspects, aucun critère spécifique, hormis l'histologie, ne permet le diagnostic différentiel avec une valvulopathie rhumatismale. Toutefois, des données cliniques peuvent être contributives, en particulier l'origine ethnique. En effet, le diagnostic de valvulopathie rhumatismale est plus probable chez des patients originaires d'une région d'endémie rhumatismale que s'ils sont nés en France. Parmi les patients nés en France, le diagnostic de valvulopathie rhumatismale est plus plausible chez les patients âgés (âge > 60 ans), c'est-à-dire qui ont été enfants ou adolescents à une époque où le rhumatisme articulaire aigu était encore endémique en France.

Si elle est possible, la récupération de données échocardiographiques concernant les 13 cas qui ne font l'objet d'aucune documentation de l'anatomie valvulaire est souhaitable.

3.2. Etudes cliniques ultérieures

Comme pour les cas de valvulopathies médicamenteuses rapportées avec les anorexigènes et les antiparkinsoniens, la réalisation d'études cas-témoin semble la méthodologies la plus appropriée dans un premier temps pour préciser l'imputabilité du benfluorex dans la survenue de valvulopathies.

Idéalement, les témoins devraient être appariés pour les principaux facteurs de risque de valvulopathie en population générale: âge, sexe, facteurs de risque cardio-

vasculaire, indice de masse corporelle, présence d'un syndrome métabolique, origine ethnique (26-29).

3.3. Études pharmacologiques ou expérimentales

Par analogie avec des études rapportées dans d'autres cas de valvulopathies médicamenteuses, en particulier avec les antiparkinsoniens agonistes dopaminergiques (19,22), les deux approches suivantes sembleraient pouvoir contribuer à évaluer imputabilité du benfluorex dans la survenue de valvulopathies :

- étude de l'affinité des récepteurs sérotoninergiques 5HT2B au benfluorex,
- recours à des modèles animaux avec injection de benfluorex visant à reproduire la survenue de valvulopathies.

Tableau 1 : Valvulopathies opérées (17 cas)

Cas	Age / Sexe	Valvulopathie Type et Grade (/4)	Doumentation anatomique (échographie)	Doumentation anatomique (chirurgie)	Anatomo-pathologie	Compatibilité avec une atteinte médicamenteuse	Alternative étiologique	Durée benfluorex	Autres traitements imputables
TO060355 S06001104	48/F	IM3, IT2	Oui, compatible	Non	Oui, compatible	Forte	Non	7 ans	Non
BR20080051 S08002916	50/F	IM3, IA3	Non	Oui	Oui, compatible	Forte	Non*	6 ans	Isoméride 3 mois
BR20090080 S09001767	54/F	IM3 , IA3	Non	Non	Oui, compatible pour la mitrale	Forte	Non*	15 mois	Amphétamines 8 ans
Littérature SP S03000422	50/F	IM, IA, IT	Oui, compatible	Oui, compatible	Oui, compatible	Forte	Non	1 an	Non
TO051212 S05002371	49/F	IM3	Partielle, compatible	Non	Oui, compatible	Forte	RAA	3 ans	Non
TO040278 S04000348	36/F	IM3, IA2	Non	Non	Oui, lésions dégénératives	Faible	Dégénératif, RAA	8 mois	Non
GR20090108 S09002164	56/F	IM3	Oui	Non	Non	Possible	RAA	14 ans	Non
BR20090084 S09001760	51/F	IM3, IA3	Non	Non	Non	Faible	Plusieurs	2,5 ans	Isoméride
BR20090079 S09001800	60/H	IM3, IA2	Non	Oui, compatible	Non	Possible	RAA	10 ans	Non
BR20090087 S09001805	79/H	IM3, IA1	Non	Oui, peu compatible	Non	Faible	IM fonctionnelle	ND	Non
BR20090078 S09001750	53/F	IM3,IA2, IT3	Non	Oui, compatible	Non	Possible	RAA	ND	Non
BR20090189 S09003279	52/F	IM3, IA2	Non	Non	Non	Faible	RAA	1 an	Non
BR20090190 S09003282	53/F	IM3	Oui, compatible	Non	Non	Possible	RAA	ND	Isoméride
BR20090188 S09003283	41/F	IM3	Non	Non	Non	Faible	RAA ou dégénératif	ND	Non
AM20090368 S09003751	59/F	IM3 (+RM), IA2	Oui, compatible	Oui, compatible	Oui, compatible	Forte	Non	6 ans	Non
AM20090512 S09004505	58/F	IM3, IA2	Oui, compatible	Non	Non	Possible	RAA	14 mois	Non
AM20090509 S09004455	69/M	IM3, IA4	Oui, compatible	Oui, compatible	Non	Possible	RAA	3 puis 5 ans	Non

* absence de valvulopathie significative observée à l'échocardiographie effectuée à distance de l'arrêt des anorexigènes.

H : homme, F: femme, IA: insuffisance aortique, IM : insuffisance mitrale, IT : insuffisance tricuspide, RAA : rhumatisme articulaire aigu, ND : non disponible

Tableau 2: Valvulopathies non opérées avec documentation anatomique (15 cas)

Cas	Age / Sexe	Valvulopathie Type et Grade (/4)	Doumentation anatomique (échographie)	Compatibilité avec une atteinte médicamenteuse	Alternative étiologique	Durée benfluorex	Autres traitements imputables
BR20090086 S09001756	60/F	IM3, IA1	Oui, compatible	Possible	RAA	10 ans	Non
TO020331 S09002129	60/F	IA2, IM2	Oui, peu compatible	Très faible	Dégénérative probable	3 ans	Non
TO070121 S07000845	44/F	IM2, IA2	Oui, compatible	Possible	RAA	9 mois	Non
MP20080857 S08006172	77/F	IM2, IA2	Oui, peu compatible	Très faible	Dégénérative probable	> 1 an	Non
BR20090085 S09001768	49/F	IM2, IA2	Oui, compatible	Possible	RAA	2 ans	Non
BR20090092 S09001799	55/F	IM2, IA2	Oui, compatible	Possible	RAA	11 ans	Non
S06001337	54/H	IM2, IA2	Oui, non compatible	Très faible	IM fonctionnelle très probable	2,5 ans	Non
AM20090507 S09004460	71/F	IM3	Oui, compatible	Possible	RAA	1,5 mois	Pondéral + Isoméride
AM20090513 S09004506	53/M	IM2	Oui, compatible	Possible	RAA	5 ans	Non
AM20090514 S09004507	43/F	IM3, IA2	Oui, compatible	Possible	RAA	ND	Non
AM20090511 S09004458	43/F	IM2, IA2	Oui, compatible	Possible	RAA	4 ans	Non
AM20090515 S09004456	47/F	IM3, IA2, IT	Oui, compatible	Très faible*	RAA	3 ans	Non
AM20090508 S09004459	73/M	RA opéré avant IM1, HTAP	Oui, peu compatible	Très faible	Dégénérative	ND	Non
AM20090481 S0900XXXX	58/M	IM4	Oui, compatible	Possible	RAA	3 ans	Non
PB20090494 S0900YYYY	33/F	IM2	Oui, compatible	Possible	RAA	6-12 mois	Non

*: notion de valvulopathie préexistante, possiblement rhumatismale

H : homme, F: femme, IA: insuffisance aortique, IM : insuffisance mitrale, RAA : rhumatisme articulaire aigu, ND : non disponible

Tableau 3 : Liste des cas sans documentation de l'anatomie valvulaire (13 cas)

MA9900176 - 125P75
MP0500076 - S05000405
MP20070034 - S07002863
NT200800555 - S09000197
NT20080556 - S09000205
NT2008005 - S09001238
BR20090082 - S09001791
BR20090089 - S09001765
BR20090088 - S09001802
GR20090109 - S09002183
CN20080152 - S08002252
BR20090143 - S09002574
BR20090142 - S09002579

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Annexe 3-82

Expertise

- Rapport d'expert sur les cas de Pharmacovigilance
- Analyse des données échocardiographiques d'une étude clinique

Recommandations ASE pour la Quantification des Régurgitations: IA

Table 6 Application of specific and supportive signs, and quantitative parameters in the grading of aortic regurgitation severity

	Mild	Moderate		Severe
Specific signs for AR severity	• Central Jet, width < 25% of LVOT[5] • Vena contracta < 0.3 cm[5] • No or brief early diastolic flow reversal in descending aorta	Signs of AR>mild present but no criteria for severe AR		• Central Jet, width ≥ 65% of LVOT[5] • Vena contracta > 0.6cm[5]
Supportive signs	• Pressure half-time > 500 ms • Normal LV size*	Intermediate values		• Pressure half-time < 200 ms • Holodiastolic aortic flow reversal in descending aorta • Moderate or greater LV enlargement**
Quantitative parameters*				
R Vol, ml/beat	< 30	30-44	45-59	≥ 60
RF, %	< 30	30-39	40-49	≥ 50
EROA, cm[2]	< 0.10	0.10-0.19	0.20-0.29	≥ 0.30

AR, Aortic regurgitation; *EROA*, effective regurgitant orifice area; *LV*, left ventricle; *LVOT*, left ventricular outflow tract; *R Vol*, regurgitant volume; *RF*, regurgitant fraction.
* *LV* size applied only to chronic lesions. Normal 2D measurements: LV minor-axis ≤ 2.8 cm/m^2, LV end-diastolic volume ≤ 82 ml/m^2 (2).
[5] At a Nyquist limit of 50–60 cm/s.
** In the absence of other causes of LV dilatation.
* Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe regurgitation as shown

(Zoghbi et al. J Am Soc Echocardiogr 2003;16:777-802)

Recommandations ASE pour la Quantification des Régurgitations: IM

Table 3 Application of specific and supportive signs, and quantitative parameters in the grading of mitral regurgitation severity

	Mild	Moderate		Severe
Specific signs of severity	• Small central jet < 4 cm² or < 20% of LA area[a] • Vena contracta width <0.3 cm • No or minimal flow convergence[c]	Signs of MR>mild present, but no criteria for severe MR		• Vena contracta width ≥ 0.7cm *with* large central MR jet (*area* > 40% of LA) or *with* a wall-impinging jet of *any size*, swirling in LA[a] • Large flow convergence[c] • Systolic reversal in pulmonary veins • Prominent flail MV leaflet or ruptured papillary muscle
Supportive signs	• Systolic dominant flow in pulmonary veins • A-wave dominant mitral inflow[a] • Soft density, parabolic CW Doppler MR signal • Normal LV size[a]	Intermediate signs/findings		• Dense, triangular CW Doppler MR jet • E-wave dominant mitral inflow (E >1.2 m/s)[a] Enlarged LV and LA size[a,e], (particularly when normal LV function is present).
Quantitative parameters[f]				
R Vol (ml/beat)	< 30	30-44	45-59	≥ 60
RF (%)	< 30	30-39	40-49	≥ 50
EROA (cm²)	< 0.20	0.20-0.29	0.30-0.39	≥ 0.40

CW, Continuous wave; *EROA*, effective regurgitant orifice area; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve; *MR*, mitral regurgitation; *R Vol*, regurgitant volume; *RF*, regurgitant fraction.

[a] LV size applied only to chronic lesions. Normal 2D measurements: LV mass/ BSA ≤ 2.6 gm/m², LV end-diastolic volume ≤ 82 ml/m², maximal LA antero-posterior diameter ≤ 2.8 cm/m², maximal LA volume ≤ 36 ml/m² (2,35,35).

[b] In the absence of other etiologies of LV and LA dilatation and acute MR.

[c] At a Nyquist limit of 50–60 cm/s.

[d] Usually above 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.

[e] Maximal and large flow convergence defined as a flow convergence radius < 0.4 cm and ≥ 0.9 cm for central jets, respectively, with a baseline shift at a Nyquist of 40 cm/s; Cut-offs for eccentric jets are higher, and should be angle-corrected (see text).

[f] Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe as shown.

(Zoghbi et al. J Am Soc Echocardiogr 2003;16:777-802)

Recommandations ASE pour la Quantification des Régurgitations

Insuffisance mitrale

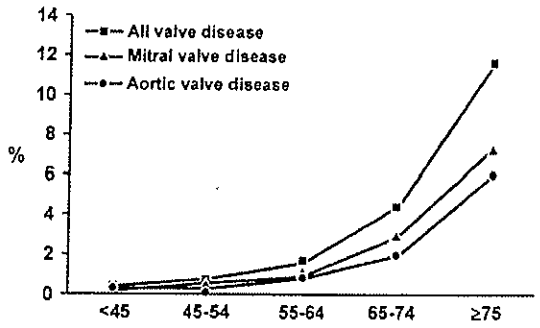
The consensus of the Task Force is to classify grading of severity of regurgitation into mild, moderate, and severe. In cases of overlap or intermediate severity, the terms "mild-to-moderate" or "moderate-to-severe" can be used. "Trace" regurgitation is also used in the event that regurgitation is barely detected. Usually this can be physiologic, particularly in right heart valves and mitral valve, and may not produce an audible murmur.

(Zoghbi et al. J Am Soc Echocardiogr 2003;16:777-802)

Epidémiologie des Valvulopathies

11 911 Echocardiographies
Sténoses ou régurgitations ≥ « *mild* »

Figure 1B



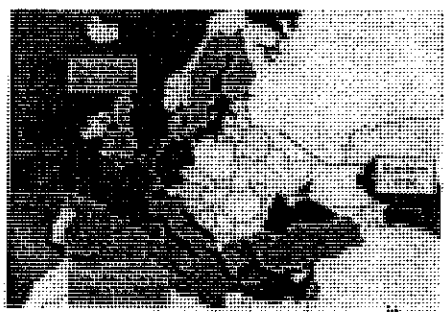
(Nkomo et al. Lancet 2006;368:1005-11)

Euro Heart Survey on Valvular Heart Disease

- 5001 pts included between April and July 2001
- In 92 centres from 25 countries
- 1269 valvular interventions during the survey period

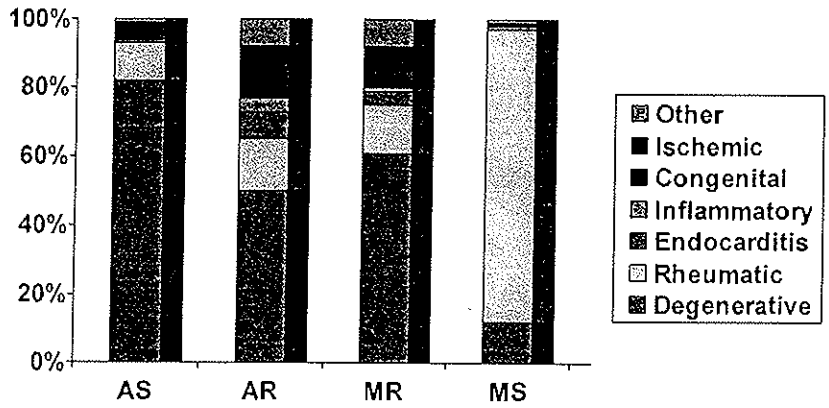
Primary and significant valve disease as defined by echocardiography :

AS = max. jet velocity ≥ 2.5 m/s.
MS = valve area ≤ 2cm²
MR = grade ≥ 2/4
AR = grade ≥ 2/4



(Iung et al. Eur Heart J 2003;24:1244-53)

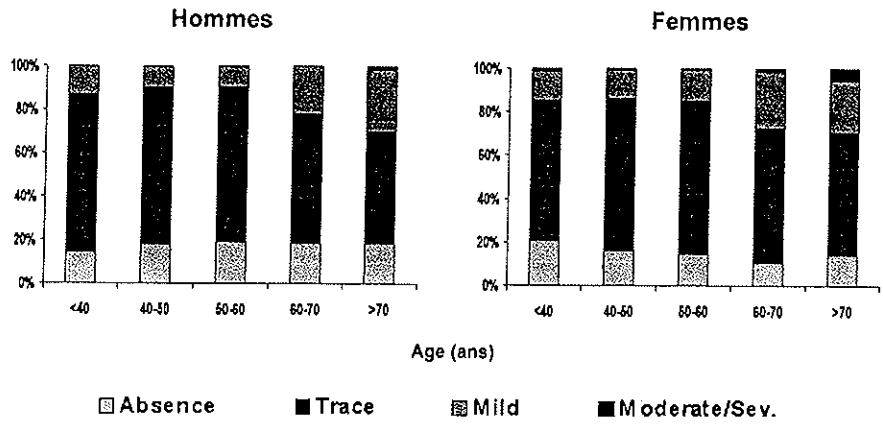
Single Native Valve Disease
Etiology



En population générale, la simple constatation d'une valvulopathie ne permet pas d'imputer celle-ci à un traitement médicamenteux

Valvulopathies en Population Générale
Insuffisance Tricuspide

3589 échocardiographies issues de la cohorte de Framingham

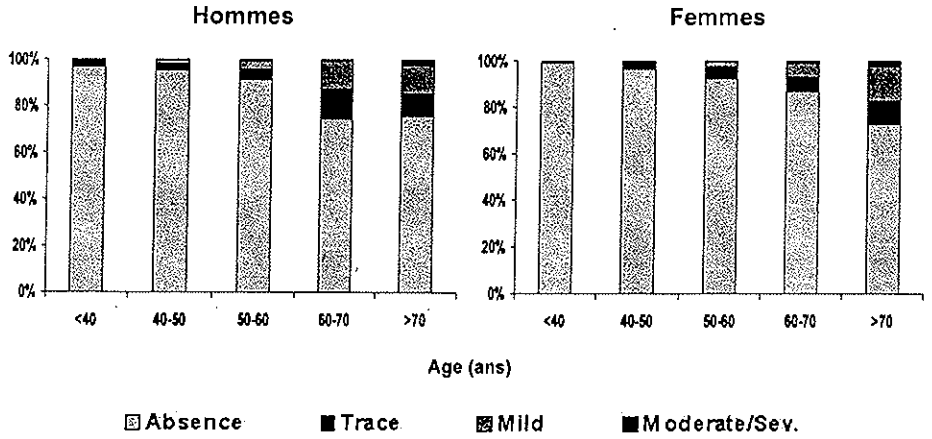


(Singh et al. Am J Cardiol 1999;83:897-902)

Valvulopathies en Population Générale

Insuffisance Aortique

3589 échocardiographies issues de la cohorte de Framingham



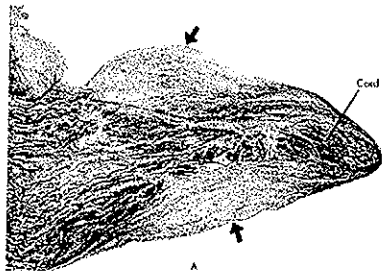
(Singh et al. Am J Cardiol 1999;83:897-902)

Critères d'imputabilité médicamenteuse

- **Échocardiographie**
  - Régurgitation plutôt que sténose, caractérisée par épaississement valvulaire et restriction de la cinétique valvulaire
  - Régurgitation au moins « *mild* » (aortique) ou « *moderate* » (mitrale) - critères FDA
- **Macroscopie**
  - Épaississement valvulaire avec plaques de fibrose blanchâtre
- **Anatomopathologie**
  - Fibrose dense en surface avec architecture valvulaire peu modifiée

Valvulopathies médicamenteuses

- valves épaissies et restrictives
- aspect macroscopique et histologique identique aux valvulopathies carcinoïdes ou secondaires au methysergide



- fibrose dense de surface sans modification de l'architecture

(Connolly N Engl J Med 1997;337:581-8)

Expertise des « cas benfluorex » : méthode

- **Cas opérés**
  - Documentation anatomique macroscopique
  - Documentation anatomopathologique
- **Cas non opérés**
  - Documentation échographique
- **Existence d'une autre cause possible**
  - Rhumatismale
  - Dégénérative
- **Autre prise médicamenteuse imputable**
  - Anorexigènes
  - Agonistes dopaminergiques
  - .../...

Expertise des « cas benfluorex »: critères

- **Fortement évocateur**
  - Anatomopathologie correspondant aux descriptions publiées
  - Pas d'autre prise médicamenteuse imputable
- **Possible**
  - Pas d'histologie
  - Échographie ou macroscopie compatible
  - Pas d'autre cause patente
- **Faible**
  - Documentation ne permettant pas de conclure
- **Très faible**
  - Autre cause très probable sur la conjonction :
    contexte clinique,
    échographie,
    ± anatomopathologie.

Expertise des « cas benfluorex » : résultats

Imputabilité	Forte	Possible	Faible	Très faible	Total
Opérés	6	6	3	2	17
Non-opérés, échographie		10		5	15
Non documentés			13		13
Total	6	16	16	7	*45*

Annexe 3-82

Interprétation

- Les données pronostiques et de surveillance ne concernent que les valvulopathies ≥ « *mild* »
- Les valvulopathies « *trivial* » sont considérées comme physiologiques en position mitrale ou tricuspide
- La comparaison des prévalences des valvulopathies en fonction du temps ne suggère pas un potentiel évolutif majeur des valvulopathies « *trivial* »

Recommandation de Surveillance des Valvulopathies ESC Guidelines 2007

Insuffisance mitrale

Serial testing

Asymptomatic patients with moderate MR and preserved LV function can be clinically followed-up on a yearly basis and echocardiography should be performed every 2 years.

Asymptomatic patients with severe MR and preserved LV function should be seen every 6 months and echocardiography performed every year, the follow-up being closer if no previous evaluation is available, and in patients with borderline values, or significant changes since the last visit. These patients should be instructed to promptly report any change in functional status.

Patients asymptomatiques avec IM « *moderate* » et fonction VG normale : surveillance écho tous les 2 ans

Insuffisance aortique

Serial testing

Patients with mild-to-moderate AR can be seen on a yearly basis and echocardiography performed every 2 years.

All patients with severe AR and normal LV function should be seen for follow-up at 6 months after their initial examination. If LV diameter and/or EF show significant changes, or they become close to the thresholds for intervention, follow-up should continue at 6 month intervals. When parameters are stable, follow-up can be yearly.

Patients avec IA > « *mild* » : surveillance écho tous les 2 ans

(Eur Heart J 2007; 28:230-68)

Anorexigènes et Valvulopathies
Evolution après Arrêt

- 50 patients sous anorexigènes arrêtés depuis 6 mois en moy.
  - 86% IA ≥ *mild* (grade 2) , 76% IM ≥ *mild* (grade 2)
  - Echo répétée après 1 an de délai moyen
    - Amélioration ≥ 1 grade pour 44% des IA et 54% des IM
    - Aggravation ≥ 1 grade pour 2,3% des IA et 2,6% des IM

(Mast et al. Ann Intern Med 2001;134:261-6)

- 711 patients sous anorexigènes arrêtés depuis 18 mois en moy.

	IA		IM	
	Dexfen.	Fen./Phen.	Dexfen.	Fen./Phen.
↑ ≥ 1 grade	1.7	0	3.7	3.0
Inchangé	91.9	95.5	87.6	90.6
↓ ≥ 1 grade	6.4	4.5	8.7	6.3

(Gardin et al. JAMA 2001;286:2011-4)

Conclusion

- Un signal est détecté sur les valves cardiaques
- Les propositions du laboratoire sont :
  - Contre indication si anomalie valvulaire
  - Surveillance échocardiographique sous traitement
- La surveillance échocardiographique proposée dans le RCP est adéquate

Audition du Laboratoire *SERVIER*

- Proposition du Laboratoire SERVIER
- Analyse des anomalies valvulaires cardiaques
  - Pr B. Iung
- Analyse diabétologique du rapport bénéfice/risque
  - Pr P.J Guillausseau

Analyses des anomalies valvulaires cardiaques

Expert cardiologue

Pr Bernard Iung

PU-PH Service de Cardiologie

Hôpital Bichat

Analyses des anomalies valvulaires cardiaques

Expert cardiologue

Pr Bernard Iung

PU-PH Service de Cardiologie

Hôpital Bichat

Expertise

- Rapport d'expert sur les cas de Pharmacovigilance
- Analyse des données échocardiographiques d'une étude clinique

Recommandations ASE pour la Quantification des Régurgitations : Insuffisance Aortique

Table 6 Application of specific and supportive signs, and quantitative parameters in the grading of aortic regurgitation severity

	Mild	Moderate		Severe
Specific signs for AR severity	• Central Jet, width < 25% of LVOT[ξ] • Vena contracta < 0.3 cm[ξ] • No or brief early diastolic flow reversal in descending aorta	Signs of AR>mild present but no criteria for severe AR		• Central Jet, width ≥ 65% of LVOT[ξ] • Vena contracta > 0.6cm[ξ]
Supportive signs	• Pressure half-time > 500 ms • Normal LV size*	Intermediate values		• Pressure half-time < 200 ms • Holodiastolic aortic flow reversal in descending aorta • Moderate or greater LV enlargement**
Quantitative parameters[ψ]				
R Vol, ml/beat	< 30	30-44	45-59	≥ 60
RF, %	< 30	30-39	40-49	≥ 50
EROA, cm^2	< 0.10	0.10-0.19	0.20-0.29	≥ 0.30

AR, Aortic regurgitation; *EROA*, effective regurgitant orifice area; *LV*, left ventricle; *LVOT*, left ventricular outflow tract; *R Vol*, regurgitant volume; *RF*, regurgitant fraction.
* LV size applied only to chronic lesions. Normal 2D measurements: LV minor-axis ≤ 2.8 cm/m^2, LV end-diastolic volume ≤ 82 ml/m^2 (2).
[ξ] At a Nyquist limit of 50–60 cm/s.
** In the absence of other etiologies of LV dilatation.
[ψ] Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe regurgitation as shown.

(Zoghbi et al. J Am Soc Echocardiogr 2003;16:777-802)

Recommandations ASE pour la Quantification des Régurgitations : Insuffisance Mitrale

Table 3 Application of specific and supportive signs, and quantitative parameters in the grading of mitral regurgitation severity

	Mild	Moderate		Severe
Specific signs of severity	• Small central jet < 4 cm^2 or < 20% of LA area[ψ] • Vena contracta width <0.3 cm • No or minimal flow convergence[ξ]	Signs of MR>mild present, but no criteria for severe MR		• Vena contracta width ≥ 0.7cm *with* large central MR jet (area > 40% of LA) or *with* a wall-impinging jet of any size, swirling in LA[ψ] • Large flow convergence[ξ] • Systolic reversal in pulmonary veins • Prominent flail MV leaflet or ruptured papillary muscle
Supportive signs	• Systolic dominant flow in pulmonary veins • A-wave dominant mitral inflow[ϕ] • Soft density, parabolic CW Doppler MR signal • Normal LV size*	Intermediate signs/findings		• Dense, triangular CW Doppler MR jet • E-wave dominant mitral inflow (E >1.2 m/s)[ϕ] Enlarged LV and LA size**, (particularly when normal LV function is present).
Quantitative parameters[ς]				
R Vol (ml/beat)	< 30	30-44	45-59	≥ 60
RF (%)	< 30	30-39	40-49	≥ 50
EROA (cm^2)	< 0.20	0.20-0.29	0.30-0.39	≥ 0.40

CW, Continuous wave; *EROA*, effective regurgitant orifice area; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve; *MR*, mitral regurgitation; *R Vol*, regurgitant volume; *RF*, regurgitant fraction.
* LV size applied only to chronic lesions. Normal 2D measurements: LV minor axis ≤ 2.8 cm/m^2, LV end-diastolic volume ≤ 82 ml/m^2, maximal LA antero-posterior diameter ≤ 2.8 cm/m^2, maximal LA volume ≤ 36 ml/m^2 (2,33,35).
** In the absence of other etiologies of LV and LA dilatation and acute MR.
[ψ] At a Nyquist limit of 50-60 cm/s.
[ϕ] Usually above 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.
[ξ] Minimal and large flow convergence defined as a flow convergence radius < 0.4 cm and ≤ 0.9 cm for central jets, respectively, with a baseline shift at a Nyquist of 40 cm/s; Cut-offs for eccentric jets are higher, and should be angle corrected (see text).
[ς] Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe as shown.

(Zoghbi et al. J Am Soc Echocardiogr 2003;16:777-802)

Recommandations ASE pour la Quantification des Régurgitations

Insuffisance mitrale

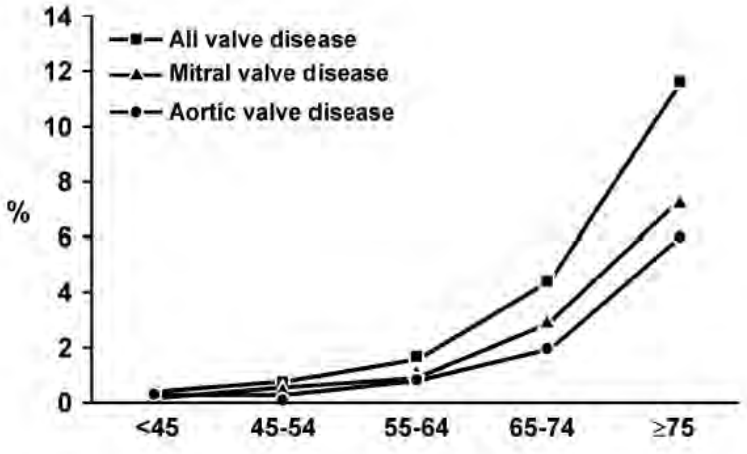
The consensus of the Task Force is to classify grading of severity of regurgitation into mild, moderate, and severe. In cases of overlap or intermediate severity, the terms "mild-to-moderate" or "moderate-to-severe" can be used. "Trace" regurgitation is also used in the event that regurgitation is barely detected. Usually this can be physiologic, particularly in right heart valves and mitral valve, and may not produce an audible murmur.

(Zoghbi et al. J Am Soc Echocardiogr 2003;16:777-802)

Epidémiologie des Valvulopathies

11 911 Echocardiographies
Sténoses ou régurgitations ≥ « *mild* »

Figure 1B



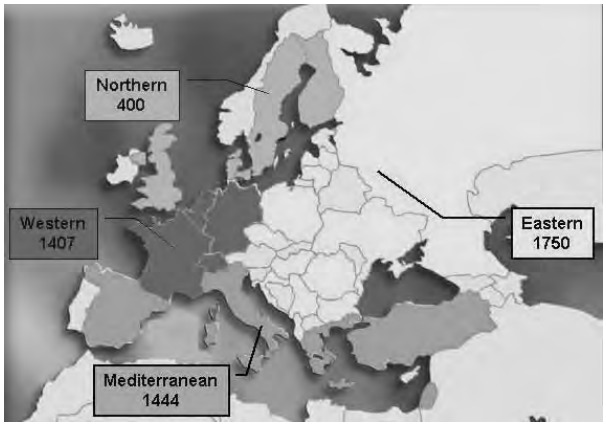
(Nkomo et al. Lancet 2006;368:1005-11)

Euro Heart Survey on Valvular Heart Disease

- 5001 pts included between April and July 2001
- In 92 centres from 25 countries
- 1269 valvular interventions during the survey period

Primary and significant valve disease as defined by echocardiography :

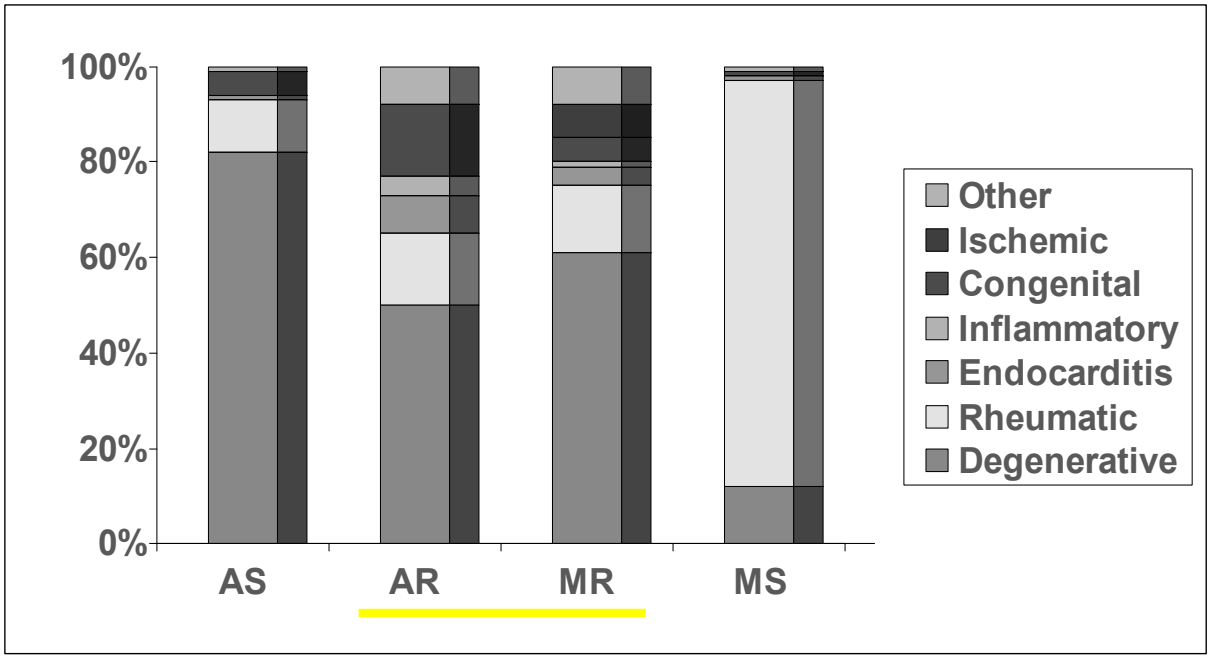
AS = max. jet velocity ≥ 2.5 m/s.
MS = valve area ≤ 2cm²
Mitral Regurgitation = grade ≥ mild
Aortic Regurgitation = grade ≥ mild



(Iung et al. Eur Heart J 2003;24:1244-53)

Single Native Valve Disease

Etiology

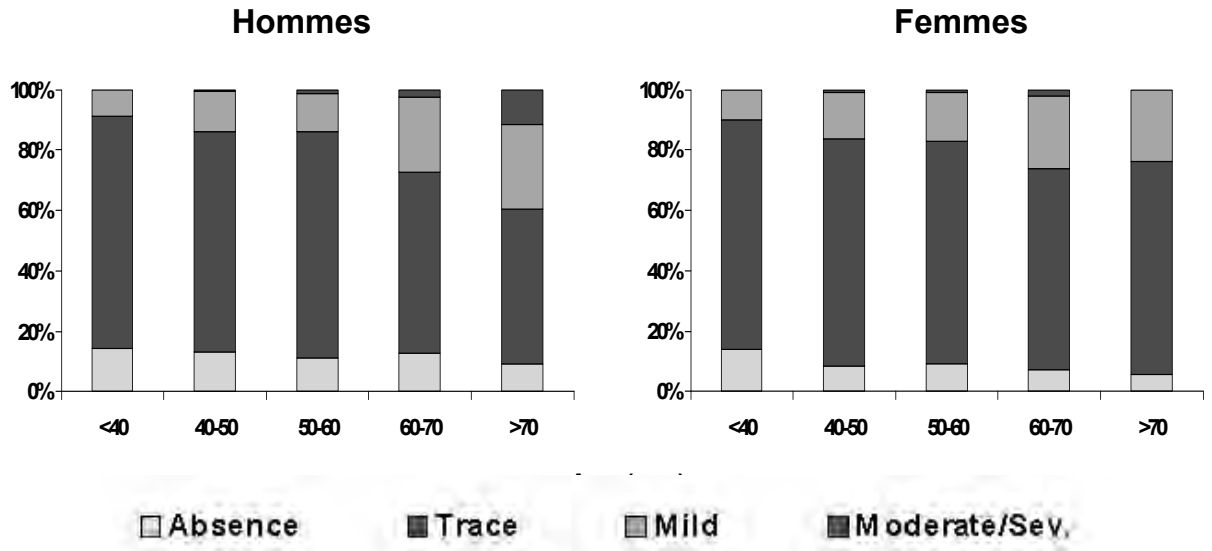


En population générale, la simple constatation d'une valvulopathie ne permet pas d'imputer celle-ci à un traitement médicamenteux

Valvulopathies en Population Générale

Insuffisance Mitrale

3589 échocardiographies issues de la cohorte de Framingham

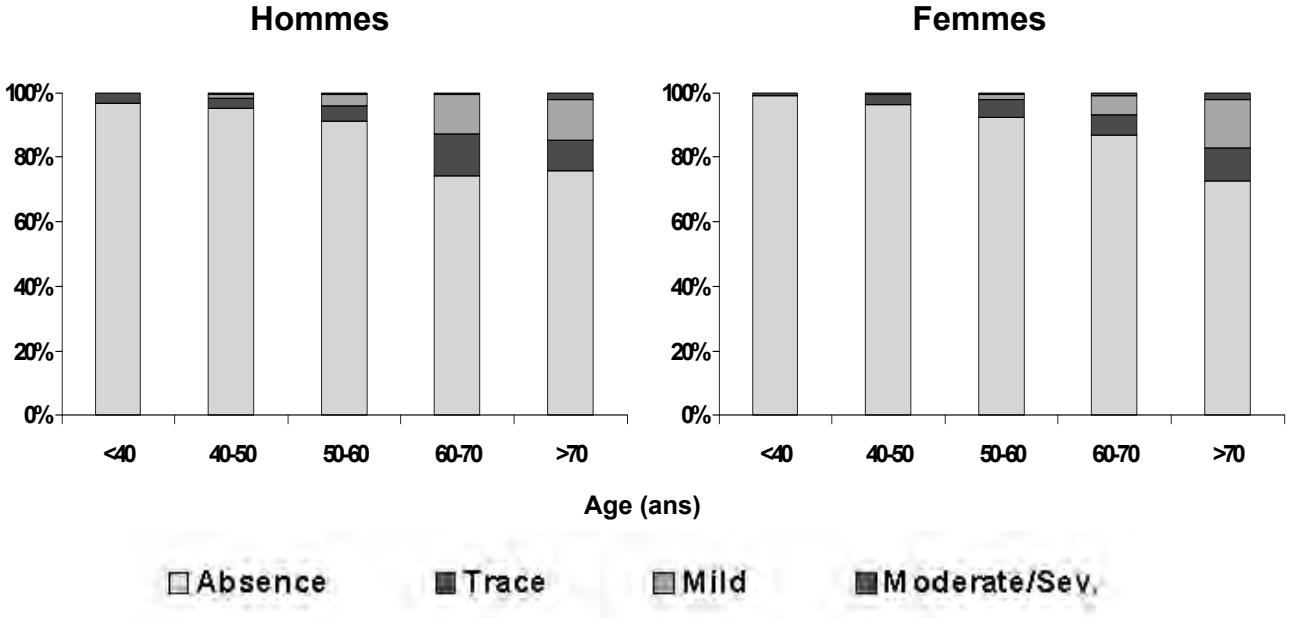


(Singh et al. Am J Cardiol 1999;83:897-902)

Valvulopathies en Population Générale

Insuffisance Aortique

3589 échocardiographies issues de la cohorte de Framingham



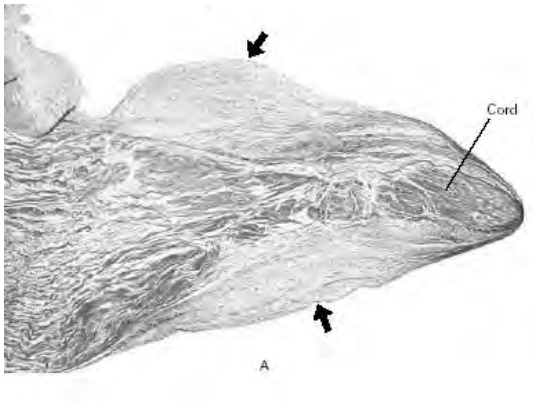
(Singh et al. Am J Cardiol 1999;83:897-902)

Critères d'imputabilité médicamenteuse

- **Échocardiographie**
  - Régurgitation plutôt que sténose, caractérisée par épaississement valvulaire et restriction de la cinétique valvulaire
  - Régurgitation au moins « *mild* » (aortique) ou « *moderate* » (mitrale) - critères FDA
- **Macroscopie**
  - Épaississement valvulaire avec plaques de fibrose blanchâtre
- **Anatomopathologie**
  - Fibrose dense en surface avec architecture valvulaire peu modifiée

Valvulopathies médicamenteuses

- valves épaissies et restrictives
- aspect macroscopique et histologique identique aux valvulopathies carcinoïdes ou secondaires au methysergide



- fibrose dense de surface sans modification de l'architecture

(Connolly N Engl J Med 1997;337:581-8)

Expertise des « cas benfluorex » : méthode

- **Cas opérés**
  - Documentation anatomique macroscopique
  - Documentation anatomopathologique
- **Cas non opérés**
  - Documentation échographique
- **Existence d'une autre cause possible**
  - Rhumatismale
  - Dégénérative
- **Autre prise médicamenteuse imputable**
  - Anorexigènes
  - Agonistes dopaminergiques
  - …/…

Expertise des « cas benfluorex »: critères

- **Fortement évocateur**
  - Anatomopathologie correspondant aux descriptions publiées
  - Pas d'autre prise médicamenteuse imputable
- **Possible**
  - Pas d'histologie
  - Échographie ou macroscopie compatible
  - Pas d'autre cause patente
- **Faible**
  - Documentation ne permettant pas de conclure
- **Très faible**
  - Autre cause très probable sur la conjonction :
    contexte clinique,
    échographie,
    ± anatomopathologie.

Expertise des « cas benfluorex » : résultats

Imputabilité	Forte	Possible	Faible	Très faible	Total
Opérés	6	6	3	2	**17**
Non-opérés, échographie		10		5	**15**
Non documentés			13		**13**
Total	**6**	**16**	**16**	**7**	***45***

Etude REGULATE
suivi échocardiographique (615 patients / 1 an)

La méthodologie, **rigoureuse, d'une grande sensibilité,**

montre :

A l'inclusion, chez les patients diabétiques en surpoids

- 51% des malades ont une ou des anomalies morphologiques prévalentes (33% aorte, 41% mitrale, 4% tricuspide)
- 84% des malades ont une ou des anomalies fonctionnelles prévalentes (17% aorte, 61% mitrale, 72% tricuspide)
- 8.9 % sans aucune anomalie

Etude REGULATE

suivi échocardiographique (615 patients / 1 an)

En final

- modification morphologique incidente chez 12 patients :

  8 Benfluorex vs 4 Pioglitazone (OR = 2.0, 95%CI [0.59 ; 6.69], p=0.26)

- modification fonctionnelle détectée chez 115 patients :

  82 Benfluorex vs 33 Pioglitazone (OR = 2.97, 95%CI [1.91 ; 4.63], p< 0.0001)

  5 patients ont une anomalie valvulaire fonctionnelle de grade ≥ 2 incidente

  2 Benfluorex vs 3 Pioglitazone (OR = 0.65, 95%CI [0.11 ; 3.94], p=0.64)

Sur le plan clinique : aucun signe ou symptôme évocateurs de valvulopathie émergente n'a été rapporté dans cette étude.

Interprétation

- Les données pronostiques et de surveillance ne concernent que les valvulopathies ≥ « *mild* »
- Les valvulopathies « *trivial* » sont considérées comme physiologiques en position mitrale ou tricuspide
- La comparaison des prévalences des valvulopathies en fonction du temps ne suggère pas un potentiel évolutif majeur des valvulopathies « *trivial* »

Recommandation de Surveillance des Valvulopathies ESC Guidelines 2007

Insuffisance mitrale

Serial testing

Asymptomatic patients with moderate MR and preserved LV function can be clinically followed-up on a yearly basis and echocardiography should be performed every 2 years.

Asymptomatic patients with severe MR and preserved LV function should be seen every 6 months and echocardiography performed every year, the follow-up being closer if no previous evaluation is available, and in patients with borderline values, or significant changes since the last visit. These patients should be instructed to promptly report any change in functional status.

Patients asymptomatiques avec IM « *moderate* » et fonction VG normale : surveillance écho tous les 2 ans

Insuffisance aortique

Serial testing

Patients with mild-to-moderate AR can be seen on a yearly basis and echocardiography performed every 2 years.

All patients with severe AR and normal LV function should be seen for follow-up at 6 months after their initial examination. If LV diameter and/or EF show significant changes, or they become close to the thresholds for intervention, follow-up should continue at 6 month intervals. When parameters are stable, follow-up can be yearly.

Patients avec IA > « *mild* » : surveillance écho tous les 2 ans

(Eur Heart J 2007; 28:230-68)

Anorexigènes et Valvulopathies

Evolution après Arrêt

- 50 patients sous anorexigènes arrêtés depuis 6 mois en moy.
  - 86% IA ≥ *mild* (grade 2) , 76% IM ≥ *mild* (grade 2)
  - Echo répétée après 1 an de délai moyen
    - Amélioration ≥ 1 grade pour 44% des IA et 54% des IM
    - Aggravation ≥ 1 grade pour 2,3% des IA et 2,6% des IM

(Mast et al. Ann Intern Med 2001;134:261-6)

- 711 patients sous anorexigènes arrêtés depuis 18 mois en moy.

	IA		IM	
	Dexfen.	Fen./Phen.	Dexfen.	Fen./Phen.
↑ ≥ 1 grade	1.7	0	3.7	3.0
Inchangé	91.9	95.5	87.6	90.6
↓ ≥ 1 grade	6.4	4.5	8.7	6.3

(Gardin et al. JAMA 2001;286:2011-4)

Conclusion

- Un signal est détecté sur les valves cardiaques

- Les propositions du laboratoire :
  - Contre indication si anomalie valvulaire
  - Surveillance échocardiographique sous traitement

  sont adéquates

Annexe 3-83

Gérard BAPT
Député de la Haute – Garonne
Maire de Saint – Jean

Saint – Jean, le 13 novembre 2010

A

Monsieur Jean MARIMBERT
Directeur Général de l'AFSSAPS
143/147 Bd Anatole France
93285 SAINT DEINIS Cedex

Monsieur le Directeur Général,

J'accuse réception de votre réponse en date du 8 novembre à mon courrier du 13 septembre, et vous avoue d'emblée qu'elle me déçoit profondément.

1 – s'agissant de la formulation des comptes rendus, votre interprétation de la directive européenne 2001 – 83 – CE est très restrictive. Il n'est pas possible de mettre en rapport telle prise de position avec tel conflit d'intérêt. Il n'est pas possible non plus de savoir qui, lors du comité technique de pharmacovigilance du 10 septembre 1998 avait posé la question pertinente de la parenté chimique du Benfluorex avec les amphétaminiques…

2 – Concernant la nature chimique du Benfluorex, vous vous contentez de reprendre l'essentiel de la réponse faite par P. Schiavi, directeur de la Division Scientifique Pharmacologique de Servier, Trésorier de la Société Française de Pharmacologie, à l'interrogation du Dr D. Kowalski, du CHU de Brest, le 7 avril 2008.
Mais dès 1999, le Dr E. Fradet, du CRPV de Limoges, classe le Benfluorex dans la catégorie des anorexigènes centraux, dérivés amphétaminiques, dont on connaît les effets cardiovasculaires constatés aux USA depuis 1990. (Lyon Pharmaceutique, 1999, 50-2)
Mais dès 1978, le Dr H. Pradal décrivait, dans le « dictionnaire critique des médicaments » (éditions du Couloir) le Benfluorex comme « un dérivé de la molécule du Pondéral », coupe faim commercialisé par le même laboratoire Servier : il s'agit « d'une amphétamine modifiée par adjonction d'un radical organique » en faisant « le traitement logique des surcharges lipido glucidiques athérogènes »…Il ajoutait que « sa parenté avec les amphétamines devrait rendre très prudent en cas d'hypertension artérielle, d'insuffisance cardiaque et chez les sujets anxieux ou présentant des antécédents de suicide »…En 1998, l'URCAM de Bourgogne avait montré que 35 % des prescriptions de Médiator se faisaient hors AMM, en grande majorité chez des femmes non diabétiques, dont les 2/3 ne présentaient même pas d'obésité avérée ! La même année, l'Agence du Médicament dans un « avis aux prescripteurs d'anorexigènes », rappelait qu'en mai 1995, elle avait restreint l'utilisation de ces produits aux seules unités hospitalières spécialisées, pour s'appliquer à des obésités majeures, après échec d'un traitement diététique adapté, pour des durées de traitement n'excédant pas trois mois…en raison de « la survenue de quelques cas de maladie vasculaire pulmonaire graves et souvent mortels ». Pourquoi s'être contenté d'interdire le Benfluorex des seules prescriptions magistrales ?

Le Médiator pourtant, dans des conditions connues et très fréquentes de prescription « hors AMM » au titre de coupe-faim, a continué sa tranquille vie jusqu'en 2007, date à laquelle une restriction a supprimé l'indication de prescription pour les hypertriglycéridémies... huit ans après que son inutilité ait été signalée par la commission de pharmacovigilance de l'Afssaps et la commission de transparence !

3 – Vous m'indiquez « qu'à partir de septembre 1997, à la suite du retrait d'Isoméride et Pondéral en raison de cas de valvulopathie rapportés aux USA, une attention particulière s'est portée aussi sur le risque possible de telles complications avec Benfluorex ».
Je n'ai retrouvé aucune trace de cette attention portée aux valvulopathies dans les comptes - rendus de commissions dont j'ai eu connaissance, jusqu'aux deux simples lignes consacrées à la publication, en 2006, de l'observation toulousaine de valvulopathie sous Médiator chez une patiente de 48 ans sans antécédent. Vous indiquez à ce sujet qu'il s'agit du premier cas publié en France : il venait néanmoins après celui publié en Espagne en 2003, qui y avait conduit au retrait du Benfluorex en 2005. Vous dites considérer le lien de causalité certain sur le cas de 2006. Quelles en ont été les suites ? Pourquoi toujours aucune alerte jusqu'en 2009 ? ... Ce n'est qu'après l'initiative du Dr Frachon à Brest qu'apparaît dans les comptes - rendus une préoccupation vers les valvulopathies !

4 – Vous me proposez une évaluation rétrospective des cas de notifications spontanées vers la base de données de pharmacovigilance. Je n'ai pas eu le temps d'expertiser l'ensemble des cas que vous réfutez. Néanmoins l'un d'entre eux m'interpelle particulièrement, ayant eu l'opportunité récente d'échanger avec les deux médecins marseillais concernés. Les deux fiches de notification y sont remarquablement claires :

- La fiche n° MA 99 00 176 du 10.02.1999 du Dr Chiche, cardiologue traitant concernant un patient médecin, traité pendant six ans par deux comprimés de Médiator pour surpoids et hypercholestérolémie. Le Dr Chiche précise bien, dans la note d'accompagnement qu'il rédige le 7.02.1999 à l'intention du CRPV, que l'insuffisance aortique n'avait pas été notée par les examens de surveillance y compris coronarographie et échocardiographie réalisés après le petit infarctus du myocarde postérieur survenu en 1992 et qui avait entrainé une petite insuffisance mitrale.
Il suggère même que « le Vidal devrait mentionner l'appartenance du Benfluorex aux groupes des amphétamines, car pouvant être utilisé comme produit dopant » et rappelle sa présence sur la liste des anorexigènes fournie par l'agence du médicament !

- La fiche de transmission du 17.02.1999 du Dr Jean Pastor, du CRPV du CHU de Marseille qui validait l'imputabilité de l'insuffisance aortique au Médiator.

Il est dommage que la perspicacité du Dr Chiche n'ait été récompensée par aucun retour de la part du dispositif de pharmacovigilance...si ce n'est par la visite qu'il a reçue quelques semaines après la notification, d'un émissaire de Servier venu lui expliquer qu'aucune causalité n'existait entre valvulopathie et Médiator ! Vous m'indiquez vous – même, sur ce cas, Monsieur le Directeur, que l'on ne peut être formel en raison de l'antécédent d'infarctus du myocarde avant la prise de Médiator. Je serais curieux d'échanger avec le « cardiologue-expert » qui a indiqué qu'une insuffisance aortique pourrait avoir été causée par un infarctus du myocarde, de surcroit postérieur : il s'agirait d'une première mondiale !

Il paraît évident que si après le cas de Brest, fin 2008, de nombreux autres ont été déclarés courant 2009, en majorité à Brest et Amiens, c'est tout simplement parce qu'ils ont commencé à être recherchés à la seule initiative des médecins brestois.

J'ai moi-même pu constater auprès de mon ancien cabinet de cardiologie, mais aussi la semaine dernière encore auprès du nouveau « patron » de la chirurgie cardiaque du CHU, que le lien valvulopathie – Médiator était toujours totalement méconnu !

Annexe 3-83

Alors que deux génériques du Médiator recevaient encore leur AMM il y a moins de deux ans, tout était pourtant écrit depuis une décennie voire 30 ans si l'on relit les avertissements du Dr Pradal ancien de chez Servier et bien au fait des pratiques mensongères de ce laboratoire !

J'ai décidé d'arrêter les échanges avec l'Afssaps sur ce sujet, las que je suis d'avoir l'impression de me battre contre des moulins à vent !

Concernant les suites à donner à l'affaire du Médiator, la balle est dans le camp de la Ministre – que j'ai alertée régulièrement depuis le 28 juin – en ce qui concerne les décisions sanitaires à prendre en direction des millions de patients concernés. Elle est aussi dans le camp de la justice en ce qui concerne les dommages, trop souvent irréparables, causés aux victimes et à leurs familles. Il faut espérer que l'étude de la CNAM nous en donnera l'ampleur...

Concernant les produits de santé, ma préoccupation va désormais aller à la question des sels d'aluminium présents dans certains vaccins, et leur éventuelle imputabilité dans des affections neurodégénératives type SEP.

Concernant la sécurité sanitaire, je suis convaincu qu'une révolution démocratique s'impose, alliant la transparence du travail des commissions d'expertise, la clarté sur les conflits d'intérêt, l'exploitation systématique de toutes les bases de données existante, les moyens donnés à des études cliniques publiques, et la présence systématique de représentants des patients afin que les alertes ne soient pas annihilées par les influences marchandes.

Je vous prie d'agréer, ***Monsieur le Directeur Général***, l'expression de mes salutations.

Cc : Mme Roselyne BACHELOT
Ministre de la Santé

GB/MTRS 13112010

Gérard BAPT
Député Maire de Saint – Jean
Rapporteur Spécial de la «Mission Santé»
Pour la Commission des Finances
De l'Assemblée Nationale

Annexe 3-84

Benfluorex, valvulopathies cardiaques et décès

Alain Weill, Michel Païta, Phillipe Tuppin, Michel Piolot

Caisse nationale de l'assurance maladie, Paris, France.

Rapport du 28/09/2010 adressé à l'Afssaps le 28/09/2010

Introduction

Quatre études observationnelles [1,2,3,4] ont montré que le benfluorex, dérivé de la fenfluramine, était significativement associé à des valvulopathies cardiaques de régurgitation mitrales et aortiques ainsi qu'à des chirurgies de remplacement valvulaire. Après exposition au benfluorex le risque de chirurgie de remplacement valvulaire cardiaque était multiplié par un facteur 4. Le mécanisme d'action rapporté est une activation des récepteurs sérotoninergiques présents à la surface des vaisseaux pulmonaires et des valves cardiaques par un métabolite toxique, la norfenfluramine [5,6,7].

Le 30 novembre 2009 l'Afssaps a suspendu l'AMM du benfluorex considérant que le rapport bénéfice-risque était défavorable compte tenu du risque avéré de valvulopathie associé à la prise de ce médicament et de son efficacité modérée dans l'indication octroyée par l'AMM : adjuvant du régime adapté chez les diabétiques avec surcharge pondérale (diabète de type 2). Suite à la décision de l'Afssaps l'European Medicines Agency (EMA) a également recommandé le 18 décembre 2009, le retrait des médicaments contenant du benfluorex dans l'Union européenne, parce que «leurs risques, notamment le risque de maladie des valvules cardiaques, sont plus importants que leurs avantages »[8].

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[1] Frachon I, Etienne Y, Jobic Y, Le Gal G, Humbert M, Leroyer C. Benfluorex and unexplained valvular heart disease: a case-control study. PLoS One. 2010 Apr 12;5(4):e10128.

[2]Tribouilloy C, Rusinaru D, Henon P, et al. Restrictive organic mitral regurgitation associated with benfluorex therapy. Eur J Echocardiogr. 2010 Mar 30.

[3] Compte rendu de l'étude regulate in National Pharmacovigilance Committee: Minutes of Tuesday 29 September 2009 meeting. http://www.afssaps.fr/var/afssaps_site/storage/original/application/d3586501cd537d588059288f37135194.pdf (accessed 5 November 2009). French.

[4] Weill A, Païta P, Tuppin P, Fagot JP, Neumann A, Simon D, Ricordeau P, Montastruc JL, Allemand H. Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus. pharmacoepidemiology and drug safety 2010; 9999: 1–7. In press.

[5] Fitzgerald LW, Burn TC, Brown BS, et al. Possible role of valvular serotonin 5-HT(2B) receptors in the cardiopathy associated with fenfluramine. Mol Pharmacol 2000; 57: 75-81.

[6] Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 2000; 102(23): 2836-41.

[7] Roth BL. Drugs and valvular heart disease. N Engl J Med. 2007; 356: 6-9.

[8] Press release European Medicines Agency 18 December 2009, EMA/CHMP/815033/2009 Press Office http://www.ema.europa.eu/pdfs/human/referral/benfluorex/Benfluorex_81503309en.pdf (accessed 28 December 2009).

Dans une thèse de diplôme d'État de docteur en pharmacie soutenue le 25 juin 2010 à Rennes et dont le sujet était *l'utilisation de nouveau outils en pharmacovigilance : à propos du retrait du Médiator® (benfluorex)* il est fait la mention suivante page 106 : « *En résumé, d'après les études réalisées, il semblerait qu'il y ait eu ces dernières années entre 150 et 250 hospitalisations chaque année en France, liées directement à une toxicité du Médiator et ayant entraîné une trentaine de décès. Si nous multiplions par 30 ans de commercialisation, le nombre de morts pourrait être entre 500 et 1000 morts. Ces dannés sont à tempérer. Il faudrait vérifier que le nombre de prescription a été stable au cours du temps.* »[9]
Le quotidien Le Monde a publié le 24 août 2010 un Point de vue intitulé « *Mediator : Combien de morts ?* » du député Gérard Bapt, rapporteur spécial de la mission santé pour la Commission des finances qui reprend ces informations : « *Une étude universitaire évalue entre 500 et 1000 le nombre de décès en relation directe avec le Médiator.* » [10]
A la suite de la parution de cet article l'Afssaps a saisi la CNAMTS dès le 25 août 2010 pour réaliser *une analyse épidémiologique sur une cohorte qui permettrait d'avoir un début de documentation de l'impact du benfluorex sur la mortalité.*

L'objectif de ce travail était de fournir des éléments objectifs pour savoir s'il existait une association possible entre des cas d'exposition au benfluorex et des décès consécutifs à une insuffisance valvulaire cardiaque.

2 Méthode

Nous avons réalisé une étude de suivi d'une cohorte de personnes exposées au benfluorex en 2006 à partir des données anonymes du système national d'information interrégimes de l'assurance maladie (SNIIRAM)[11,12]. A la date de ce travail nous ne disposions plus, dans le SNIIRAM, des données individuelles anonymes de consommation médicamenteuse d'avant 2006.

Toutes les personnes affiliées au régime général étaient éligibles à l'exception de celles des sections locales mutualistes (étudiants et fonctionnaires). La population source était ainsi

[9] Michelet F. Utilisation de nouveaux outils en pharmacovigilance ; à propos du retrait du Médiator® (benfluorex). Thèse pour le diplôme d'état de docteur en pharmacie présentée et soutenue le 25 juin 2010. Université de Rennes 1. Faculté de pharmacie.

[10] Gérard Bapt. Point de vue : Mediator : Combien de morts ? Le monde du 24/08/2010. http://www.lemonde.fr/idees/article/2010/08/24/mediator-combien-de-morts_1402014_3232.html

[11] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique. 2010 Aug;58(4):286-90.

[12] Martin-Latry K, Bégaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf. 2010; 19: 256-265.

composée de 48,4 millions de personnes assurées au régime général, soit environ 76% de la population résidente en France. Les personnes exposées étaient définies par le remboursement d'au moins une boite de benfluorex en 2006.

Après chaînage des données les événements recherchés dans le PMSI [médecine-chirurgie-obstétrique (MCO)] de la période 2006 à 2009 étaient une ou plusieurs hospitalisations pour une insuffisance valvulaire toutes valves cardiaques et toutes causes confondues (tableau 1).

Tableau 1 : critères utilisés pour définir la maladie valvulaire cardiaque de régurgitation

	PMSI MCO avec un diagnostic principal ou relié =
hospitalisation pour insuffisance valvulaire	I340 Insuffisance (de la valvule mitrale) non rhumatismale I051 Insuffisance (de la valvule mitrale) rhumatismale I351 Insuffisance (de la valvule) aortique non rhumatismale I061 Insuffisance (de la valvule) aortique rhumatismale I361 Insuffisance (de la valvule) tricuspide non rhumatismale I071 Insuffisance (de la valvule) tricuspide rhumatismale

Nous avons recherché pour chacune de ces personnes le statut vital jusqu'au 31 juillet 2010, soit un suivi de 55 mois. Le décès dans le SNIIRAM est connu pour les personnes du régime général (hors fonctionnaires et étudiants), à partir des données issues du statut vital Insee. Ces données sont alimentées par les fichiers du Répertoire national des identifiants des personnes physiques (RNIPP) puis du RNIAM (Répertoire national des identifiants de l'assurance maladie), du RFI (Référentiel individus) et enfin du SNIIRAM. Tous les décès certifiés par l'Insee sont transmis au RNIAM. Ce RNIAM est aussi enrichi de décès dit « non certifié » par l'INSEE (par exemple personne née à l'étranger, résidant en France et décédant à l'étranger).

Nous avons étudié pour chaque personne décédée toutes les hospitalisations à partir du PMSI (Groupe homogène de malade (GHM), diagnostic principal et relié, durée de chaque séjour, ainsi que le mode de sortie : transfert, domicile ou décès). Il existait environ 800 codes dans la nomenclature des GHM sur la période 2006-2008 (PMSI V9 puis V10) et près de 2 300 en 2009 (PMSI V11). L'hypothèse implicite est que les éléments médicaux contenus dans le résumé standardisé anonymisé (RSA) du PMSI, notamment pour les hospitalisations conduisant au décès, vont permettre de connaître la cause la plus probable du décès.

Deux exemples illustrent cette démarche.
Cas n° 1 : homme de 78 ans décédé en soins palliatifs avec un diagnostic de leucémie myéloïde chronique. La cause du décès retenue est une leucémie myéloïde chronique.
Cas n° 2 : femme de 53 ans décédée au cours d'une hospitalisation pour insuffisance de la valvule aortique non rhumatismale et insuffisance de la valve mitrale avec une chirurgie de remplacement valvulaire sous circulation extracorporelle. Cette hospitalisation suivait une

précédente en cardiologie avec un acte diagnostic de cathétérisme cardiaque avec un diagnostic d'insuffisance de la valvule aortique non rhumatismale et insuffisance de la valve mitrale. La cause du décès retenue est l'insuffisance valvulaire mitrale et aortique.
Pour chaque cas de décès l'ensemble des hospitalisations étaient analysées. Par ailleurs nous avons recueilli la notion d'Affection de Longue durée (ALD) avec le diagnostic (code CIM-10) et la date de début, la quantité de benfluorex délivrée entre le 1er janvier 2006 et la date du décès et les traitements antidiabétiques et anticoagulants.

En définitive la détermination des causes supposées de décès à l'aide du PMSI a répondu en règle générale au schéma suivant[13] :
Si le décès avait eu lieu à l'hôpital, la cause de décès supposée correspondait au diagnostic principal du séjour au cours duquel le décès est survenu, quand le code CIM 10 de ce diagnostic principal était une maladie. Lorsque le code CIM 10 était un traitement (chimiothérapie, radiothérapie...), on utilisait alors le diagnostic relié pour déterminer la cause de décès supposée (par exemple cancer du poumon).
Si le décès n'avait pas eu lieu à l'hôpital mais que l'individu avait été hospitalisé au cours des quatre derniers mois (c'est-à-dire au cours du mois de décès ou de l'un des trois mois précédents), on utilisait de la même manière les diagnostics principaux et reliés des deux derniers séjours à l'hôpital.
Si le décès n'avait pas eu lieu à l'hôpital et que l'individu n'avait pas été hospitalisé au cours des quatre derniers mois, la cause de décès retenue était déterminée de façon probabiliste en tenant compte des affections les plus graves. Il était tenu compte des comorbidités, notamment potentiellement létales comme les tumeurs et affections malignes, les autres pathologies cardiovasculaires et différents facteurs pouvant avoir une influence sur le décès (âge...).
A la date de ce travail nous ne disposions pas du PMSI 2010. Pour les décès survenus à la fin du premier semestre 2010 la cause était le plus souvent ignorée. Dans quelques cas néanmoins l'analyse de l'ensemble des hospitalisations de 2006 à 2009 a permis de donner des éléments d'orientation. Cette méthode de détermination des causes probables de décès produit un biais dû au fait que seuls les décès précédés d'une hospitalisation sont parfaitement documentés. En particulier, elle ne permet de renseigner aucun décès brutal à domicile ou sur la voie publique : AVC, arrêt cardiaque sur trouble du rythme, suicide, accident....

L'utilisation du SNIIRAM par les agents habilités de la CNAMTS a fait l'objet d'un avis favorable de la Cnil en novembre 2001 et d'un arrêté ministériel du 11 avril 2002 relatif à sa mise en œuvre. En octobre 2007, un second arrêté a permis l'utilisation de la variable décès

[13] Cette méthode de détermination des causes probables de décès a été utilisée pour un travail médico-économique : Myriam Mezzarobba. Les coûts de le dernière année de vie en 2008 et ses conséquences pour les dépenses de santé. DSES, Caisse nationale de l'assurance maladie.

avec la date exacte issue des données de statut vital de l'Insee et de la Caisse nationale de l'assurance vieillesse. Le statisticien ayant extrait les données était habilité « *profil 30* » pour le croisement de données médicales sensibles.

Les traitements des données ont été réalisés avec le logiciel SAS version 9.01.

3 Résultats

3.1. Description de la population de la cohorte

L'étude portait sur 303 259 personnes exposées au benfluorex en 2006 dont 72,6% de femmes (tableau 2). L'âge moyen était de 52,8 ans.

Tableau 2 : caractéristiques d'âge et de sexe des personnes exposées au benfluorex en 2006

classe d'âge	hommes	femmes	Total
0-19	630	2 314	2 944
20-24	677	5 273	5 950
25-29	1 303	9 136	10 439
30-34	2 458	13 169	15 627
35-39	4 240	17 493	21 733
40-44	6 477	21 411	27 888
45-49	8 987	24 452	33 439
50-54	11 526	28 554	40 080
55-59	14 514	30 968	45 482
60-64	11 732	23 723	35 455
65-69	8 339	16 472	24 811
70-74	6 471	13 717	20 188
75-79	3 819	8 518	12 337
80-84	1 561	3 641	5 202
85-89	372	1 062	1 434
90+	71	179	250
Total	83 177	220 082	303 259

Données SNIIRAM régime général hors SLM

3.2 Hospitalisations pour valvulopathie cardiaque par régurgitation et décès dans la cohorte des exposés

Parmi les 303 259 personnes 556 avaient été hospitalisées au moins une fois pour valvulopathie cardiaque par régurgitation durant la période 2006-2009 soit 184 pour 100 000 (46 pour 100 000 personnes-années). Pour 303 (54%) la ou les hospitalisations étaient motivées par une insuffisance de la valvule mitrale, pour 270 (48%) une insuffisance aortique et pour 77 (18%) une insuffisance tricuspidienne. Le total est supérieur à 100% en raison des atteintes polyvalvulaires.

Parmi les 556 personnes hospitalisées une ou plusieurs fois pour valvulopathie cardiaque par régurgitation durant la période 2006-2009 on a observé 58 décès (10,4%) en 55 mois (figure 1). Les taux de décès observés pour les différentes valvulopathies étaient respectivement de 12,5% pour les atteintes de la valve mitrale et de 7,4 % pour les atteintes de la valve aortique.

Dans le sous-groupe des 180 patients ayant eu une chirurgie de remplacement valvulaire pour insuffisance valvulaire 17 patients étaient décédés (9,4%).

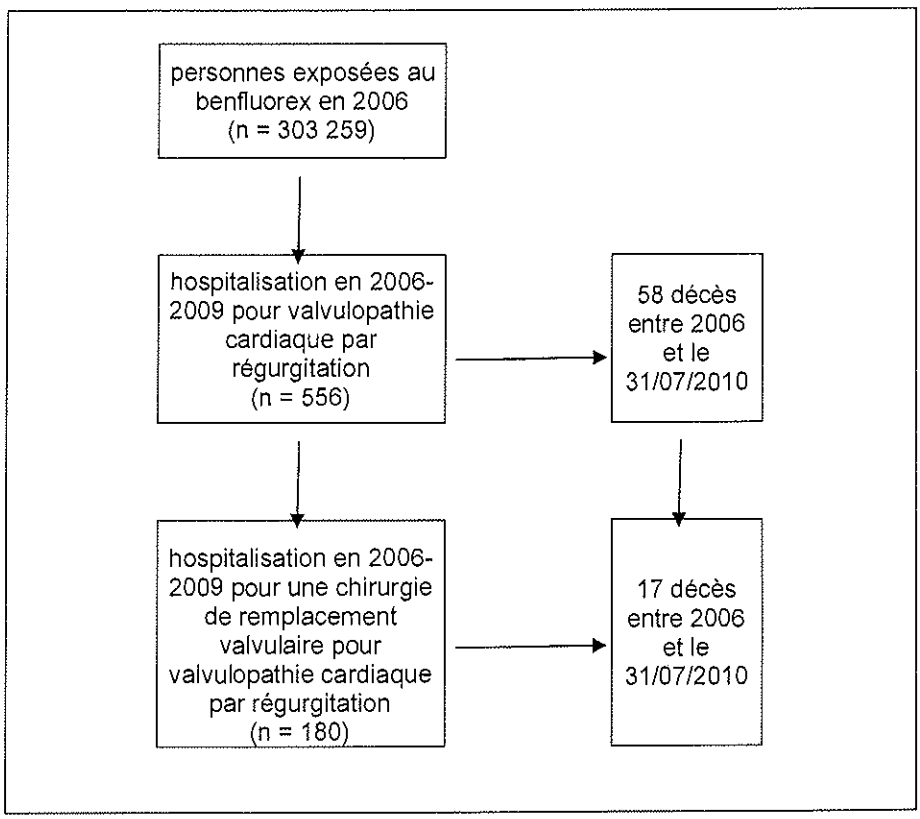


Figure 1 : suivi de la cohorte des personnes traitées pour benfluorex du 1er janvier 2006 au 31 juillet 2010. *Données SNIIRAM régime général hors SLM*

L'insuffisance valvulaire des personnes décédées était 54 fois décrite comme non rhumatismale et 13 fois rhumatismale (tableau 3). Parmi les 58 patients la valvulopathie était constamment codée comme non rhumatismale pour 47 d'entre eux, rhumatismale pour 7 et tantôt rhumatismale et non rhumatismale selon les hospitalisations pour 4 personnes.

Table 3 : type de valvulopathies codées dans le PMSI pour les valvulopathies cardiaques par régurgitation des personnes exposées au benfluorex en 2006 et décédées

CIM-10	libellé	effectif
I340	Insuffisance (de la valvule) mitrale (non rhumatismale)	32
I351	Insuffisance (de la valvule) aortique (non rhumatismale)	18
I051	Insuffisance mitrale rhumatismale	9
I361	Insuffisance non rhumatismale (de la valvule) tricuspide	4
I061	Insuffisance aortique rhumatismale	2
I071	Insuffisance tricuspidienne (rhumatismale)	2
	total des valvulopathies	67

Presque la moitié des 58 décès sont survenus en 2008 (23 décès). L'histogramme suivant présente la répartition selon la date du décès des personnes exposées au benfluorex en 2006 et ayant eu une hospitalisation dans la période 2006-2009 pour valvulopathie cardiaque par régurgitation. Les 9 décès en 2010 correspondaient à un suivi du statut vital jusqu'au 31 juillet 2010, soit 7/12ème d'une année pleine (figure 2). La figure 3 présente les mêmes données sous forme d'une courbe de survie avec son intervalle de confiance.

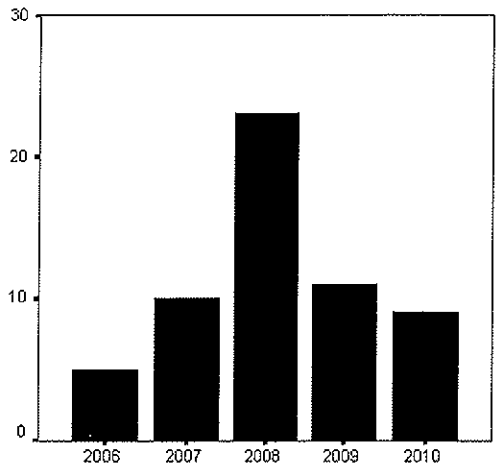
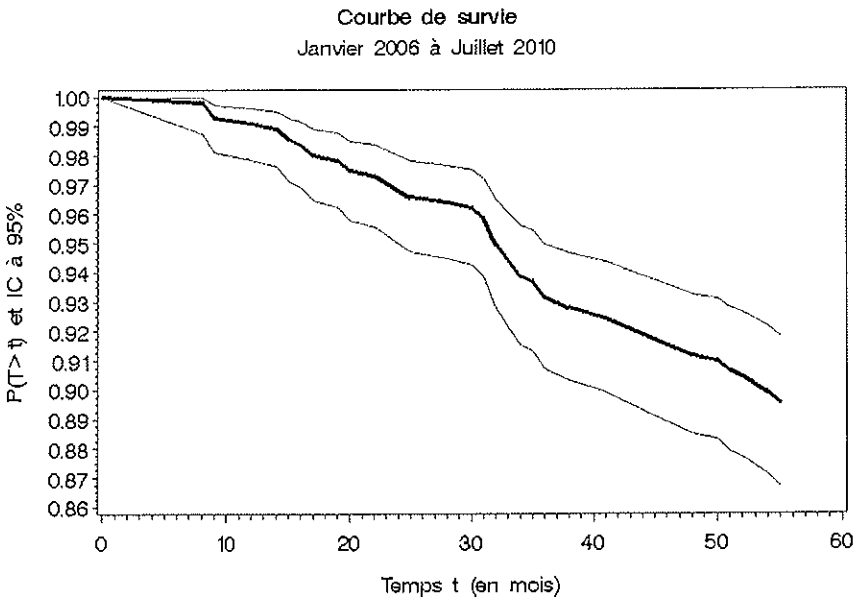


Figure 2 : histogramme présentant la répartition selon l'année du décès des personnes exposées au benfluorex en 2006 et ayant eu une hospitalisation dans la période 2006-2009 pour valvulopathie cardiaque par régurgitation (n = 58) *Données SNIIRAM régime général hors SLM*



Méthode : Courbe de Kaplan–Meier (PROC LIFETEST de SAS)

Figure 3 : Courbe de survie de Kaplan-Meier des personnes exposées au benfluorex en 2006 et ayant eu une hospitalisation dans la période 2006-2009 pour valvulopathie cardiaque par régurgitation (n = 556) *Données SNIIRAM régime général hors SLM*

3.3 Etude des causes probables du décès

L'âge moyen des 58 personnes décédées était de 69 ans au jour du décès (extrême de 38 à 88 ans). Il y avait 36 femmes (62%) pour 22 hommes (38%). On retrouvait dans le PMSI en moyenne 9 séjours hospitaliers entre 2006 et le jour du décès. En moyenne les 58 patients avaient eu 165 grammes de benfluorex remboursés (extrême 4,5 grammes à 490 grammes, soit 1 à 109 boites entre le 1er janvier 2006 et le décès).

Plus de 90% des patients, soit 53 sur 58 patients, étaient en affection de longue durée (ALD) à la date du décès : la plupart des personnes étaient en ALD pour pathologie cardiovasculaire et/ou diabète. Il est notable de constater que six patients étaient en ALD pour affection psychiatrique de longue durée : épisodes dépressifs (3), troubles spécifiques de la personnalité (2) et psychose non organique (1). Pour deux personnes le diagnostic exact de l'ALD n'a pu être retrouvé.

Tableau 4 : nature des affections de longue durée des 58 patients décédés (à la date du décès)

Libelle de l'ALD	effectif
Insuffisance cardiaque grave, troubles du rythme graves, cardiopathies valvulaires graves, cardiopathies congénitales graves	24
Diabète de type 1 et diabète de type 2	19
Hypertension artérielle sévère	9
Maladie coronaire	9
Affections psychiatriques de longue durée	6
Artériopathies chroniques avec manifestations ischémiques	5
Tumeur maligne, affection maligne du tissu lymphatique ou hématopoïétique	5
Insuffisance respiratoire chronique grave	4
Polyarthrite rhumatoïde évolutive grave	2
Accident vasculaire cérébral invalidant	1
Déficit immunitaire primitif grave nécessitant un traitement prolongé et infection par le VIH	1
Néphropathie chronique grave et syndrome néphrotique primitif	1
Polypathologie invalidante	1
Spondylarthrite ankylosante grave	1

Données SNIIRAM régime général hors SLM

L'analyse de la consommation médicamenteuse montrait que 28 patients (48%) avaient consommé des antidiabétiques (hors benfluorex), 35 (60%) des anticoagulants de type antivitamines K (avec 17 délivrances médicamenteuses en moyenne) et 23 (40%) des héparíniques. Les deux tiers des personnes soit 39 (67%) des 58 avaient consommé soit des AVK soit de l'héparine.

Le tableau suivant présente les causes probables de décès des 58 personnes.

Tableau 5 : caractéristique d'âge et sexe, cause probable du décès de 58 personnes ayant consommé du benfluorex en 2006 et ayant été hospitalisées au moins une fois pour insuffisance valvulaire cardiaque sur la période 2006-2009

Cas n°	sexe	âge au décès	Conso benflu (grs) 2006 au décès.	nb hospit de 2006 au décès	cause la plus probable du décès	circonstance du décès
1	homme	70-74	9,0	41	Leucémie myéloïde aiguë	Leucémie myéloïde aiguë sous chimiothérapie
2	homme	65-69	216,0	10	Endocardite infectieuse précédant une insuffisance des valvules mitrale et aortique	décès hospitalier en post chirurgie valvulaire sous CEC
3	femme	70-74	94,5	5	Insuffisance des valvules mitrale et aortique	décès hospitalier en post chirurgie valvulaire sous CEC
4	femme	65-69	99,0	1	Insuffisance de la valvule mitrale	décès non hospitalier 5 mois après une hospitalisation pour ins mitrale sans notion d'aucune autre pathologie
5	homme	75-79	4,5	4	myopathie	décès hospitalier 1 mois après une chirurgie valvulaire mitrale sous CEC dans un contexte de myopathie
6	homme	75-79	40,5	4	Cardiovasculaire (insuffisance mitrale + sténose carotidienne)	décès non hospitalier 2 ans après une chirurgie de remplacement valvulaire mital
7	femme	65-69	490,5	6	cardiovasculaire : ins card et insuffisance mitrale	décès 7 mois après une hospit. pour insuffisance mitrale (PMSI 2010 absent)
8	femme	75-79	81,0	8	Ins. valvulaire mitrale, aortique et tricuspidienne	décès hospitalier en post chirurgie valvulaire sous CEC
9	femme	75-79	220,5	3	Insuffisance de la valvule mitrale	décès hospitalier en post chirurgie valvulaire sous CEC
10	femme	65-69	40,5	11	Tumeur maligne de l'encéphale	décès hospitalier avec un diagnostic de tumeur maligne de l'encéphale
11	femme	75-79	337,5	4	tumeur maligne utérus	décès hospitalier post chirurgical pour tumeur maligne utérus – contexte d'insuffisance mitrale
12	femme	60-64	13,5	9	Inconnue	décès non hospitalier ; contexte de tumeur maligne du sein (chimio) et d'insuffisance de la valve aortique
13	femme	55-59	472,5	5	Trouble vascul. aigu de l'Intestin	décès hospitalier au cours d'un séjour trouble vasculaire intestinaux avec un contexte d'insuffisance mitrale et d'infarctus 2 mois auparavant
14	femme	75-79	9,0	8	tumeur maligne secondaire des os et de la moelle	décès hors hôpital avec tumeur maligne secondaire ; chirurgie valvulaire 2 années avant
15	femme	60-64	54,0	2	Insuffisance cardiaque et état de choc circulatoire	décès hospitalier pour ins cardiaque 6 mois après un cathétérisme cardiaque pour ins mitrale ; pas d'autres pathologies retrouvées

16	femme	75-79	31,5	9	septicémie	décès hospitalier 7 mois après une 2ème chirurgie de remplacement valvulaire sous CEC (nombreuses complications endocardite, hémorragie, septicémie avec insuffisance rénale et cardiaque)
17	homme	55-59	310,5	8	tr du rythme	décès hospitalier pour tr de rythme et insuffisance cardiaque, ins. mitrale, VIH et carcinome hépatocellulaire
18	femme	70-74	13,5	10	insuffisance mitrale	décès hospitalier en post chirurgie valvulaire mitrale sous CEC ; contexte de cardiopathie hypertensive préalable
19	femme	60-64	310,5	13	tr du rythme	décès en 2010 (PMSI 2010 manquant) mais tableau caractéristique, insuffisance cardiaque, insuffisance aortique, hypertension artérielle pulmonaire (HTAP)
20	homme	60-64	189,0	2	insuffisance aortique.	décès hospitalier en post chirurgie valvulaire sous CEC ; aucune autre pathologie mentionnée
21	homme	70-74	202,5	13	tumeur maligne du cardia	décès soins palliatifs pour tumeur maligne
22	homme	70-74	153,0	43	insuffisance rénale et diabète	décès d'un patient diabétique dialysé
23	femme	55-59	297,0	12	Insuffisance tricuspidienne	décès hospitalier en post intervention card sous CEC pour insuffisance tricuspidienne ; ins mitrale et cardiaque connues
24	homme	55-59	13,5	8	IRC terminale	décès hospitalier dans un tableau IRC, insuffisance cardiaque 20 mois après remplacement valvulaire mitral ; insuffisance mitrale, insuffisance cardiaque, tr du rythme
25	femme	60-64	27,0	2	tr lignée érythrocytaire	décès non hospitalier ; insuffisance mitrale,
26	homme	55-59	288,0	3	insuffisance cardiaque	décès hospitalier en post chirurgie valvulaire mitrale sous CEC
27	homme	60-64	189,0	7	insuffisance mitrale	décès hospitalier en chirurgie cardiaque sous CEC pour insuffisance mitrale ; contexte de bronchopathie chronique
28	femme	70-74	72,0	2	insuffisance mitrale	décès hospitalier en post chirurgie valvulaire mitrale sous CEC
29	femme	80-84	207,0	3	encéphalopathie, insuffisance mitrale	décès non hospitalier
30	homme	65-69	297,0	13	Suite de péritonite	décès hospitalier par péritonite, stomie.13 mois après chirurgie valvulaire sous CEC ; insuffisance mitrale, insuffisance ventriculaire gauche
31	femme	75-79	337,5	8	infarctus	décès hospitalier par infarctus du myocarde ; insuffisance mitrale et insuffisance ventriculaire gauche
32	femme	85-89	4,5	7	anémie hémolytique	décès non hospitalier ; circonstances imprécises ; notion d'insuffisance valvulaire mitrale, insuffisance ventriculaire gauche

33	homme	70-74	301,5	73	insuffisance rénale terminale	décès d'un patient dialysé et avec une tumeur maligne (chirurgie majeure) ; tumeur maligne du caecum
34	femme	60-64	90,0	8	insuffisance mitrale	décès au cours du mois suivant une chirurgie valvulaire mitrale sous CEC ; contexte d'apnée du sommeil
35	femme	65-69	121,5	5	Insuffisance mitrale	décès hospitalier post chirurgical de remplacement valvulaire mitral
36	femme	60-64	351,0	2	insuffisance mitrale	décès en 2010 deux ans après un cathétérisme pour insuffisance mitrale (absence PMSI 2010)
37	femme	55-59	94,5	4	insuffisance mitrale	décès hospitalier en post chirurgie cardiaque pour insuffisance mitrale, ins cardiaque
38	femme	70-74	252,0	3	hémorragie intracérébrale hémisphérique	décès hospitalier pour hémorragie cérébrale 3 mois après une prise en charge pour insuffisance aortique
39	femme	75-79	130,5	3	choc cardiogénique	décès 2 ans par chirurgie de remplacement valvulaire par choc cardiogénique sans infarctus, sans autres pathologies
40	femme	80-84	189,0	1	insuffisance valvulaire aortique	décès hospitalier au cours d'une hospitalisation pour insuffisance aortique
41	femme	75-79	342,0	2	insuffisance valvulaire aortique	décès 2 mois après 2 hospitalisations pour insuffisance de la valve aortique
42	homme	85-89	49,5	2	insuffisance valvulaire tricuspide	décès hospitalier au cours d'une hospitalisation pour ins. valvulaire tricuspide
43	femme	75-79	202,5	12	insuffisance rénale	décès hospitalier au cours d'une hospitalisation avec ins rénale terminale et pancréatite ; contexte de valvulopathie aortique avec nombreuses hospitalisations
44	homme	55-59	72,0	3	ischémie cérébrale	décès hospitalier dans le mois suivant une chirurgie valvulaire sous CEC ; ins mitrale
45	femme	80-84	144,0	16	Ins respiratoire aiguë	décès en 2010 (pas de PMSI disponible pour 2010) ; oedème pulmonaire, ins card, ins valv. aortique
46	femme	75-79	121,5	6	lésion traumatique intracrânienne	décès hospitalier avec lésion cérébrale anoxique
47	femme	75-79	81,0	5	inconnue	décès en 2010 trois ans après une chirurgie pour insuffisance tricuspidienne (PMSI 2010 absent)
48	homme	65-69	54,0	3	patho cardiaque, insuffisance aortique	décès en 2010 27 mois après une chirurgie pour insuffisance aortique ; pas de pathologie autre déclarée en ALD
49	homme	55-59	72,0	5	inconnue	décès en 2010 4 ans après une chirurgie pour ins mitrale
50	homme	65-69	198,0	2	myocardiopathie ischémique	décès hospitalier en post chirurgie valvulaire mitrale sous CEC

51	homme	70-74	472,5	12	tr du rythme	décès hospitalier après 11 hospitalisations en cardiologie par trouble du rythme/ ins. ventriculaire G, chirurgie de rempl. valvulaire sous CEC ; , insuffisance cardiaque, insuffisance aortique et mitrale
52	homme	65-69	225,0	9	abcès de la rate	décès hospitalier dans les suites d'une endoscopie biliaire (abcès de la rate)
53	homme	80-84	99,0	7	insuffisance ventriculaire gauche	décès en 2010 ; 6 mois après une hospitalisation par ins ventr G et 3 ans après remp. val sous CEC ; autres pathologies connues bénignes
54	femme	80-84	252,0	3	endocardite	décès hospitalier pour endocardite inf après 2 transferts pour insuffisance aortique et embolie pulmonaire
55	femme	75-79	265,5	15	ins card congestive : ins aortique et mitrale	décès hospitalier pour insuffisance cardiaque 23 mois après une chir urgie de remplacement valvulaire (IM et Iao)
56	femme	55-59	229,5	6	embolie et thrombose des artères des MI	décès hospitalier embolie et thrombose des artères des MI au cours d'une intervention de chir. asc. Contexte insuffisance mitrale
57	femme	35-39	13,5	5	cardiovasculaire	décès 4 mois après chirurgie de rempacementl valvulaire tricuspidienne + Aortique et 2 mois après thrombose intracardiaque
58	homme	65-69	135	6	cardiovasculaire	décès non hospitalier 15 mois après chirurgie de remplacement valvulaire mitrale

4 Discussion

Cette étude montre qu'au sein de la population du régime général des consommations de benfluorex en 2006 étaient associées, dans les 55 mois suivant, à des valvulopathies cardiaques à l'origine de décès. Des atteintes plurivalvulaires sans contexte cardiologique préalable, des lésions de la tricuspide, l'âge relativement jeune de certains patients et un cas associé de valvulopathie et d'HTAP sont autant d'éléments qui pourraient conforter une hypothèse causale.

Plusieurs facteurs doivent être pris en compte :

1. la population concernée correspondait à 76% de la population résidente en France. Un facteur correctif de 1,33 devrait être appliqué pour extrapoler à la France entière.

2. Un deuxième élément est le codage des valvulopathies lors des hospitalisations. Il n'est pas exclu que des hospitalisations pour insuffisance valvulaire soit codées en rétrécissement valvulaire qui est presque 10 fois plus fréquent (source PMSI : Agence Technique de l'Information sur l'Hospitalisation (ATIH)[14]). Pour 180 remplacements valvulaires de notre cohorte le diagnostic d'insuffisance était mentionné, mais pour 350 autres remplacements valvulaires non pris en compte dans la présente analyse un diagnostic de rétrécissement ou sténose était indiqué. Dans certains cas rapportés les lésions valvulaires (remaniements importants) peuvent débuter par aspect de pseudo-sténose, notamment pour la valve aortique. Un des 58 patients présentait d'ailleurs un diagnostic de sténose de la valvule aortique avec insuffisance (I352 ; code non pris en compte dans notre étude) puis lors d'une hospitalisation ultérieure un diagnostic d'insuffisance de la valvule aortique (I351).

3. Certaines des valvulopathies rapportées sont décrites comme rhumatismales (pour 7 patients) et d'autres codées à la fois, selon les séjours, comme rhumatismale et non rhumatismale pour 4 personnes. Plusieurs experts interrogés s'accordent sur le caractère très imprécis de l'utilisation d'un code (non rhumatismal) ou de l'autre (rhumatismal), particulièrement pour d'éventuelles valvulopathies médicamenteuses opérées qui restent des pathologies extrêmement rares à l'échelle d'un chirurgien cardiovasculaire qui bien souvent ne pourra en préciser l'étiologie. De plus les cas d'insuffisance mitrale d'origine rhumatismales sont très rares dans la population française, mais ne peuvent être exclus pour des populations d'origine nord-africaine. En raison du caractère anonyme de ces données nous ignorons le pays de naissance des personnes concernées.

[14] Site de l'Agence Technique de l'Information sur l'Hospitalisation. http://www.atih.sante.fr/

4. Un suivi plus long serait nécessaire avec notamment le devenir des chirurgies de remplacement valvulaire, ainsi d'ailleurs que les complications des traitements associés (anticoagulants). La mortalité post-opératoire ne dépend pas du type de valves (mécaniques ou bioprothèses) mais essentiellement du type d'orifices traités[15]. Ainsi la mortalité hospitalière à 30 jours serait de 3 % pour un remplacement valvulaire aortique, 4 à 8 % pour un remplacement valvulaire mitral et 10 à 15 % pour un double remplacement mitro-aortique. La mortalité post-opératoire immédiate est essentiellement liée à l'état préopératoire et à l'âge du patient. Un des facteurs prédictif de mortalité constamment mis en avant est l'âge après 70 ans.
Globalement dans la littérature la survie moyenne à 10 ans après remplacement valvulaire aortique est de 60 à 70 %[16] ; elle est inférieure après remplacement valvulaire mitral (40 à 50 %). Nous retrouvons également une mortalité mitrale (12,5 %) supérieure à celle des remplacements aortiques (7,5 %) avec un recul moyen d'environ deux années. Soulignons que le calcul de nos taux de mortalité ne respecte pas strictement la méthodologie complexe conforme au *Guideline for reporting morbidity and mortality after cardiac valve operations*[17].

5. Une analyse plus fine des complications de l'insuffisance cardiaque et des valvulopathies avec un retour au dossier médical serait peut-être plus performante que notre méthode. On peut imaginer de retrouver les comptes rendus d'anatomopathologie des valves cardiaques remplacées par des prothèses. Toutefois la mise en œuvre prendrait plusieurs mois (ou années) sans compter un dossier informatique et liberté *a priori* très complexe car les données du SNIIRAM sont irréversiblement anonymes. Il est probable qu'il faille recourir à un décret en conseil d'Etat. Les complications les plus classiques comme les accidents de thromboses valvulaires, les maladies thromboemboliques, l'altération de la prothèse valvulaire, les complications hémorragiques et la contribution d'anémies hémolytiques sévères (un cas dans notre série) devraient être prise en compte. La question des décès brutaux sur la voie publique ou à domicile qu'il est recommandé d'inclure systématiquement dans les complications pour les registres de suivi de remplacement valvulaire mérite d'être mieux analysée que dans notre observation.

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[15] Leguerrier A, Flecher E, Fouquet O, Lelong B. Prothèses valvulaires cardiaques. EMC, Cardiologie, 11-013-A-30,2009.

[16] Kalkat MS, Edwards MB, Taylor KM, Bonser RS. Composite aortic valve graft replacement: mortality outcomes in a national registry. Circulation. 2007 Sep 11;116(11 Suppl):I301-6

[17] Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of The American Association for Thoracic Surgery and The Society of Thoracic Surgeons. J Thorac Cardiovasc Surg. 1996 Sep;112(3):708-11.

6. La prise en compte de l'hypertension artérielle pulmonaire (HTAP) (autre complication des fenfluraminiques avec des cas rapportés dans la littérature en lien avec le benfuorex)[18,19] pourrait augmenter le nombre de décès observé. Dans les 58 cas de valvulopathies présentées avec décès il existait un cas associé d'HTAP.

[18] EUROPEAN COMMISSION DECISION of 14.6.2010 concerning, in the framework of Article 107 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations for medicinal products for human use which contain the active substance "benfluorex"

[19] Boutet K, Frachon I, Jobic Y, et al. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 2009 Mar; 33: 684-8.

Plusieurs facteurs pourraient être minorants

1. Tout d'abord toutes les valvulopathies de régurgitation ne sont pas associées au benfluorex. Le risque relatif ajusté était de 4 dans une population de diabétiques [4]. Il conviendrait d'appliquer un facteur correctif de 0.80.

2. Il n'est pas exclu que des expositions antérieures avec des fenfluraminiques retirés du commerce en 1997 aient pu provoquer des centaines de valvulopathies. L'hypothèse du benfluorex potentialisant après une courte exposition (et une faible dose) un premier effet de fenfluraminiques retiré du commerce depuis 1997 serait à tester.

3. Un autre point est celui d'une estimation par les autorités sanitaires sur plusieurs années à partir d'une cohorte d'exposés en 2006. Les patients sous benfluorex sont souvent restés plusieurs années sous traitement. L'assurance maladie ignore la durée moyenne par patient de la prise du benfluorex en France sur les trente dernières années ainsi que les quantités de benfluorex délivrés en France entre 1976 et 2000[20]. D'autres bases seraient susceptibles de répondre à ces questions.

4. La recherche des causes médicales de décès par le PMSI n'est pas la méthode de référence en France où la déclaration du décès est systématique avec un certificat médical complété par un médecin. La cause du décès est mentionnée *(maladie(s) ou affection(s) morbides ayant directement provoqué le décès - en dernière ligne la cause initiale) et dans la partie suivante - Autres états morbides, facteurs ou états physiologiques ayant contribué au décès).* Les données sur les causes médicales de décès constituent une source essentielle d'informations épidémiologiques avec la base nationale des causes médicales de décès, élaborées annuellement par le CépiDc-Inserm. Les différentes causes sont codées et catégorisées selon la Classification internationale des maladies [21,22]. La procédure habituelle dans les cohortes de recherche du statut vital et de la cause de décès est décrite dans le décret n° 98-37 autorisant l'accès aux données relatives au décès des personnes inscrites au Répertoire National d'Identification des Personnes Physiques (RNIPP) dans le cadre des recherches dans le domaine de la santé[23]. Mais ce dispositif ne peut s'appliquer dans notre cas, les données du SNIIRAM étant anonymes.

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[20] Le codage dans les bases de l'assurance maladie des médicaments remboursés a débuté en mars 1997 et est devenu presque exhaustif en 2000.

[21] Pavillon G, Coilland P, Jougla E.Mise en place de la certification électronique des causes médicales de décès en France : premier bilan et perspectives. Bul Epidémiol Hebd. 2007 ;35-36:306-8.

[22] Aouba A, Péquignot F, Le Toullec A, Eric Jougla E. Les causes médicales de décès en France en 2004 et leur évolution 1980-2004. . Bul Epidémiol Hebd. 2007 ;35-36:308-14.

[23] Procédure décrite : http://ifr69.vjf.inserm.fr/svcd.html

Le projet du chaînage des données anonymes du PMSI, du SNIIRAM et des causes médicales de décès a progressé avec des tests concluants : une convention tripartite (Drees, CépiDc-Inserm et CNAMTS) est en cours de signature avec une demande à la Cnil. Il est parfaitement concevable de suivre les personnes de cette cohorte (au moins les 556 personnes hospitalisées pour valvulopathie en utilisant les causes médicales de décès du CépiDc-Inserm : risque thromboembolique des prothèses mécaniques et le risque associé des anticoagulants notamment. Ces éléments permettront de compléter les dossiers pour lesquels la cause du décès était très incertaine.

Un dernier point pourrait être discuté : l'absence de groupe contrôle. Nous considérons comme acquis le lien entre benfluorex et valvulopathie après quatre études observationnelles avec des méthodologies très différentes, un mécanisme d'action décrit et les conclusions des autorités sanitaires française et européenne. Notre objectif était de vérifier s'il y avait ou non des consommations de benfluorex associées à des valvulopathies de régurgitation avec décès.

Une autre application de ce travail pourrait être la mesure du taux de notifications spontanées rapporté au nombre de cas observés pour différentes situations : par exemple benfluorex avec valvulopathie de régurgitation hospitalisée ; benfluorex et décès au cours d'une hospitalisation pour valvulopathies de régurgitation.

5. Conclusion

Le suivi, à partir du SNIIRAM, pendant 55 mois de 303 000 patients sous benfluorex en 2006 montre qu'il existait des cas de valvulopathie cardiaque avec décès associés au benfluorex. Un suivi à plus long terme et un chaînage avec les causes médicales de décès devrait permettre de mieux estimer le nombre de décès en France pour les effets indésirables graves de cette molécule. La connaissance précise de la quantité de benfluorex commercialisée en France en 33 années, devrait également améliorer l'estimation globale du risque.

Ce travail a été réalisé à la Caisse natianale de l'assurance maladie à la suite de la saisine de l'Afssaps le 25/8/2010.

Déclaration de conflit d'intérêt : les auteurs de ce travail sont salariés de la caisse nationale de l'assurance maladie (établissement public) ; aucun des auteurs de ce rapport n'a perçu dans les trois dernières années de revenu d'une entreprise de l'industrie pharmaceutique commercialisant un antidiabétique.

Annexe 3-85

Note complémentaire destinée à l'Afssaps : benfluorex et décès

CNAMTS-DSES-DEPP
(Département des études sur les pathologies et les patients)

Cette note complète et précise la précédente note intitulée « *Benfluorex, valvulopathies cardiaques et décès* » demandée par l'Afssaps le 25/8/2010 et transmise à cette dernière le 28/9/2010 par la Cnamts.

1 Introduction

La mise en œuvre de cette analyse complémentaire a été décidée lors de la réunion à l'Afssaps du 20/10/2010. L'objectif spécifique était de compléter les recherches précédentes en incluant une étude plus approfondie sur les atteintes pluri-valvulaires (deux ou trois valves cardiaques atteintes). Ce travail complémentaire s'inscrivait dans l'objectif plus général de mieux caractériser d'éventuels critères de risque d'événements indésirables graves au sein de la population exposée au benfluorex.

2 Méthode

Ce travail complémentaire a nécessité une approche méthodologique modifiée par rapport à celle de la précédente note du 28/09/2010. Schématiquement les apports supplémentaires ont consisté à analyser plus précisément les lésions multivalvulaires. Nous les avons caractérisées, à la fois par les actes chirurgicaux détaillés (CCAM), et par la recherche associée des codes CIM-10[1] en I08 (maladies multivalvulaires cardiaques) ; enfin les complications à type d'hypertension artérielle pulmonaire (HTAP) ont été prises en compte dans cette analyse.

Nous avons repris la cohorte des 303 336 personnes exposées au benfluorex en 2006 à partir des données anonymes du système national d'information interrégimes de l'assurance maladie (SNIIRAM)[2,3]. Toutes les personnes affiliées au régime général étaient éligibles à l'exception de celles des sections locales mutualistes (étudiants et fonctionnaires). La population source était ainsi composée de 48,4 millions de personnes assurées au régime général, soit environ 76% de la population résidente en France. Les personnes exposées étaient définies par le remboursement d'au moins une boite de benfluorex en 2006. La liste des codes utilisés pour sélectionner les patients exposés et pour mesurer la quantité de benfluorex remboursée est présentée en table 1

[1] CIM-10 : classification statistique internationale des maladies et des problèmes de santé connexes 10ème révision, est publiée par l'OMS pour l'enregistrement des causes de maladie et de mortalité touchant les êtres humains à travers le monde.
[2] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique. 2010 Aug;58(4):286-90.
[3] Martin-Latry K, Bégaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf. 2010; 19: 256-265.

Table 1 Liste des codes CIP utilisés pour sélectionner les patients exposés au benfluorex et pour mesurer la quantité remboursée

Code CIP	nom du médicament
3175579	MEDIATOR 150MG CPR 30
3175591	MEDIATOR 150MG CPR 100
3790267	BENFLUOREX MYLAN 150 MG 1 BOITE DE 30, COMPRIMES
3828277	BENFLUOREX QUALIMED 150 MG 1 BOITE DE 30, COMPRIMES

Les deux derniers produits (génériques) n'ont été commercialisés qu'en 2009. Les codes ont été utilisés afin de pouvoir mesurer l'exposition au benfluorex jusqu'au retrait du benfluorex (30/11/2009) de chaque patient exposé au moins une fois en 2006.

Après chaînage des données, les événements recherchés pendant 48 mois dans le PMSI [médecine-chirurgie-obstétrique (MCO)] de la période 2006 à 2009, étaient une ou plusieurs hospitalisations pour une insuffisance valvulaire toutes valves cardiaques et toutes causes confondues (tableau 2) ou pour une maladie multivalvulaire cardiaque codée en un seul code (tableau 3). La recherche sur 48 mois correspond à 1,2 million de personnes-années analysées.

Table 2 : critères utilisés pour définir la maladie valvulaire cardiaque de régurgitation (critères de la note 28/9/2010)

	PMSI MCO avec un diagnostic principal ou relié =
hospitalisation pour insuffisance valvulaire	I340 Insuffisance (de la valvule mitrale) non rhumatismale
	I051 Insuffisance (de la valvule mitrale) rhumatismale
	I351 Insuffisance (de la valvule) aortique non rhumatismale
	I061 Insuffisance (de la valvule) aortique rhumatismale
	I361 Insuffisance (de la valvule) tricuspide non rhumatismale
	I071 Insuffisance (de la valvule) tricuspide rhumatismale

Table 3 : critères complémentaires utilisés pour définir les maladies multivalvulaires cardiaques

	PMSI MCO avec un diagnostic principal ou relié =
hospitalisation pour maladies de plusieurs valvules (DP ou DR)	I080 Atteintes des valvules mitrale et aortique (précisée ou non d'origine rhumatismales)
	I081 Atteintes des valvules mitrale et tricuspide (précisée ou non d'origine rhumatismales)
	I082 Atteintes des valvules aortique et tricuspide (précisée ou non d'origine rhumatismales)
	I083 Atteintes des valvules mitrale, aortique et tricuspide (précisée ou non d'origine rhumatismales)
	I088 Autres maladies valvulaires multiples (précisée ou non d'origine rhumatismales)
	I089 Maladie de plusieurs valvules (précisée ou non d'origine rhumatismales)

Nous avons recherché pour chacune des personnes exposées au benfluorex et ayant un diagnostic d'hospitalisation de la table 2 (insuffisance valvulaire cardiaque) ou de la table 3 (atteinte plurivalvulaire cardiaque) une chirurgie de remplacement valvulaire. A la différence de l'étude précédente du 28/9/2010, nous avons analysé les codes détaillés de la classification communes des actes médicaux (CCAM), utilisée par le PMSI tant pour les hospitalisations du secteur public et privé que pour la facturation des actes en médecine libérale. L'analyse précédente avaient été faite à partir des trois GHM : GHM 05C02Z Chirurgie de remplacement valvulaire avec circulation extracorporelle et avec cathétérisme cardiaque ou coronarographie ; GHM 05C03V Chirurgie de remplacement valvulaire avec circulation extracorporelle, sans cathétérisme cardiaque, ni coronarographie, sans CMA GHM 05C03W Chirurgie de remplacement valvulaire avec circulation extracorporelle, sans cathétérisme cardiaque, ni coronarographie, avec CMA. Elle ne permettait pas de savoir si les remplacements valvulaires concernaient une ou plusieurs valves. De plus certains remplacements valvulaires ne sont pas groupés par le groupeur de l'ATIH en un des trois GHM.

Les codes CCAM de remplacement valvulaire sont présentés dans la table 4 ; par exemple le code CCAM *DBKA009* correspond à l'intervention « *Remplacement de la valve aortique et de la valve atrioventriculaire gauche*[4] *par prothèse mécanique ou par bioprothèse avec armature, par thoracotomie avec CEC* » (c'est-à-dire un double remplacement de la valve aortique et mitrale).

Table 4 : liste exhaustive des actes de la CCAM correspondant à un acte de remplacement valvulaire cardiaque

Code	Libellé des actes de remplacement valvulaire
DBKA001	Remplacement de la valve aortique par homogreffe, par thoracotomie avec CEC
DBKA002	Remplacement de la valve atrioventriculaire gauche par prothèse en position non anatomique, par thoracotomie avec CEC
DBKA003	Remplacement de la valve aortique par bioprothèse sans armature, par thoracotomie avec CEC
DBKA004	Remplacement de la valve atrioventriculaire droite par prothèse mécanique ou bioprothèse avec armature, par thoracotomie avec CEC
DBKA005	Remplacement de la valve atrioventriculaire gauche par homogreffe, par thoracotomie avec CEC
DBKA006	Remplacement de la valve aortique par prothèse mécanique ou bioprothèse avec armature, par thoracotomie avec CEC
DBKA007	Remplacement de la valve pulmonaire par prothèse mécanique ou bioprothèse avec armature, par thoracotomie avec CEC
DBKA008	Remplacement de la valve atrioventriculaire droite par homogreffe, par thoracotomie avec CEC
DBKA009	Remplacement de la valve aortique et de la valve atrioventriculaire gauche par prothèse mécanique ou par bioprothèse avec armature, par thoracotomie avec CEC
DBKA010	Remplacement de la valve atrioventriculaire gauche par prothèse mécanique ou bioprothèse avec armature, par thoracotomie avec CEC
DBKA011	Remplacement de la valve aortique par prothèse en position non anatomique, par thoracotomie avec CEC
DBKA012	Remplacement de la valve pulmonaire par homogreffe ou bioprothèse sans armature, par thoracotomie avec CEC
DBLA004	Pose d'une bioprothèse de la valve aortique, par abord de l'apex du cœur par thoracotomie sans CEC
DBLF001	Pose d'une bioprothèse de la valve aortique, par voie artérielle transcutanée
DBMA001	Reconstruction de la voie aortique par élargissement antérodroit de l'anneau avec remplacement de la valve, par thoracotomie avec CEC
DBMA004	Reconstruction de la voie aortique par transfert de la valve pulmonaire en position aortique avec reconstruction de la voie pulmonaire, par thoracotomie avec CEC
DBMA005	Reconstruction de l'anneau atrioventriculaire gauche avec remplacement de la valve par homogreffe, par thoracotomie avec CEC
DBMA006	Reconstruction de l'anneau aortique avec remplacement de la valve par bioprothèse sans armature, par thoracotomie avec CEC

[4] Les termes officiels français de la nomenclature d'anatomie ont été modifiés en 1995. Néanmoins ils sont peu utilisés par les médecins et plus encore le grand public. Pour faciliter la compréhension le texte de ce document reprend l'ancienne nomenclature. (valve atrioventriculaire gauche = valve mitrale ; valve atrioventriculaire droite = valve tricuspide).

DBMA009	Reconstruction de l'anneau aortique avec remplacement de la valve par prothèse mécanique ou bioprothèse avec armature, par thoracotomie avec CEC
DBMA010	Reconstruction de l'anneau aortique avec remplacement de la valve par homogreffe, par thoracotomie avec CEC
DBMA013	Reconstruction de l'anneau atrioventriculaire gauche avec remplacement de la valve par prothèse mécanique ou bioprothèse avec armature, par thoracotomie avec CEC
DBMA015	Reconstruction de la voie aortique par élargissement antérogauche de l'anneau et ouverture de l'infundibulum pulmonaire, avec remplacement de la valve, par thoracotomie avec CEC

Le statut vital, avec la date éventuelle de décès, ont été analysé jusqu'au 31 juillet 2010, soit un suivi de 55 mois. Le décès dans le SNIIRAM est connu pour les personnes du régime général (hors fonctionnaires et étudiants), à partir des données issues du statut vital Insee. Ces données sont alimentées par les fichiers du Répertoire national des identifiants des personnes physiques (RNIPP) puis du RNIAM (Répertoire national des identifiants de l'assurance maladie), du RFI (Référentiel individus) et enfin du SNIIRAM. Tous les décès certifiés par l'Insee sont transmis au RNIAM. Ce RNIAM est aussi enrichi de décès dit « non certifié » par l'INSEE (par exemple personne née à l'étranger, résidant en France et décédant à l'étranger).

Nous avons étudié pour chaque personne décédée toutes les hospitalisations à partir du PMSI (Groupe homogène de malade (GHM), diagnostic principal et relié, durée de chaque séjour, ainsi que le mode de sortie : transfert, domicile ou décès). Il existait environ 800 codes dans la nomenclature des GHM sur la période 2006-2008 (PMSI V9 puis V10) et près de 2 300 en 2009 (PMSI V11). L'hypothèse implicite est que les éléments médicaux contenus dans le résumé standardisé anonymisé (RSA) du PMSI, notamment pour les hospitalisations conduisant au décès, vont permettre de connaître la cause la plus probable du décès.

Deux exemples illustrent cette démarche.
Cas n° 1 : homme de 78 ans décédé en soins palliatifs avec un diagnostic de leucémie myéloïde chronique. La cause du décès retenue est une leucémie myéloïde chronique
Cas n° 2 : femme de 53 ans décédée au cours d'une hospitalisation pour insuffisance de la valvule aortique non rhumatismale et insuffisance de la valve mitrale avec une chirurgie de remplacement valvulaire sous circulation extracorporelle. Cette hospitalisation suivait une précédente en cardiologie avec un acte diagnostic de cathétérisme cardiaque avec un diagnostic d'insuffisance de la valvule aortique non rhumatismale et insuffisance de la valve mitrale. La cause du décès retenue est l'insuffisance valvulaire mitrale et aortique.

Pour chaque cas de décès l'ensemble des hospitalisations étaient analysées. Par ailleurs nous avons recueilli la notion d'Affection de Longue durée (ALD) avec le diagnostic (code CIM-10) et la date de début, la quantité de benfluorex délivrée entre le 1er janvier 2006 et la date du décès et les traitements antidiabétiques et anticoagulants. Les points concernant les ALD et les traitements médicamenteux antidiabétiques (hors benfluorex) et anticoagulants ont été traités dans la note du 28/9/2010 et en sont pas repris dans cette analyse.
En définitive la détermination des causes supposées de décès à l'aide du PMSI a répondu en règle générale au schéma suivant[5].

- Si le décès avait eu lieu à l'hôpital, la cause de décès supposée correspondait au diagnostic principal du séjour au cours duquel le décès est survenu, quand le code CIM 10 de ce diagnostic principal était une maladie. Lorsque le code CIM 10 était un traitement (chimiothérapie, radiothérapie...), on utilisait alors le diagnostic relié pour déterminer la cause de décès supposée (par exemple cancer du poumon).
- Si le décès n'avait pas eu lieu à l'hôpital mais que l'individu avait été hospitalisé au cours des quatre derniers mois (c'est-à-dire au cours du mois de décès ou de l'un des trois mois précédents), on utilisait de la même manière les diagnostics principaux et reliés des deux derniers séjours à l'hôpital.

[5] Cette méthode de détermination des causes probables de décès a été utilisée pour un travail médico-économique : Myriam Mezzarobba. Les coûts de la dernière année de vie en 2008 et ses conséquences pour les dépenses de santé. DSES, Caisse nationale de l'assurance maladie.

- Si le décès n'avait pas eu lieu à l'hôpital et que l'individu n'avait pas été hospitalisé au cours des quatre derniers mois, la cause de décès retenue était déterminée de façon probabiliste en tenant compte des affections les plus graves. Il était tenu compte des comorbidités, notamment potentiellement létales comme les tumeurs et affections malignes, les autres pathologies cardiovasculaires et différents facteurs pouvant avoir une influence sur le décès (âge...).

A la date de ce travail nous ne disposions pas du PMSI 2010. Pour les décès survenus à la fin du premier semestre 2010 la cause était le plus souvent ignorée. Dans quelques cas néanmoins l'analyse de l'ensemble des hospitalisations de 2006 à 2009 a permis de donner des éléments d'orientation. Cette méthode de détermination des causes probables de décès produit un biais dû au fait que seuls les décès précédés d'une hospitalisation sont parfaitement documentés. En particulier, elle ne permet de renseigner aucun décès brutal à domicile ou sur la voie publique : AVC, arrêt cardiaque sur trouble du rythme, suicide, accident....

Ce travail complémentaire a aussi analysé, toujours dans la perspective de recommandations aux médecins et aux patients exposés les hospitalisations pour hypertension artérielle pulmonaire primitive (HTAP). Le Code CIM-10 de l'HTAP et I270 ; cette complication a été reconnu dans l'avis de la commission européenne du 14/6/2010.

L'utilisation du SNIIRAM par les agents habilités de la Cnamts a fait l'objet d'un avis favorable de la Cnil en novembre 2001 et d'un arrêté ministériel du 11 avril 2002 relatif à sa mise en œuvre. En octobre 2007, un second arrêté a permis l'utilisation de la variable décès avec la date exacte issue des données de statut vital de l'Insee et de la Caisse nationale de l'assurance vieillesse. Le statisticien ayant extrait les données était habilité « *profil 30* » pour le croisement de données médicales sensibles.

Les traitements des données ont été réalisés avec le logiciel SAS version 9.01 et le logiciel SPSS version 11.5.

3 Résultats

3.1 Caractéristiques d'âge et de sexe des personnes exposées au benfluorex en 2006

L'étude portait sur 303 336 personnes exposées au benfluorex en 2006 (au moins un remboursement) dont 72,6% de femmes (tableau 2). L'âge moyen des personnes était de 52,8 ans.

Table 5 : caractéristiques d'âge et de sexe des personnes exposées au benfluorex en 2006

classe d'âge	hommes	femmes	Total*
0-19	630	2 314	2 944
20-24	677	5 273	5 950
25-29	1 303	9 136	10 439
30-34	2 458	13 169	15 627
35-39	4 240	17 493	21 733
40-44	6 477	21 411	27 888
45-49	8 987	24 452	33 439
50-54	11 526	28 554	40 080
55-59	14 514	30 968	45 482
60-64	11 732	23 723	35 455
65-69	8 339	16 472	24 811
70-74	6 471	13 717	20 188
75-79	3 819	8 518	12 337
80-84	1 561	3 641	5 202
85-89	372	1 062	1 434
90+	71	179	250
Total	**83 177**	**220 082**	**303 259**

Données SNIIRAM régime général hors SLM
*pour 107 personnes l'âge et/ou sexe sont inconnus

Cette population avait été remboursée entre le 1er janvier 2006 et le retrait du benfluorex le 30 novembre 2009 d'environ 10,3 millions de boites de benfluorex, soit en moyenne 34 boites (153 grammes de benfluorex) par personne.

Table 6 : consommation en benfluorex des 303 336 personnes exposées au benfluorex en 2006

Année	Effectif des patients de la cohorte ayant eu ≥ 1 remboursement de benfluorex	Nombre de boites	Moyenne
2006	303 336	3 792 275	13
2007	165 144	2 865 682	17
2008	118 407	2 085 332	18
2009	94 927	1 574 278	17
2010	0	0	

3.2 Hospitalisations pour valvulopathie cardiaque et décès dans la cohorte des personnes exposées

Parmi les 303 336 personnes 556 avaient été hospitalisées au moins une fois avec un diagnostic de valvulopathie cardiaque par régurgitation codé en CIM-10 I340, I051, I351, I061, I361, I071. A ces 556 personnes s'ajoutaient 41 personnes supplémentaires hospitalisées pour une lésion multivalvulaire cardiaque codée en I08 (figure 1). Le total des personnes sélectionnées avec une valvulopathie d'insuffisance ou multivalvulaire par notre algorithme était de 597.

Parmi les 597 personnes hospitalisées pour valvulopathie le nombre de personnes ayant eu au moins un remplacement valvulaire chirurgical était de 298 (50,0%) . Nous avons distingué trois situations pour ces 298 personnes ayant subi un remplacement valvulaire : le remplacement valvulaire aortique isolé, le remplacement mitral ou tricuspidien isolé et les remplacements bi ou tri-valvulaire (le plus souvent associant mitral et aortique).

On observait (figure 2)

- 93 remplacements aortiques isolés avec 5 décès (taux de décès 5,4%) ;
- 72 remplacements mitraux ou tricuspidiens isolés avec 7 décès (taux de décès 9,7%) ;
- 133 remplacements bi ou trivalvulaire avec 21 décès (taux de décès 15,8%).

Entre les trois groupes les doses cumulées moyenne de benfluorex, les doses journalières moyenne et le taux de personnes consommant déjà du benfluorex en début d'année 2006 ne variaient pas de façon significative. Il n'existait pas non plus de différence avec le groupe de non-opérés.

3.3 Hospitalisations pour hypertension artérielle pulmonaire (HTAP) et décès dans la cohorte des exposés

Parmi les 303 336 personnes exposées au benfluorex en 2006, on a observé 99 personnes hospitalisées avec un diagnostic principal (ou relié) d'hypertension artérielle pulmonaire[6] (figure 3). L'âge moyen était de 60 ans et le rapport de 25 hommes pour 74 femmes. A la fin de la période d'observation de 55 mois le nombre de décès étaient de 22 (22,2%). Parmi les décédés la proportion d'hommes était supérieure (13 hommes pour 8 femmes). L'âge médian au décès était de 72 ans avec des extrêmes de 32 à 89 ans. Les 21 cas cliniques ayant conduit à un décès sont résumés dans le tableau 9. Aux 21 décès du tableau s'ajoute le décès (cas n°19 du tableau 7) qui concerne une pathologie valvulaire et une HTAP. Les cas cliniques décrit dans le tableau 9 sont souvent complexes semblant marqués par des difficultés au diagnostic, de très nombreuses hospitalisations et des complications multiples.

[6] G rounds for the revocation of the marketing autorisation : Whereas, The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing benfluorex. The Committee concluded, after having reviewed the available data, that benfluorex is harmful under normal conditions of use leading to pulmonary hypertension and cardiac valvulopathies..... Cet avis européen est notamment motivé par la publication *Boutet K et al. Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 2009 Mar; 33: 684-8.*

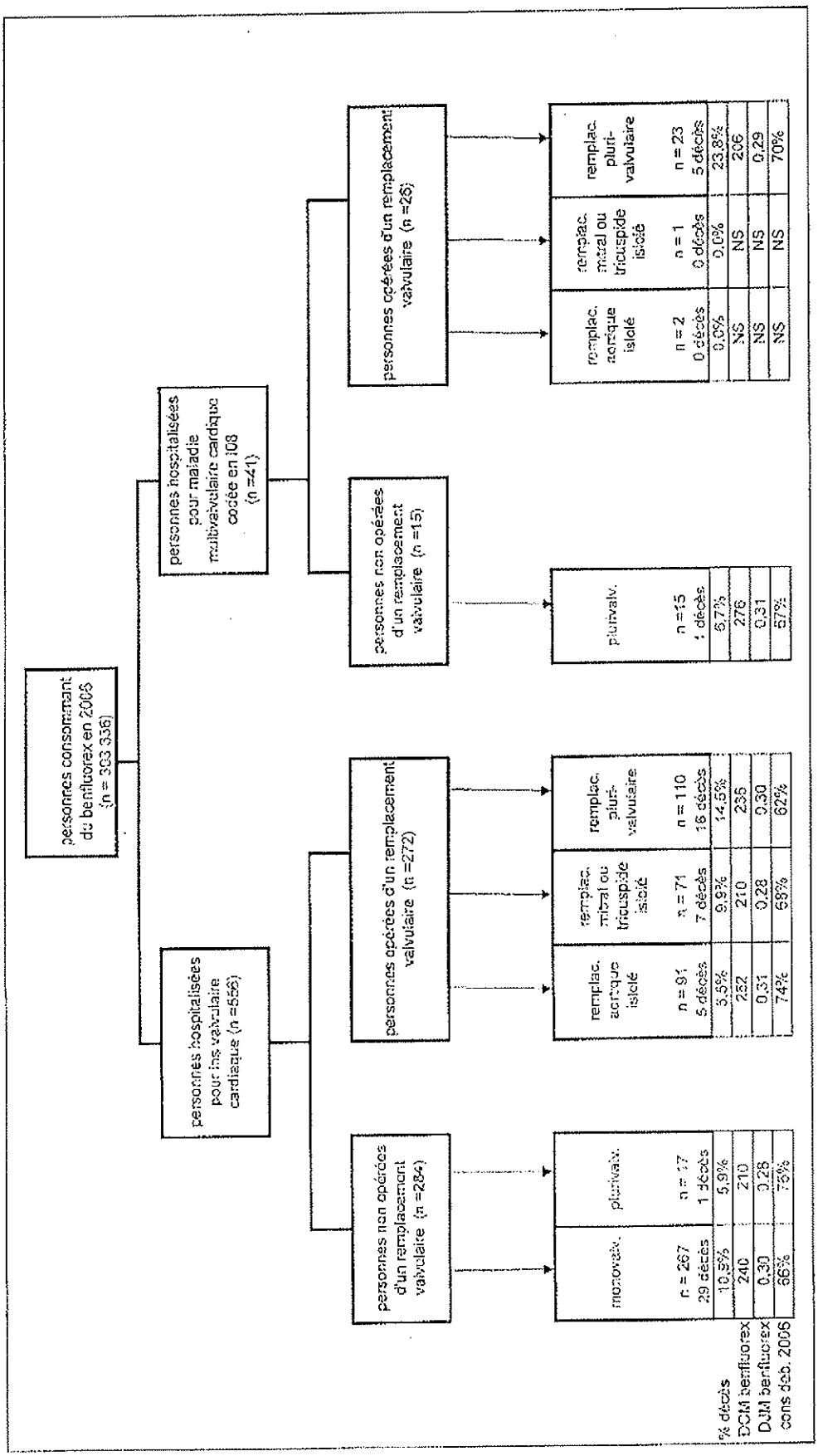

Figure 1 : suivi de la cohorte des personnes traitées en 2006 de benfluorex : analyse des hospitalisations pour valvulopathie cardiaque par régurgitation (insuffisance) et des lésions multivalvulaires Suivi PMSI de 48 mois : 2006 à 2009. Suivi statut vital de 55 mois. *Données SNIIRAM régime général hors SLM*

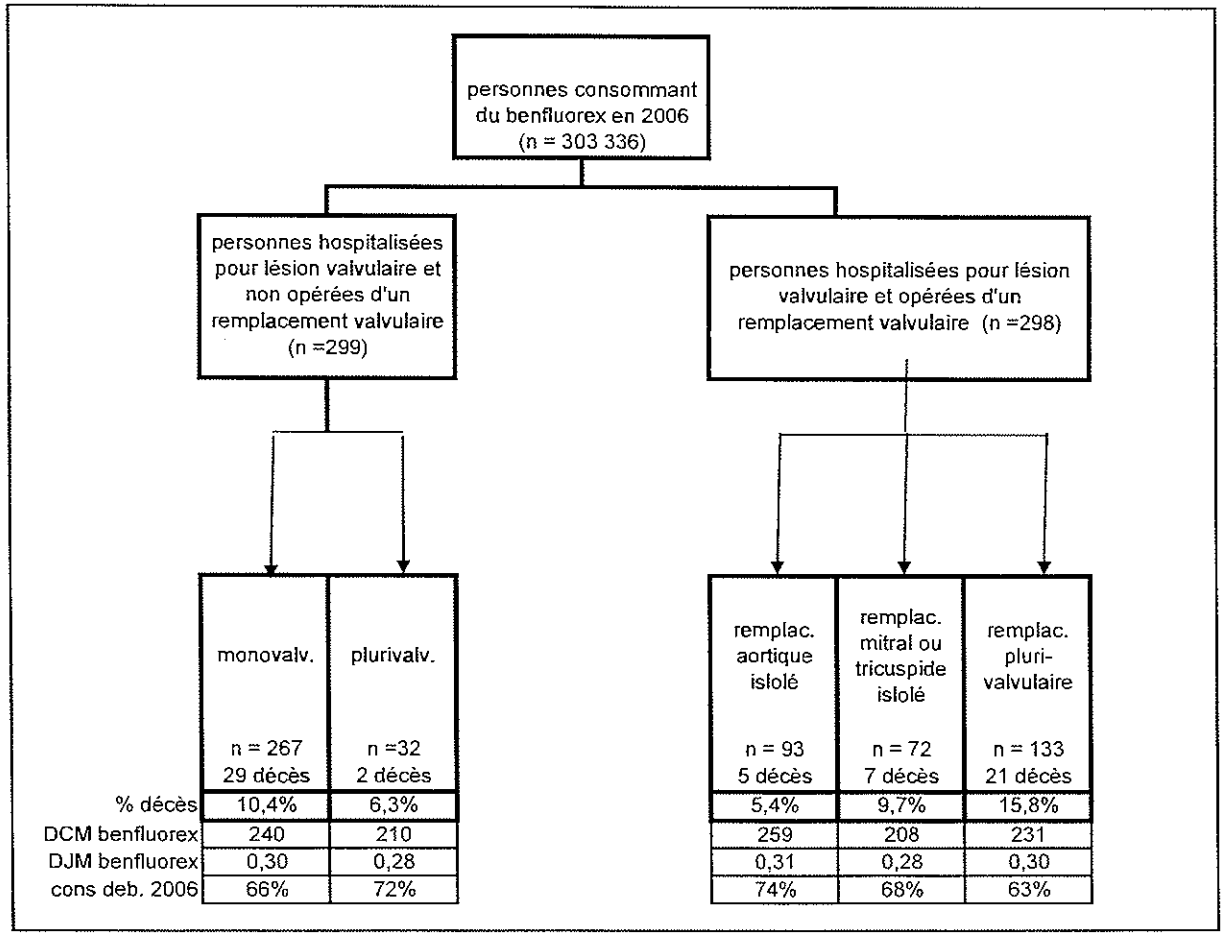

Figure 2 : suivi de la cohorte des personnes traitées pour benfluorex en 2006. Ventilation en deux groupes des personnes hospitalisées pour lésion valvulaire cardiaque [I340, I051, I351, I061, I361, I071, I080, I081, I082 I083, I088 et I089] selon l'existence ou non d'un remplacement chirurgical valvulaire cardiaque. Suivi PMSI de 48 mois : 2006 à 2009. Suivi statut vital de 55 mois.

Données SNIIRAM régime général hors SLM

Tableau 7 : caractéristiques d'âge et sexe, cause probable du décès de 58 personnes ayant consommé du benfluorex en 2006 et ayant été hospitalisées au moins une fois pour insuffisance valvulaire cardiaque sur la période 2006-2009 (cas numéroté 1 à 58)

Cas n°	sexe	âge au décès	Conso benflu (grs) 2006 au décès.	nb hospit de 2006 au décès	cause la plus probable du décès	circonstance du décès
1	homme	70-74	9	41	Leucémie myéloïde aiguë	Leucémie myéloïde aiguë sous chimiothérapie
2	homme	65-69	216	10	Endocardite infectieuse précédant une insuffisance des valvules mitrale et aortique	décès hospitalier en post chirurgie valvulaire sous CEC
3	femme	70-74	94,5	5	Insuffisance des valvules mitrale et aortique	décès hospitalier en post chirurgie valvulaire sous CEC
4	femme	65-69	99	1	Insuffisance de la valvule mitrale	décès non hospitalier 5 mois après une hospitalisation pour ins mitrale sans notion d'aucune autre pathologie
5	homme	75-79	4,5	4	myopathie	décès hospitalier 1 mois après une chirurgie valvulaire mitrale sous CEC dans un contexte de myopathie
6	homme	75-79	40,5	4	Cardiovasculaire (insuffisance mitrale + sténose carotidienne)	décès non hospitalier 2 ans après une chirurgie de remplacement valvulaire mitral
7	femme	65-69	490,5	6	cardiovasculaire : ins card et insuffisance mitrale	décès 7 mois après une hospit. pour insuffisance mitrale (PMSI 2010 absent)
8	femme	75-79	81	8	Ins. valvulaire mitrale, aortique et tricuspidienne	décès hospitalier en post chirurgie valvulaire sous CEC
9	femme	75-79	220,5	3	Insuffisance de la valvule mitrale	décès hospitalier en post chirurgie valvulaire sous CEC
10	femme	65-69	40,5	11	Tumeur maligne de l'encéphale	décès hospitalier avec un diagnostic de tumeur maligne de l'encéphale
11	femme	75-79	337,5	4	tumeur maligne utérus	décès hospitalier post chirurgical pour tumeur maligne utérus – contexte d'insuffisance mitrale
12	femme	60-64	13,5	9	Inconnue	décès non hospitalier ; contexte de tumeur maligne du sein (chimio) et d'insuffisance de la valve aortique
13	femme	55-59	472,5	5	Trouble vascul. aigu de l'Intestin	décès hospitalier au cours d'un séjour trouble vasculaire intestinaux avec un contexte d'insuffisance mitrale et d'infarctus 2 mois auparavant
14	femme	75-79	9	8	tumeur maligne secondaire des os et de la moelle	décès hors hôpital avec tumeur maligne secondaire ; chirurgie valvulaire 2 années avant
15	femme	60-64	54	2	Insuffisance cardiaque et état de choc circulatoire	décès hospitalier pour ins cardiaque 6 mois après un cathétérisme cardiaque pour ins mitrale : pas d'autres pathologies retrouvées
16	femme	75-79	31,5	9	septicémie	décès hospitalier 7 mois après une 2ème chirurgie de remplacement valvulaire sous CEC (nombreuses complications endocardite, hémorragie, septicémie avec insuffisance rénale et cardiaque)

17	homme	55-59	310,5	8	tr du rythme	décès hospitalier pour tr de rythme et insuffisance cardiaque, ins. mitrale, VIH et carcinome hépatocellulaire
18	femme	70-74	13,5	10	insuffisance mitrale	décès hospitalier en post chirurgie valvulaire mitrale sous CEC ; contexte de cardiopathie hypertensive préalable
19	femme	60-64	310,5	13	tr du rythme	décès en 2010 (PMSI 2010 manquant) mais tableau caractéristique, insuffisance cardiaque, insuffisance aortique, hypertension artérielle pulmonaire (HTAP)
20	homme	60-64	189	2	insuffisance aortique.	décès hospitalier en post chirurgie valvulaire sous CEC ; aucune autre pathologie mentionnée
21	homme	70-74	202,5	13	tumeur maligne du cardia	décès soins palliatifs pour tumeur maligne
22	homme	70-74	153	43	insuffisance rénale et diabète	décès d'un patient diabétique dialysé
23	femme	55-59	297	12	Insuffisance tricuspidienne	décès hospitalier en post intervention card sous CEC pour insuffisance tricuspidienne ; ins mitrale et cardiaque connues
24	homme	55-59	13,5	8	IRC terminale	décès hospitalier dans un tableau IRC, insuffisance cardiaque 20 mois après remplacement valvulaire mitral ; insuffisance mitrale, insuffisance cardiaque, tr du rythme
25	femme	60-64	27	2	tr lignée érythrocytaire	décès non hospitalier ; insuffisance mitrale,
26	homme	55-59	288	3	insuffisance cardiaque	décès hospitalier en post chirurgie valvulaire mitrale sous CEC
27	homme	60-64	189	7	insuffisance mitrale	décès hospitalier en chirurgie cardiaque sous CEC pour insuffisance mitrale ; contexte de bronchopathie chronique
28	femme	70-74	72	2	insuffisance mitrale	décès hospitalier en post chirurgie valvulaire mitrale sous CEC
29	femme	80-84	207	3	encéphalopathie, insuffisance mitrale	décès non hospitalier
30	homme	65-69	297	13	Suite de péritonite	décès hospitalier par péritonite, stomie.13 mois après chirurgie valvulaire sous CEC ; insuffisance mitrale, insuffisance ventriculaire gauche
31	femme	75-79	337,5	8	infarctus	décès hospitalier par infarctus du myocarde ; insuffisance mitrale et insuffisance ventriculaire gauche
32	femme	85-89	4,5	7	anémie hémolytique	décès non hospitalier ; circonstances imprécises ; notion d'insuffisance valvulaire mitrale, insuffisance ventriculaire gauche
33	homme	70-74	301,5	73	insuffisance rénale terminale	décès d'un patient dialysé et avec une tumeur maligne (chirurgie majeure) ; tumeur maligne du caecum
34	femme	60-64	90	8	insuffisance mitrale	décès au cours du mois suivant une chirurgie valvulaire mitrale sous CEC ; contexte d'apnée du sommeil
35	femme	65-69	121,5	5	Insuffisance mitrale	décès hospitalier post chirurgical de remplacement valvulaire mitral
36	femme	60-64	351	2	insuffisance mitrale	décès en 2010 deux ans après un cathétérisme pour insuffisance mitrale (absence PMSI 2010)
37	femme	55-59	94,5	4	insuffisance mitrale	décès hospitalier en post chirurgie cardiaque pour insuffisance mitrale, ins cardiaque
38	femme	70-74	252	3	hémorragie intracérébrale hémisphérique	décès hospitalier pour hémorragie cérébrale 3 mois après une prise en charge pour insuffisance aortique
39	femme	75-79	130,5	3	choc cardiogénique	décès 2 ans par chirurgie de remplacement valvulaire par choc cardiogénique sans infarctus, sans autres pathologies
40	femme	80-84	189	1	insuffisance valvulaire aortique	décès hospitalier au cours d'une hospitalisation pour insuffisance aortique
41	femme	75-79	342	2	insuffisance valvulaire aortique	décès 2 mois après 2 hospitalisations pour insuffisance de la valve aortique

42	homme	85-89	49,5	2	insuffisance valvulaire tricuspide	décès hospitalier au cours d'une hospitalisation pour ins. valvulaire tricuspide
43	femme	75-79	202,5	12	insuffisance rénale	décès hospitalier au cours d'une hospitalisation avec ins rénale terminale et pancréatite ; contexte de valvulopathie aortique avec nombreuses hospitalisations
44	homme	55-59	72	3	ischémie cérébrale	décès hospitalier dans le mois suivant une chirurgie valvulaire sous CEC ; ins mitrale
45	femme	80-84	144	16	Ins respiratoire aiguë	décès en 2010 (pas de PMSI disponible pour 2010) ; oedème pulmonaire, ins card, ins valv. Aortique
46	femme	75-79	121,5	6	lésion traumatique intracrânienne	décès hospitalier avec lésion cérébrale anoxique
47	femme	75-79	81	5	inconnue	décès en 2010 trois ans après une chirurgie pour insuffisance tricuspidienne (PMSI 2010 absent)
48	homme	65-69	54	3	patho cardiaque, insuffisance aortique	décès en 2010 27 mois après une chirurgie pour insuffisance aortique ; pas de pathologie autre déclarée en ALD
49	homme	55-59	72	5	inconnue	décès en 2010 4 ans après une chirurgie pour ins mitrale
50	homme	65-69	198	2	myocardiopathie ischémique	décès hospitalier en post chirurgie valvulaire mitrale sous CEC
51	homme	70-74	472,5	12	tr du rythme	décès hospitalier après 11 hospitalisations en cardiologie par trouble du rythme/ ins. ventriculaire G, chirurgie de rempl. valvulaire sous CEC ; , insuffisance cardiaque, insuffisance aortique et mitrale
52	homme	65-69	225	9	abcès de la rate	décès hospitalier dans les suites d'une endoscopie biliaire (abcès de la rate)
53	homme	80-84	99	7	Insuffisance ventriculaire gauche	décès en 2010 ; 6 mois après une hospitalisation par ins ventr G et 3 ans après remp. val sous CEC ; autres pathologies connues bénignes
54	femme	80-84	252	3	endocardite	décès hospitalier pour endocardite inf après 2 transferts pour insuffisance aortique et embolie pulmonaire
55	femme	75-79	265,5	15	ins card congestive : ins aortique et mitrale	décès hospitalier pour insuffisance cardiaque 23 mois après une chirurgie de remplacement valvulaire (IM et Iao)
56	femme	55-59	229,5	6	embolie et thrombose des artères des MI	décès hospitalier embolie et thrombose des artères des MI au cours d'une intervention de chir. asc. Contexte insuffisance mitrale
57	femme	35-39	13,5	5	cardiovasculaire	décès 4 mois après chirurgie de remplacement valvulaire tricuspidienne + Aortique et 2 mois après thrombose intracardiaque
58	homme	65-69	135	6	cardiovasculaire	décès non hospitalier 15 mois après chirurgie de remplacement valvulaire mitrale

Tableau 8: caractéristique d'âge et sexe, cause probable du décès de 6 personnes ayant consommé du benfluorex en 2006 et ayant été hospitalisées au moins une fois pour maladie multivalvulaire valvulaire cardiaque (codification en I08) sur la période 2006-2009 (cas numérotés 59 à 64)

Cas n°	sexe	âge au décès	Conso benflu (grs) 2006 au décès.	nb hospit de 2006 au décès	cause la plus probable du décès	circonstance du décès
59	femme	75-79	139,5	3	Insuffisance cardiaque congestive	Atteinte des valves mitrales et aortiques (notion de sténose aortique). Deux chirurgies de replacement valvulaire à 3 mois d'écart.la première ets un double remplacement mitral et aortique. Décès hospitalier lors du séjour pour la deuxième intervention.
60	femme	60-64	486	2	inconnue	Chirurgie de remplacement valvulaire cardiaque 10 mois avant le décès. Atteinte valvulaire mitrale, aortique et tricuspide ; pas d'autre pathologie mentionnée. Décès non hospitalier.
61	homme	65-69	76,5	11	Myocardiopathie avec dilatation.	11 hospitalisations en 40 mois, la plupart pour insuffisance cardiaque et insuffisance ventriculaire G. Intervention cardiaque sous CEC. Atteinte des valves mitrale et tricuspide. Décès hospitalier lors d'un séjour pour myocardiopathie avec dilatation
62	homme	80-84	135	13	Insuffisance rénale aigue ave nécrose tubulaire	Terrain athérosclérose. Sténose carotidienne opérée. Ins. Card. Et état de choc (IVG). Après cathétérisme, double remplacement valvulaire mital et aortique sous CEC. Dg atteinte des valvules mitrales et aortiques. Complication une année après Ins.VG + troubles du rythme ;. Décès hospitalier 2 années après un double remplacement mitral et aortique dans un tableau d'insuffisance rénale aigue.
63	femme	70-74	40,5	5	Atteinte valvulaire mitrale et aortique	2 séjours pour pneumopathie. Puis acte thérapeutique par voie vasculaire pour une sténose mitrale. Deux mois après cathétérisme avec un diagnostic d'atteinte des valves mitrale et aortique. 4 mois après décès hospitalier au cours d'un séjour pour chirurgie de remplacement valvulaire sous CEC.
64	femme	50-55	238,5	12	inconnue	Tableau complexe associant plusieurs épisodes de broncho-pneumopathie (6 hospitalisations), un diagnostic de sténose mitrale et 5 mois après une double chirurgie de remplacement valvulaire sous CEC pour atteinte des valvules mitrale et aortique. 6 mois après hospitalisation pour épisodes dépressif précédant une nouvelle hospitalisation « intoxication par médicament psychotropes » évoquant une tentative d'autolyse et une dernière hospitalisation pour « syndrome post-commotionnel ». La patiente décède 10 mois après (décès non hospitalier)

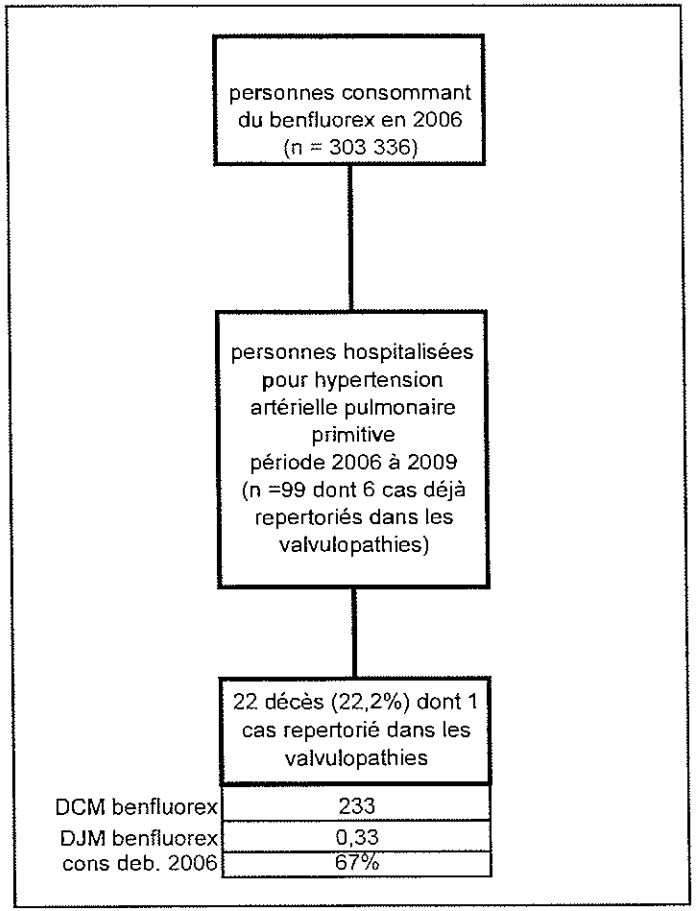

Figure 3 : suivi de la cohorte des personnes traitées pour benfluorex en 2006. Recherche d'hospitalisation pour hypertension artérielle pulmonaire I270. Suivi PMSI de 48 mois : 2006 à 2009. Suivi statut vital de 55 mois.

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Tableau 9: caractéristique d'âge et sexe, cause probable du décès des 21 personnes ayant consommé du benfluorex en 2006 et ayant été hospitalisées au moins une fois pour hypertension artérielle pulmonaire (codification en I270) sur la période 2006-2009 (cas numérotés 65 à 85)

Cas n°	sexe	âge au décès	Conso benflu (grs) 2006 au décès.	nb hospit de 2006 au décès	cause la plus probable du décès	circonstance du décès
65	homme	70-74	180	13	Insuffisance respiratoire	Trois hospitalisations pour apnée du sommeil, bronchite chronique et insuffisance respiratoire ; un acte diagnostique par voie vasculaire porte le diagnostic d'hypertension artérielle pulmonaire ; un traitement est mis en route en hôpital de jour ; 8 mois après œdème pulmonaire, IVG, insuffisance respiratoire. Décès hospitalier en soins palliatif (diagnostic insuffisance respiratoire aigue)
66	homme	55-59	9	9	Inconnue (HTAP ?)	.En 18 mois 3 hospitalisations pour hypertension pulmonaire (primitive), 3 autres pour ins. ventriculaire gauche et une pour complication d'un traitement anticoagulant. La cause terminale du décès est inconnue ; le patient décède au milieu de l'année 2010. (PMSI 2010 absent).
67	homme	75-79	36	5	Tr mentaux d'origine organique	5 hospitalisation en moins de 6 mois : Tr du rythme, hémorragie digestive, HTAP, Diabète sucré insulino-dépendant, avec complications multiples et trouble mentaux d'origine organique lors de l'hospitalisation conduisant au décès
68	homme	75-79	279	23	ins. rénale terminale	23 hospitalisations en 29 mois. 5 pour ins ventriculaire G ou ins card cong. Embolie thrombose, apnée du sommeil. Un trait est mis en œuvre en hôpital de jour après un diagnostic d'hypertension artérielle pulmonaire. Ins rénale chronique, puis hémorragie gastro-intestinale. Décès hospitalier (ins. rénale terminale)
69	homme	75-79	243	5	HTAP.	Première hospitalisation pour ins. respiratoire aigue, pneumopathie bactérienne. Un mois avant le décès hospitalisation avec le dg principal d'hypertension artérielle pulmonaire. Décès non hospitalier le mois suivant.
70	femme	70-74	108	5	Insuffisance respiratoire	5 hospitalisation en 10 mois : embolie pulmonaire, un acte diagnostique par voie vasculaire porte le diagnostic d'HTAP, 2 hospitalisation rapprochée pour HTAP puis ins respiratoire aigue avec décès
71	homme	80-84	54	8	HTAP	Pathologie pulmonaire bronchite, mal pulmonaire obstructive. 3 hospitalisations avec le dg d'HTAP ; la dernière précède de 2 mois le décès non hospitalier.
72	femme	60-64	202,5	27	Insuffisance respiratoire	27 hospitalisations en 3 années dont 15 avec le dg principal d'HTAP. Par ailleurs diabète, obésité ; décès hospitalier (insuffisance respiratoire aigue)
73	femme	65-69	337,5	11	Inconnue (HTAP ?)	5 hospitalisations en 2 ans et demi avec pour dg principal HTAP avec à 3 reprise un acte dg par voie vasculaire ; pins card congestive et hémorragie gastro-intestinale ; la patiente décède au milieu de l'année 2010. (PMSI 2010 absent).
74	femme	60-64	184,5	25	Ins rénale	Le tableau débute par un syndrome de détresse respiratoire puis 14 hospitalisations en 2 années pour HTAP ; ins rénale et dialyse dans le mois qui précède le décès
75	homme	45-49	216	8	Insuffisance respiratoire	Ins cardiaque congestive puis acte dg par voie vasculaire avec dg d'HTAP ; 3 hospitalisations avec le dg principal d'HTAP et décès avec un dg d'ins. respiratoire aigue
76	femme	70-74	54	2	inconnue	Hospitalisation pour dyspnée puis acte dg par voie vasculaire avec dg d'HTAP ; décès en 2010 (PMSI absent)
77	femme	85-89	117	4	inconnue	HTAP, démence et lombalgie basse précédant un décès non hospitalier
78	femme	80-84	4,5	1	inconnue	Une seule hospitalisation pour HTAP 6 mois avant le décès en 2010 (PMSI 2010 absent).
79	homme	60-64	36	6	Inconnue (HTAP ?)	6 hospitalisations en une année dont 4 avec comme dg principal HTAP ; décès non hospitalier 7 mois après la dernière hospitalisation.

80	homme	50-54	27	3	inconnue	En moins d'une année, chez un homme de la cinquantaine 3 hospitalisations pour pneumopathie à pseudomonas, HTAP et autre pour affection pulmonaire interstitielle avec fibrose ; la dernière hospitalisation précède de 2 mois un décès non hospitalier.
81	homme	75-79	387	7	HTAP	4 hospitalisations pour HTAP et une pour ins. resp. aigue. Décès 4 mois après en 2010 (PMSI 2010 absent).
82	homme	50-54	13,5	13	Tumeur maligne du poumon	3 hospitalisations pour HTAP avec contexte de cirrhose du foie alcoolique. Tumeur du lobe moyen du poumon. Chimiothérapie décès hospitalier en soins palliatifs
83	homme	30-34	13,5	24	Syndrome de détresse respiratoire	Début 2008 maladie de Hodgkin traitée par chimiothérapie. En fin de la même année dg de synd. d'apnée du sommeil puis HTAP après acte dg par voie vasculaire. Plusieurs hospitalisations pour ins resp puis décès hospitalier en milieu d'année suivante lors d'une hospitalisation pour syndrome de détresse respiratoire.
84	homme	75-79	9	10	Paraplégie	En moins de 10 mois le patient est hospitalisé à plusieurs reprises pour des convulsions et un trouble du comportement avec un diagnostic de tumeur bénigne des méninges cérébrales. Par la suite une hospitalisation unique conduit au dg d'HTAP. Puis le patient présente une compression médullaire, une occlusion intestinale non due à une hernie et enfin une paraplégie 2 mois avant un décès non hospitalier
85	femme	65-69	495	6	Inconnue	3-4 années avant le décès 3 hospitalisations pour HTAP et trois autres pour trouble du rythme, cardiopathie hypertensive et ins. cardiaque. Décès en 2010 (PMSI 2010 absent)

3.4 Quantité de benfluorex délivrée et apparition d'une complication

Les quantités de benfluorex délivrées chez les non-malades étaient inférieures sur les trois paramètres analysés à celles délivrées aux personnes ayant contracté une complication.

Tableau 10 présentant les éléments connus sur la quantité de benfluorex délivrée chez les personnes exposées selon l'apparition ou non d'une complication (valvulopathie ou HTAP)

	Exposés au benfluorex (non malades) Non décédés n = 302 646	Exposés au benfluorex (malades : valvulopathie ou HTAP) Non décédés (n = 605)	Décédés (n = 85)
% consommateur de benfluorex en début d'année 2006[1]	53,7%	64,3%	80,0%
dose journalière moyenne[2]	246 mg	301 mg	327 mg
dose cumulée moyenne à compter du 1/1/2006[3]	153 grs	333 grs	162 grs*

(1) correspond à une consommation de benfluorex déjà observée en janvier ou février 2006 : cet indicateur est le reflet d'une consommation très probablement antérieur à 2006
(2) calculée par patient (quantité de benfluorex remboursée / (date de fin – date de début + 30))
(3) calculée par patient en cumulant tous les remboursements de benfluorex du 1/1/2006 à la fin 2009. (le médicament a été retiré de la commercialisation le 30/11/2009).
** censure liée au décès*

3.5 Délai d'apparition d'une complication après l'arrêt du benfluorex

Il faut souligner au préalable que l'apparition d'une complication peut entraîner l'arrêt du benfluorex. Nous avons analysé le sous groupe des 138 192 patients ayant consommé du benfluorex en 2006 et n'en ayant pas consommé dans les années suivantes. L'incidence d'une hospitalisation pour une complication valvulaire et/ou une HTAP a été suivie sur les 4 années. En 2006 (année de consommation) le taux d'incidence d'apparition d'une complication était de 0,82 pour 1000, puis 0,27 pour 1000 en 2007, 0,18 pour 1000 en 2008 et 0,05 pour 1000 en 2009. Le taux de 0,05 pour 1000 correspond à 7 patients différents pour les 138 000. Dans 62% des cas les complications étaient apparues dans l'année calendaire de l'arrêt, dans 21% dans l'année suivante et dans 14 et 4% dans les années n+2 et n + 3. Notons toutefois que cette information (Tableau 11) est d'interprétation délicate car les résultats portent sur un sous groupe de malades très spécifique (patients ayant arrêté leur traitement pour des raisons diverses) dont la durée totale des traitements nous est inconnue. Par ailleurs on ne peut exclure des effets décalés dans le temps (au-delà des 3 années d'observation).

Tableau 11 : délai d'apparition des complications chez les personnes ayant consommé du benfluorex en 2006 et n'en ayant pas consommé en 2007, 2008 et 2009.

		Délai d'apparition de la complication en année				
	Groupe	0	1	2	3	Total
1	diagnostic non opéré monovalvulaire	32	18	11	3	64
2	diagnostic non opéré plurivalvulaire	8	0	0	0	8
3	diagnostic opéré aortique	14	4	3	0	21
4	diagnostic opéré mitrale ou tricuspide	16	2	2	1	21
5	diagnostic opéré plurivalvulaire	26	4	4	1	35
10	HTAP	17	10	5	2	34
Total		113	38	25	7	183

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Point de presse sur Benfluorex (Médiator) du 16 novembre 2010

Intervention introductive de Jean Marimbert, Directeur Général de l'Afssaps

I – Le Benfluorex (Médiator), était un médicament autorisé en 1974 et commercialisé depuis 1976, pour deux indications : adjuvant du régime adapté dans les hyper-triglycéridémies et traitement des patients diabétiques en surcharge pondérale, en complément d'un régime adapté.

L'Afssaps a suspendu à compter du 30 novembre 2009 l'AMM de ce médicament, en considérant que la balance bénéfice/risque était désormais négative en raison d'un risque de valvulopathies établi en 2009 par la convergence de données nouvelles venant des signalements de pharmacovigilance, des résultats d'une étude d'efficacité et de sécurité que l'Afssaps avait demandée au laboratoire, ainsi que des résultats d'une étude cas/témoins réalisée dans la région Brestoise. Ce faisceau d'éléments qui fondait la position de l'agence était conforté par les résultats d'une étude que la Cnamts a réalisée à la fin de l'été 2009 et communiquée à l'Afssaps, et qui faisait apparaître, chez les patients diabétiques exposés au benfluorex en 2006, un risque nettement plus élevé d'hospitalisations et d'interventions chirurgicales pour valvulopathies.

Après confirmation de la position de l'Afssaps sur le rapport bénéfice/risque dans le cadre d'une procédure européenne d'harmonisation déclenchée par l'agence, la suspension a été transformée le 20 juillet 2010 en un retrait définitif.

II - L'agence a souhaité s'exprimer de nouveau sur ce sujet ce matin pour aborder essentiellement trois aspects.
Tout d'abord nous souhaitons remettre en perspective l'action qu'a menée l'Afssaps vis-à-vis de ce produit avant 2009, car certaines présentations du sujet qui ont été faites au cours des derniers mois étaient très discutables.

Ensuite l'agence souhaite vous livrer les éléments dont elle dispose aujourd'hui pour essayer de cerner l'impact de l'utilisation de benfluorex, en particulier sur le nombre de valvulopathies et de décès pour valvulopathies. L'existence d'un impact n'est pas douteuse, à partir du moment où, comme l'a exprimé notre décision de 2009, il est désormais établi que le benfluorex pouvait susciter ou favoriser l'émergence de ces atteintes valvulaires. Mais l'Afssaps a voulu essayer de cerner même approximativement cet impact en demandant à la Cnamts une étude à partir des bases de données de remboursements et d'hospitalisations qu'elle gère. Les possibilités d'utilisation de ces bases étaient fortement limitées jusqu'à récemment par des contraintes juridiques et surtout techniques, mais elles ont été desserrées récemment, ce qui ouvre, j'y reviendrai, des perspectives importantes pour une articulation renforcée entre la pharmacovigilance fondée sur la notification spontanée des effets indésirables et la pharmacoépidémiologie.

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Enfin et surtout, il s'agit pour nous de vous exposer aujourd'hui les conséquences que l'agence peut tirer de ces échanges récents avec la Cnamts en ce qui concerne le suivi des patients traités dans le passé avec benfluorex, qui avait fait l'objet de recommandations dans notre communication du 26 novembre 2009.

III - Je souhaite donc revenir en premier lieu sur l'action menée par l'agence vis-à-vis de ce médicament avant la nouvelle réévaluation de 2009 et la décision de suspension qui s'en est suivie. Il est important de le faire avec précision, pour tempérer la tentation toujours forte de l'anachronisme, c'est-à-dire d'apprécier ce qui a été fait ou aurait dû être fait hier ou avant-hier sur la base de toutes les données qui sont disponibles aujourd'hui. Cet examen rétrospectif montrera qu'il n'était nullement évident jusqu'en 2009, d'établir de façon étayée et robuste à la fois l'existence du risque de valvulopathie sur lequel l'agence s'est fondée pour mettre fin à la commercialisation du produit, et a fortiori l'étendue de ce risque.

Mais avant de venir à cette analyse rétrospective sur le risque, je voudrais souligner que ce produit autorisé il y a fort longtemps a donné lieu à partir de la fin des années 90 à plusieurs réévaluations qui ont concerné également son efficacité.
C'est ainsi que l'agence a refusé en 2000 une demande du laboratoire d'étendre les indications à un traitement de première ligne pour le diabète de type II lorsque le régime n'était pas suffisant pour rétablir à lui seul l'équilibre glycémique, en considérant que la démonstration d'efficacité (Etude Del Prato) était insuffisante pour une telle indication. A la suite de cette évaluation, l'agence a demandé au laboratoire concerné que soit réalisée une nouvelle étude (Etude Moulin) évaluant l'efficacité du benfluorex utilisé seul ou en association à d'autres médicaments pour traiter le diabète.
En 2007, sur la base notamment de cette étude qu'elle avait demandée au laboratoire, l'agence a retiré l'indication concernant les hyper-tryglycéridémies pour insuffisance de preuve de la taille effective de l'effet du médicament. Seule l'indication du benfluorex comme « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » a été maintenue. Néanmoins, l'Agence a demandé au laboratoire une nouvelle étude, selon les standards contemporains de démonstration, pour réévaluer l'efficacité du benfluorex dans la seule indication qui subsistait. Elle consistait à tester sa non-infériorité par rapport à un autre traitement du diabète, la pioglitazone, chez des patients diabétiques par ailleurs insuffisamment équilibrés pour leur diabète par un sulfamide hypoglycémiant (autre médicament antidiabétique). Cette nouvelle étude (Etude Regulate) comportait aussi un volet de sécurité d'emploi (ou de tolérance) dont les résultats connus en 2009 ont contribué à établir ce risque de valvulopathies.

En ce qui concerne la gestion du risque par l'agence avant la réévaluation de 2009, je voudrais insister sur quatre points essentiels.
Le premier point consiste à souligner que la problématique de ce produit n'était pas identique à celles des médicaments anorexigènes comme Isoméride et Ponderal qui ont été retirés par l'agence en 1996 et 1997, même s'il y a entre ces médicaments et benfluorex une parenté et des points de recoupement qui devaient retenir et qui ont effectivement retenu l'attention de l'agence, et justifié un suivi attentif du profil de sécurité de ce produit.

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Sans entrer dans le détail des précisions scientifiques qui pourront vous être apportées par celles et ceux qui m'entourent, il faut retenir que le benfluorex et les anorexigènes retirés antérieurement n'appartiennent pas à la même classe thérapeutique, et qu'ils ont des propriétés pharmacologiques et des modes d'action principaux distincts. Pour autant une partie de la structure chimique de benfluorex est commune avec celle des fenfluramines ; ils interagissent tous les deux (mais différemment) avec une substance physiologique, la sérotonine et ses récepteurs, et ils ont un métabolite commun, la norfenfluramine. En effet, la norfenfluramine est l'un des métabolites du benfluorex, c'est-à-dire une des substances dans lesquelles se transforment la molécule dans l'organisme. Or cette norfenfluramine, qui n'est présente que minoritairement dans le benfluorex, appartient au groupe des fenfluramines, qui étaient les composants principaux dans les anorexigènes retirés dans les années 90.

A la fin des années 90, ces anorexigènes de type isoméride ont été associés à des effets indésirables graves, principalement des cas d'hypertension artérielle pulmonaire (HTAP), et beaucoup plus rarement des cas d'atteintes valvulaires. Les mécanismes de développement de ces effets indésirables n'ont été élucidés qu'après le retrait des anorexigènes, par des études publiées successivement dans les années 2000. Ces études ont permis d'expliquer comment ces types d'effets indésirables pouvaient être déclenchés, mais elles ont aussi montré que ces mécanismes n'étaient vraisemblablement pas les mêmes dans les deux cas, HTAP et atteintes valvulaires.

En deuxième lieu, il faut souligner que cette parenté partielle du benfluorex avec les anorexigènes fenfluraminiques, liée notamment au fait que la norfenfluramine est un des métabolites du benfluorex,, a conduit l'agence à prendre des mesures de minimisation et de suivi du risque.

D'une part, dès 1996, les préparations magistrales à base de benfluorex ont été interdites, en vue de limiter le mésusage de ce médicament comme produit amaigrissant.
D'autre part, l'agence s'est attachée dès 1998 à suivre attentivement le risque potentiel d'HTAP, et elle a renforcé ce suivi à partir du signalement en mars 2005 d'un cas en pharmacovigilance.
Les points successifs qui ont été faits dans le cadre de la commission nationale de pharmacovigilance à partir de juin 2005 et qui sont accessibles en ligne sur le site de l'Afssaps depuis 2006 dans le cadre de sa démarche de transparence, n'ont pas fait apparaître de signal de toxicité cardiovasculaire significatif par rapport à l'incidence de ces troubles dans la population générale.

En ce qui concerne les valvulopathies, il faut avoir à l'esprit que le signal issu de la notification spontanée en pharmacovigilance avant la fin de l'année 2008 était extrêmement faible. Si l'on met à part le cas espagnol publié en 2003, il y a eu en tout et pour tout en France un cas bien documenté et confirmé par examen anatomopathologique qui a été signalé à Toulouse en 2006 et a donné lieu à une publication. Quelques autres cas signalés en pharmacovigilance faisaient intervenir une notion d'atteinte valvulaire, mais pour les plus documentés de ces quelques cas, d'autres causes que les médicaments pouvaient entrer en ligne de compte, par exemple un traitement antérieur par Isoméride.
Il n'y avait donc pas matière avant 2009 à prendre une décision de retrait, qui n'aurait pas pu être étayée par des données épidémiologiques robustes. Il est même vraisemblable, en l'état de

la jurisprudence qui exerce un contrôle approfondi sur les décisions de retrait, qu'une telle décision aurait été annulée par le juge en cas de contestation.

Le troisième point que je voudrais souligner est que le tableau d'évaluation du risque a changé de façon très nette à partir de fin 2008/début 2009.
En effet, plusieurs données nouvelles sont apparues et ont contribué à forger de façon convaincante une présomption sur le caractère significatif du risque valvulopathie.
Tout d'abord, à la suite du signalement d'un deuxième cas bien documenté et publié en provenance de Brest, l'Afssaps a déclenché une nouvelle réévaluation du risque, qui a donné lieu à trois passages en commission nationale de pharmacovigilance en quelques mois à partir du printemps 2009. Des cas d'atteintes valvulaires parfois antérieures, sont alors déclarés, notamment en provenance d'Amiens et de Brest à partir d'une exploitation des données de la base de PMSI sur les hospitalisations et d'un registre d'échographies. Au total, pas moins de 42 cas ont été déclarés entre janvier et novembre 2009, et depuis l'arrêt de commercialisation de novembre 2009, 18 cas se sont ajoutés ensuite, le plus souvent rétrospectifs.

Dans le même temps, les résultats de la deuxième étude (Etude Regulate) demandée par l'agence au laboratoire faisaient notamment ressortir un nombre préoccupant d'anomalies valvulaires après 52 semaines de traitement. Et les résultats de l'étude cas/témoins conduite à Brest, disponibles durant l'été 2009, allaient dans le même sens. Enfin, et à un moment où la procédure de réévaluation et de suspension était déjà bien avancée, les résultats de la première étude de la Cnamts que j'ai mentionnée au début de mon intervention sont venus apporter une confirmation nette du signal dégagé par toutes les données nouvelles de 2009.

IV - En ce qui concerne les résultats de la deuxième étude que l'Afssaps a demandé cet été à la Cnamts pour essayer de mieux cerner l'impact de l'utilisation de benfluorex sur les pathologies valvulaires, je laisserai les responsables scientifiques de l'agence qui m'entourent s'exprimer dans quelques minutes pour vous exposer à la fois la méthodologie et les conclusions.
Avec toutes les précautions qu'appelle ce type d'estimation nécessairement approximative, on peut tenir pour certain, que des décès ont pu être provoqués ou favorisés par l'utilisation de benfluorex dans quelques centaines de cas sur la période d'un peu plus de 30 ans pendant laquelle le produit a été disponible (1976-2009). L'ordre de grandeur, de l'ordre d'au moins 500, vous sera précisé tout à l'heure, et dépend des méthodes et hypothèses de calcul retenues.
Il va de soi que ces estimations à caractère statistique ne préjugent en rien de l'analyse au cas par cas qui s'impose pour apprécier l'imputabilité partielle ou totale au médicament dans des situations individuelles.

V – Reste un aspect essentiel qui est celui du suivi des patients ayant été traités sous benfluorex.

Lorsque l'agence a communiqué le 26 novembre 2009 pour annoncer la suspension de l'AMM, elle a formulé des recommandations à la fois auprès du public et des professionnels de santé.

Les patients ont été invités à rappeler à leur médecin qu'ils ont pris du benfluorex lors de leur prochaine consultation médicale de suivi. Les médecins ont reçu une lettre les incitant, pour les patients en cours de traitement à rechercher lors de l'interrogatoire et de l'examen clinique d'éventuels symptômes ou signes d'une atteinte valvulaire et de demander si nécessaire des examens complémentaires, voire une consultation spécialisée. S'agissant des patients traités par benfluorex dans le passé, les médecins ont été incités par mesures de précaution à interroger les patients diabétiques sur les expositions éventuelles au benfluorex et à procéder à un interrogatoire et à un examen clinique en vue de rechercher des symptômes ou des signes évocateurs d'une valvulopathie susceptible de rendre nécessaire la réalisation d'examens complémentaires, voire d'une consultation spécialisée.
Sans modifier fondamentalement ces recommandations, l'agence est conduite aujourd'hui à les préciser sur la base d'un examen à la fois des cas notifiés, des études publiées et de certaines données de la deuxième étude de la Cnamts. Il ressort en effet de ces éléments, d'une part que le risque de développer une valvulopathie paraît s'accroitre à partir d'un durée de consommation de benfluorex de l'ordre de 3 mois, et d'autre part que ce risque apparaît majoritairement dans les deux premières années d'utilisation, persiste dans les deux années qui suivent l'arrêt du benfluorex et devient très faible au-delà.
C'est pourquoi l'agence souligne aujourd'hui tout particulièrement la nécessité d'une consultation médicale chez le médecin traitant pour les personnes ayant consommé pendant au moins 3 mois du benfluorex au cours des quatre dernières années de sa commercialisation, c'est-à-dire entre le 1er janvier 2006 et le 30 novembre 2009. Cette consultation doit être suivie d'une consultation spécialisée cardiologique en cas de détection à l'auscultation de signes évocateurs d'anomalies valvulaires ou même simplement en cas de doute. Des échanges sont en cours avec la Cnamts en vue de l'envoi par les Caisses primaires d'assurance maladie de courriers individuels de rappel aux patients concernés. Il s'agit de s'assurer que toutes ces personnes ont bien été informées par leur médecin traitant des recommandations émises par l'Afssaps en novembre 2009. Cet envoi de lettre personnalisée n'est juridiquement et pratiquement possible que pour une partie de ces patients car les organismes d'assurance maladie ne peuvent pas conserver les données personnelles de consommation de médicament pendant une durée de 24 mois.

Mon dernier message, particulièrement important à mes yeux pour l'avenir, est de souligner l'enjeu majeur que représente la complémentarité entre la pharmacovigilance fondée sur la notification spontanée par les professionnels de santé et les études pharmacoépidémiologiques qui peuvent être réalisées notamment à partir de bases de données telles que celles de la Cnamts.

Bien entendu, il faut poursuivre sans relâche les efforts engagés pour encourager et favoriser la notification des effets indésirables par les professionnels de santé, y compris quand l'imputabilité n'est pas évidente à priori et qu'il y a une simple suspicion d'un rôle possible du médicament. La notification d'une masse critique de cas est « une matière première » indispensable pour pouvoir travailler efficacement à la minimisation du risque. Et la généralisation prochaine de la possibilité de déclaration par les patients eux-mêmes, expérimentée au cours de la pandémie grippale, pourra contribuer à renforcer le système de notification.

Mais, il est des situations dans lesquelles un système de pharmacovigilance, même organisé de façon structurée comme il l'est chez nous, peut ne produire qu'un signal faible voire très faible pour un risque qui s'avère ensuite plus net. C'est le cas en particulier lorsque l'effet indésirable est relativement répandu dans la population générale, et que les patients concernés ont d'autres pathologies proches ou similaires qui peuvent conduire le professionnel de santé à ne pas penser faire le lien entre l'effet indésirable et la prise du médicament.
Le cas de benfluorex illustre bien la répercussion de ces «effets confondants», puisque l'examen des données de la Cnamts montre que la plupart des patients sous benfluorex hospitalisés et le cas échéant opérés pour des atteintes valvulaires étaient en affection de longue durée (ALD), au titre d'autres affections cardiovasculaires ou bien d'un diabète chronique susceptible d'engendrer des troubles cardiovasculaires. Dans un tel contexte, la possibilité de recourir rapidement et facilement à des études utilisant de grandes bases de données pour confirmer ou non le signal faible est absolument cruciale. C'est pourquoi l'Afssaps s'est dotée depuis 3 ans d'une structure interne tournée vers la pharmacoépidémiologie, apte non seulement à identifier des besoins d'études dans le cadre des plans de gestion des risques mais aussi à dialoguer avec des équipes extérieures et notamment avec la Cnamts pour faire réaliser des études confirmatives. L'agence a également constitué en 2008 un groupe de travail spécialisé associant des scientifiques de ses propres équipes et des experts pharmacovigilants et pharmacoépidémiologistes issus d'horizons et d'organismes divers. Les freins juridiques et techniques qui entravaient l'utilisation des bases de données de l'assurance-maladie étant progressivement levés, la coopération opérationnelle entre l'Afssaps et la Cnamts, engagée récemment sur des sujets comme benfluorex ou Gardasil, va pouvoir se développer plus largement, dans le cadre d'une convention que nous sommes en train de mettre au point et qui sera signée dans les prochaines semaines.

Je m'arrête là pour céder la parole aux membres de l'équipe scientifique de l'Afssaps qui vont brièvement approfondir les aspects relatifs à la pharmacologie du benfluorex, aux résultats de la deuxième étude de la Cnamts et aux conséquences à tirer pour le renforcement du suivi des patients.

Annexe 3-87

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

COUR DES COMPTES

Sixième chambre

Troisième section

44250

RELEVE DE CONSTATATIONS PROVISOIRES

(art. R. 141-8 du code des juridictions financières)

LES COMPTES ET LA GESTION DE L'AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE (AFSSAPS)

exercices 1999 à 2004

16 janvier 2006

Le présent document est destiné à recevoir les remarques des organismes contrôlés et des autres personnes qui en sont destinataires. Il est provisoire et confidentiel.

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c. Les préparations hospitalières

Autre exemple de missions remplies a minima faute de moyens : l'obligation faite aux les hôpitaux, depuis le mois de décembre 2004[59], de déclarer leurs préparations hospitalières (médicaments fabriqués en interne par les hôpitaux). 3000 déclarations ont été reçues en six mois. Seul un pharmacien à 60% de son temps est en charge de cette mission. Il n'est donc pas question d'évaluation du rapport bénéfices/risque comme pour l'AMM. La mission se borne à vérifier si la préparation hospitalièree est indispensable (absence de médicament équivalent) ou non.

Mais la contrainte de moyens peut également favoriser la créativité et susciter des procédures innovantes. En effet, la gestion administrative de cette nouvelle procédure a été simplifiée au maximum, grâce au développement d'une base de données avec télédéclaration (PROSPERH) directe par les hôpitaux. Ce projet-pilote PROSPERH va faire des émules : la base ATU, en cours de remodelage, et la base essais cliniques, en cours d'élaboration, auront une procédure de télédéclaration ou de soumission électronique des dossiers.

d. Les produits biologiques à effet thérapeutique

Issu de la loi du 1er juillet 1998, il s'agit d'un champ de compétence nouveau, à structurer et manifestement en souffrance. En effet, l'effectif actuel se réduit à 4,5 évaluateurs, ½ interne, 2 vacataires et ½ stagiaire. De plus, cette activité ne bénéficie pas du suivi organisationnel de la « GARE » (cf. plus haut). Les produits concernés sont les suivants :

- Les **produits de thérapie génique** (TG) démarrent : il y a des demandes d'essais cliniques, mais pas encore d'AMM ; presque tous auront un statut de médicament.
- Les **produits de thérapie cellulaire** (TC), issus de la directive européenne, peuvent être un médicament (donc soumis à AMM) ou non. La loi de 1998 a créé l'autorisation de TC, mais le département de l'évaluation des produits biologiques, au sein de la DEMEB, n'a pas les moyens de l'évaluer. Huit demandes avaient été reçues à la date de l'enquête, toutes insuffisantes.
- Les **produits thérapeutiques annexes** (PTA) sont des produits qui se trouvent en contact avec des tissus humains[60]. Leur statut juridique a tardé (le décret d'application de la loi de 1998 n'a été pris qu'en août 2004) et demeure spécifiquement français, n'existant pas ailleurs en Europe. Selon la chef de département, ce statut est complexe et conflictuel : les PTA ne sont a priori pas des médicaments (sauf peut-être l'albumine) et pourraient être des dispositifs médicaux au sens de la directive européenne... Entre 70 et 100 dossiers ont été déposés par des fournisseurs de matières premières depuis le début de 2005, la qualité en est médiocre. Malgré l'application de normes ISO et CE, d'importants problèmes de qualité ont été constatés (utilisation de l'eau du robinet...), qui ont conduit en particulier à la fermeture d'un site à Toulouse. Il manquerait ½ poste.
- Quant aux **tissus**, ils sont évalués par une seule personne, ce qui serait insuffisant. Il s'agit dans ce cas d'autoriser des procédés et non des produits (les autorisations d'établissement sont gérées depuis 1999 par la DIE et ont permis d'éliminer les

[59] Le décret d'application de la disposition de la loi du 1er juillet 1998, qui prévoyait la mise en place d'une déclaration à l'AFSSAPS des PH, n'a été pris qu'en décembre 2004.

[60] Il s'agit par exemple des milieux de cryoconservation des embryons congelés.

plus gros problèmes). L'exploration de ce nouveau domaine est réalisée progressivement. Un groupe de travail sur les cornées a été créé il y a deux ans : 20 à 25 banques de cornées ont déposé 70 dossiers, qui ont été examinés transversalement et ont fait l'objet d'une autorisation globale récemment. Le thème des os est abordé à partir de l'automne 2005.

Au sein de ce même département de la DEMEB, la cellule de biovigilance n'a qu'un demi poste, alors qu'il faudrait un poste à temps plein. Il est prévu qu'un groupe d'experts préfigure la future commission de biovigilance.

La lenteur des travaux dans ces nouveaux domaines ne suscite guère de protestations des firmes concernées. Contrairement aux génériqueurs qui se plaignent des délais d'autorisation, les fabricants de ces produits biologiques à effet thérapeutique se satisfont de cette lenteur, s'agissant d'un régime déclaratif.

L'agence devrait poursuivre ses efforts en matière de gestion des ATU et redéployer au sein de la DEMEB des moyens en direction des secteurs en expansion, comme les essais cliniques, les préparations hospitalières et les produits biologiques à effet thérapeutique.

4. La pharmacovigilance

La pharmacovigilance est l'une des vigilances gérées par l'AFSSAPS, à côté de l'hémovigilance[61], matériovigilance, cosmétovigilance, etc. Elle repose en France sur un réseau de surveillance des effets indésirables des médicaments constitué de 31 centres régionaux de pharmacovigilance (CRPV). Ces centres régionaux, situés dans de grands hôpitaux, sont subventionnés par l'AFSSAPS à hauteur de 2,9 M€ (montant assez stable depuis la création de l'agence).

Contrairement à certains pays et au projet initial de directive communautaire sur les médicaments parue en 2004), les patients ne peuvent signaler directement les effets indésirables aux autorités.

En 2004, 4 190 effets graves liés à des médicaments ayant eu une AMM centralisée ont été transmis par la France à l'EMEA. En sens inverse ont eu lieu 16 525 transmissions de l'EMEA vers la France. La France a donc notifié environ le cinquième des effets graves liés à des médicaments ayant eu une AMM centralisée. Ces nombres sont en forte augmentation : la transmission France vers EMEA était de 700 en 1997 et la notification EMEA vers France s'élevait à 2100 cette même année.

[61] Au sein de la DEMEB, l'unité d'hémovigilance est dépourvue de chef d'unité. La loi de 1993 avait confié à l'agence du médicament les médicaments dérivés du sang. La loi de 1998 a confié à l'AFSSAPS les produits sanguins labiles. Or, l'agence n'a pas les moyens d'évaluation suffisants : 2,3 ETP actuellement. L'EFS a plus de moyens.

a. Un système d'information longtemps insuffisant

Le rapport IGF-IGAS constatait en 2002 que la base nationale de pharmacovigilance présentait de sérieuses lacunes et qu'elle n'était pas reliée au système d'information d'AMM.

Depuis 2002, aucune interface entre les systèmes d'information de pharmacovigilance et d'AMM n'a été mise en place. Une nouvelle application de pharmacovigilance est fonctionnelle depuis le 20 novembre 2005, selon le secrétaire général de l'AFSSAPS. Elle intègre « *toutes les données migrées et transcodées de l'ancienne application, pour être éprouvée sur 6 semaines de tests* ». Cette application est conforme à la réglementation internationale, « *permettant d'adresser le flux des incidents graves recensés (statistiquement, 20 par jour) aux partenaires européens à partir de la base Eudravigilance* ».

Cette application s'appuie sur un progiciel standard (ArisG - éditeur américain) adapté aux besoins de l'agence. Elle est interfacée avec la base de données sur le médicament « Codex » et d'une manière générale avec le système d'information de l'agence grâce au code unique de spécialité pharmaceutique provenant de Codex associé à chaque incident répertorié. Le futur PDSI assurera l'interaction entre les applications de l'agence, en particulier la base de pharmacovigilance nouvellement installée.

b. Selon certains avis médicaux, la pharmacovigilance ne serait ni assez transparente, ni assez réactive en France

Les rapports d'enquête de pharmacovigilance ne sont pas publiés, ni, sauf exceptions, les données de pharmacovigilance qui ont conduit à des modifications de RCP ; le signalement par l'AFSSAPS des modifications de RCP pour raisons de pharmacovigilance n'est pas systématique d'après la revue indépendante *Prescrire*[62].

Les données de pharmacovigilance permettent de réaliser des synthèses : les études de pharmaco-épidémiologie. Seules six de ces études ont été réalisées entre 1999 et juin 2005. L'une de ces études, intitulée « iatrogénie médicamenteuse des 31 CRPV », a été réalisée en 2000 sur le thème de l'incidence des hospitalisations motivées par la survenue d'un effet indésirable. L'agence ne prévoit de la renouveler qu'en 2006 ou 2007.

Le choix des thèmes à retenir est déterminé, sur proposition des différentes directions opérationnelles, au cours d'un comité des études présidé par le directeur général de l'agence. Ces thèmes découlent des questions que se posent ces différentes directions dans l'accomplissement de leurs missions. Ils sont ensuite soumis au conseil scientifique de l'agence, sur la base de leurs protocoles, avant le déclenchement du financement par l'agence. Le budget annuel pour les études est de 800 000 euros en 2005.

La revue *Prescrire*, qui reconnaît que l'AFSSAPS a pris en 2004 « *quelques mesures de pharmacovigilance qui vont dans le bon sens* » (modifications de RCP signalant des effets indésirables, « mises au point » sur la sécurité d'emploi ou les indications de certains médicaments…)[63], relève néanmoins l'attentisme de l'agence sur certains dossiers :

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[62] Prescrire, février 2004, page 145.

[63] Prescrire février 2005, page 143.

⇨ Pour les classes de médicaments à risques majeurs (coxibs, antidépresseurs, par exemple), la revue estime que les mesures sont longues à venir, l'AFSSAPS se retranchant derrière les travaux en cours à l'EMEA. « *Des communiqués toujours succints sont publiés tardivement, alors que les risques sont établis* ».

⇨ Associations de dextropropoxyphène + paracétamol (de type Di-Antalvic®) : alors que leur retrait du marché est programmé pour fin 2005 en Suède ou au Royaume-Uni, l'Agence les maintient sur le marché français. Est-ce à dire que ces médicaments, pourtant non indispensables [selon *Prescrire*], ne présentent pas les mêmes risques en France ?

⇨ Quand des médicaments dont la balance bénéfices-risques est connue depuis longtemps comme défavorable, tels le benfluorex (Mediator®) ou le véralipride (Agréal®), sont retirés du marché espagnol, l'AFSSAPS n'en dit rien, et ils continuent à être vendus en France.

Exemple du Reminyl®

Le 8 novembre 2005 est diffusée sur le site internet de l'agence une « lettre aux prescripteurs » du 21 octobre 2005 du laboratoire Janssen-Cilag au sujet du Reminyl®, indiqué dans le « traitement symptomatique de la maladie d'Alzheimer dans ses formes légères à modérément sévères ». Ce médicament, commercialisé en France depuis 2001, est le 3ème de la classe des anticholinestérasiques (après Aricept® et Exelon®). Cette lettre aux prescripteurs indique que les résultats finaux de deux études cliniques réalisées pendant deux ans chez des patients non déments présentant des troubles cognitifs légers montraient que :

-le taux de mortalité a été significativement plus élevé dans le groupe Reminyl (1,4%) que dans le groupe placebo (0,3%) ;

-le traitement par Reminyl n'a pas démontré de bénéfice dans le ralentissement du déclin cognitif et n'a pas retardé l'apparition de la démence[64].

Ces études démontrent clairement une balance bénéfices/risques défavorable (aucun bénéfice pour des risques accrus par rapport au placebo), qui devrait en principe conduire à s'interroger sur le maintien de l'AMM du produit. L'AFSSAPS a simplement diffusé la lettre d'information du laboratoire (qui conclut que les prescripteurs doivent respecter strictement l'indication) et modifié le RCP pour tenir compte des résultats des études. On peut s'interroger sur la faiblesse des conséquences tirées par l'agence de ces études de longue durée aux résultats significatifs.

Malgré des améliorations significatives, notamment sur le système d'information, la pharmacovigilance pourrait encore progresser sur le plan de sa réactivité et de la transparence des données.

[64] Déjà l'évaluation pré-AMM de chacun des 3 anticholinestérasiques avait montré, contre placebo, des résultats qualifiés par les experts de très modestes, à la limite du significatif, voire non significatifs.

Annexe 3-87

RÉPUBLIQUE FRANÇAISE

afssaps

Agence française de sécurité sanitaire des produits de santé

Le Directeur Général
Tél. +33 (0)1 55 87 30 14
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Saint-Denis, le 28 AVR. 2006

Le Directeur Général de l'Agence française de sécurité sanitaire des produits de santé
à
Monsieur le Président de la sixième chambre de la Cour des comptes
13 rue Cambon
75 100 PARIS cedex 01

Objet : Relevé de constatations provisoires sur les comptes et la gestion de l'Agence française de sécurité sanitaire des produits de santé

Réf. : Votre lettre RC 44250 du 28 mars 2006

P.J : Réponse de l'Afssaps au relevé de constatations provisoires

Suite aux investigations des rapporteurs de la Cour sur les comptes de l'Afssaps pour les exercices 1999 à 2004 et au relevé de constatations provisoires que vous m'avez transmis par lettre citée en référence, je vous prie de trouver ci-après les remarques et observations que ce document appelle de ma part.

Sur un plan général, je prends acte de ce que les rapporteurs ont bien pris en compte les importants chantiers d'amélioration des fonctions de gestion de l'agence et noté les progrès d'ores et déjà enregistrés, même si le chemin qui reste à parcourir est encore important, particulièrement en ce qui concerne les systèmes d'information.

S'agissant des principales problématiques qui concernent les fonctions médico-scientifiques – déontologie des experts, transparence, sécurité du médicament – vous noterez dans les observations qui suivent que l'agence ne partage pas toujours le point de vue des rapporteurs quant à l'importance des efforts entrepris et le niveau des résultats obtenus. Elle a donc cherché à préciser et compléter à chaque fois les données citées par les rapporteurs.

Pour plus de lisibilité, ces observations sont exposées selon la trame du relevé de constatations provisoires.

Par ailleurs, je vous indique que je ne demande pas à présenter d'observations orales devant la Cour, sauf à ce qu'elle le souhaite elle-même.

Le Directeur général

Annexe 3-87

27/04/06

REPONSE DE L'AGENCE DE SECURITE SANITAIRE DES PRODUITS DE SANTE AU RELEVE DE CONSTATATIONS PROVISOIRES DE LA COUR DES COMPTES POUR LES EXERCICES 1999 A 2004

(Les titres en italique sont repris du projet de relevé de constatations provisoires)

PARTIE I : LES COMPTES

I. LES COMPTES EN JUGEMENT

A. LA PERIODE CONTROLEE

B. L'ENCHAINEMENT ET LA PRESENTATION DES COMPTES

1. L'enchaînement des comptes

2. La présentation des comptes

Concernant les améliorations intervenues dans la gestion financière, il paraît utile de noter le recrutement d'un Contrôleur de Gestion au sein d'un pôle de l'Unité Budget qui permet aujourd'hui une nette amélioration des prévisions budgétaire de l'Afssaps notamment dans le cadre de la mise en place de la LOLF.

II. LE COMPTABLE

PARTIE II : LA GESTION DE L'AFSSAPS

I. L'ORGANISATION ET LE PILOTAGE DE L'AFSSAPS

1. L'exercice de la tutelle

Fin janvier 2006, la DAGPB a annoncé qu'elle cessait d'exercer la tutelle budgétaire de l'agence et qu'elle se retirait de son conseil d'administration.

Evaluer le bénéfice risque serait donc très difficile dans ce domaine si la mission en était confiée à l'agence. Celle-ci ne peut, comme le souligne la mission, que vérifier qu'il n'existe pas des spécialités pharmaceutiques rendant un service équivalent.

d. Les produits biologiques à effet thérapeutique

Un poste supplémentaire a été affecté dans ce secteur en 2006.

4. La pharmacovigilance

Page 121 : La pharmacovigilance – 2ème paragraphe
A ce jour, il n'existe pas de disposition, tant d'un point de vue légal que réglementaire, permettant la déclaration des événements indésirables des produits de santé directement par les patients ou les associations de patients. Toutefois, la Commission Européenne demande aux autorités nationales compétentes d'inciter les patients à signaler les évènements indésirables aux professionnels de santé (article 22 du règlement CE 726/2004 du 31 mars 2004 établissant des procédures communautaires pour l'autorisation et la surveillance en ce qui concerne les médicaments à usage humain et à usage vétérinaire, et instituant une Agence européenne des médicaments). A la connaissance de l'Agence, seul le Danemark a instauré, en juin 2003, un système permettant au patient de déclarer les événements indésirables : le « Council for Adverse Drug Reactions ». Cette notification directe est notamment possible sur Internet (www.laegemiddelstyrelsen.dk) ou dans les pharmacies.

En France, on constate, depuis quelques années, qu'il arrive que les patients contactent directement les centres régionaux de pharmacovigilance (CRPV) ou les industriels afin de signaler la survenue d'un événement indésirable. L'ouverture aux patients de la notification des événements indésirables apparaît donc comme une évolution logique du système. Sa mise en œuvre doit être considérée et précisée, non comme une remise en cause des capacités d'analyse et d'alerte du système actuel, mais plutôt comme une source complémentaire d'informations.

Dans le cadre du partenariat Afssaps / Associations de Patients, lancé en décembre 2004 et ayant déjà débuté en mars 2004 sur la présentation d'une gamme de mesures, le principe d'une association des patients aux mécanismes de déclaration a été retenu Une étude pilote est mise en place, à partir du mois de mai 2006 et pour 6 mois au moins, dont les objectifs sont d'évaluer la qualité et la pertinence des signalements adressés par les patients à une vingtaine d'associations qui se sont portées volontaires pour participer à cette expérience, ainsi que le circuit de recueil, de traitement et d'analyse qu'il serait nécessaire d'instaurer. A l'issue de la période test, il sera alors envisagé une généralisation du système.

S'agissant des progrès attendus en matière de transparence, l'Afssaps souligne que le communiqué de presse « Médicament et démarche de transparence » en date du 16 mars 2006 s'accompagne de la publication du premier compte-rendu de la commission nationale de pharmacovigilance du 29 novembre 2005. L'Afssaps est en

pratique une des premières agences en Europe, si ce n'est la première, à mettre effectivement en œuvre cette mesure de publication.

Page 122 et 123 :
De manière générale, la conception même du paragraphe qui débute à la page 122 est très discutable.
En effet, la mission esquisse une appréciation sur la réactivité et la transparence de la pharmacovigilance dans notre pays en s'appuyant sur « certains avis médicaux » dont la lecture attentive du paragraphe révèle qu'il s'agit uniquement d'opinions émises par la revue Prescrire dont elle reprend au demeurant deux ou trois exemples figurant dans une des livraisons de cette revue datant du second semestre 2006.

Une appréciation dans un domaine aussi sensible ne peut se fonder de façon robuste sur la reproduction des allégations d'un acteur parmi bien d'autres.

Plus spécifiquement, sur les points relevés par cette revue et repris par les rapporteurs , il y a lieu d'apporter les précisions suivantes.

Concernant le 1er point, où il est fait grief à l'Agence, par la revue Prescrire de communiquer tardivement alors que les risques sont établis, l'Afssaps a toujours joué la transparence en publiant des communiqués ou des points d'étapes faisant part de la problématique et dans l'attente de résultat de l'évaluation européenne diffusant des messages de mise en garde.

Concernant le 2ème point, relatif à l'association dextroproxyphène/paracétamol, le maintien sur le marché français se justifie à l'issue de l'évaluation du profil de sécurité d'emploi et d'une utilisation du produit plus encadrée, en 2e intention, ce qui n'était pas le cas au Royaume-Uni.

Enfin, le 3ème point mentionne l'absence du retrait du marché de 2 produits dont la balance bénéfice/risque serait connue pour être défavorable. Ces 2 produits ont fait l'objet d'une enquête approfondie : pour l'un, Agréal®, il a été considéré que la balance bénéfice/risque était favorable et pour l'autre après un examen des données de sécurité, la commission a demandé une réévaluation du bénéfice/risque et le produit a en définitive cessé d'être commercialisé en avril 2006 (voir PV du 26 novembre 2006).

Encadré « exemple du Reminyl® » : Contrairement à ce qui est écrit, la balance bénéfice/risque reste favorable dans l'indication du « traitement symptomatique de la maladie d'Alzheimer ». Cependant, il a été demandé une étude épidémiologique pour confirmer les conclusions de novembre 2005.

Annexe 3-87

Sixième chambre

Le Président

LP 46672

A Paris, le 16 NOV. 2006

Le Président de la Sixième chambre
de la Cour des comptes

à

Monsieur Jean MARIMBERT
Directeur général de l'agence française
de sécurité sanitaire des produits de santé
143, Boulevard Anatole France
93285 SAINT-DENIS Cedex

[redacted] 20 NOV. 2006
N° 3812
JM
AB
M Pot
Vu du 20/11

Objet : Relevé d'observations définitives sur les comptes et la gestion de l'Agence française de sécurité sanitaire des produits de santé

Après avoir examiné votre réponse à ma lettre du 28 mars 2006 et en avoir pris acte, la Cour a arrêté ses observations définitives dont vous trouverez ci-joint le relevé.

La présente lettre met fin à l'enquête.

Michel CRETIN

Annexe 3-87

Sixième chambre

OBSERVATIONS DEFINITIVES

AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ (AFSSAPS)

exercices 1999 à 2004

Le présent rapport, qui a fait l'objet d'une contradiction avec les personnes et les organismes concernés, a été délibéré par la Cour des comptes le 9 octobre 2006.

De son côté, l'AFSSAPS a pris du retard dans l'enregistrement des essais cliniques dans la base européenne EUDRAVIGILANCE, qui depuis novembre 2005 devrait recenser tous les effets indésirables graves et inattendus de ces essais.

Par ailleurs, l'attractivité de la France en matière de recherche clinique suppose des délais d'autorisation courts, et par conséquent un redéploiement des moyens de la DEMEB sur ce secteur. La Cour prend acte de ce qu'un poste supplémentaire d'évaluateur a été affecté à l'unité en 2006.

3. Les préparations hospitalières et les produits biologiques à effet thérapeutique

La Cour a constaté que le contrôle de ces secteurs en expansion était exercé *a minima* faute de moyens humains suffisants.

Les hôpitaux ont l'obligation, depuis le mois de décembre 2004[3], de déclarer leurs préparations hospitalières. Alors que 3000 déclarations ont été reçues en six mois, seul un pharmacien à 60% de son temps était en charge de leur contrôle fin 2005.

Le même manque de moyens humains a été constaté s'agissant du contrôle des produits biologiques à effet thérapeutique, confié à l'AFSSAPS par la loi du 1er juillet 1998. En effet, fin 2005, l'effectif se réduisait à 4,5 évaluateurs (½ interne, deux vacataires et ½ stagiaire).

La Cour prend toutefois acte de la réponse de l'AFSSAPS, qui a indiqué avoir redéployé deux postes dans ces secteurs en 2006.

D. LA PHARMACOVIGILANCE

Le système d'information dans le domaine de la pharmacovigilance, qui était très insatisfaisant, a été nettement amélioré grâce à la mise en place d'une nouvelle application fin 2005.

En matière de transparence, la Cour prend acte l'expérimentation en cours tendant à impliquer les associations de patients dans les mécanismes de déclaration des effets indésirables. Toutefois, les rapports d'enquête de pharmacovigilance ne sont pas publiés, ni, sauf exception, les études de pharmaco-épidémiologie ayant conduit à des modifications de résumés des caractéristiques du produit (RCP). Le signalement par l'AFSSAPS des modifications de RCP pour raisons de pharmacovigilance n'est pas systématique. Les comptes-rendus de la commission de pharmacovigilance sont été mis en ligne très tardivement (cf. *infra*).

Par ailleurs, la réactivité de l'AFSSAPS dans le domaine de la pharmacovigilance pourrait être améliorée. Seules six études de pharmacovigilance ont

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[3] Le décret d'application de la disposition de la loi du 1er juillet 1998, qui prévoyait la mise en place d'une déclaration à l'AFSSAPS des PH, n'a été pris qu'en décembre 2004.

été réalisées entre 1999 et juin 2005. Certains médicaments dont la balance bénéfice/risques était controversée ont continué d'être commercialisés, tandis que d'autres médicaments, retirés du marché de pays européens en raison d'une balance bénéfice/risques jugée défavorable, ont mis plusieurs années à être retirés du marché français.

La Cour recommande par conséquent d'accroître la transparence et la réactivité de l'AFSSAPS en matière de pharmacovigilance.

E. LA MISSION D'INFORMATION DU PUBLIC

1. La directive communautaire 2004/27/EC du 31 mars 2004 relative au médicament

L'AFSSAPS a attendu l'automne 2005 pour préparer la mise en œuvre de la directive communautaire 2004/27/EC du 31 mars 2004 relative au médicament. La Cour observe que l'agence ne respecte pas toutes les obligations découlant de cette directive en matière de transparence. Certes, cette directive n'a pas encore été transposée en droit interne. Mais elle était prévue pour être appliquée dès le 30 octobre 2005, et reprend plusieurs obligations déjà en vigueur pour l'AFSSAPS.

a. Les déclarations d'intérêt des agents de l'AFSSAPS

Ainsi, la déclaration d'intérêts des agents de l'AFSSAPS, d'ailleurs mentionnée dans son règlement intérieur, n'a commencé à être mise en œuvre qu'au premier semestre 2006.

b. Les rapports d'évaluation d'AMM

La publication des rapports d'évaluation d'AMM (RAPPE), prévue par ce texte et figurant déjà à l'article 6 de loi de 1998 sur la sécurité sanitaire (art. L.793-1, devenu L.5311-1 du CSP), n'a débuté qu'en juin 2004.

Elle est encore loin de concerner toutes les AMM. Depuis janvier 2006, la commission d'AMM est saisie d'un projet de RAPPE pour toutes les AMM correspondant à de nouvelles entités chimiques ou biologiques ainsi que pour les extensions d'indications majeures qui, sans être directement concernées par la directive, présentent un intérêt particulier. Ce n'est que dans un second temps que les RAPPE seront réalisés pour l'ensemble des spécialités donnant lieu à l'octroi d'une AMM.

Par ailleurs, la Cour a constaté que la découverte de risques sanitaires sérieux peu après la délivrance de l'AMM de deux spécialités pharmaceutiques avait bloqué la publication des rapports publics d'évaluation, alors que c'est précisément dans de tels cas que la transparence des données aurait été la plus utile.

Annexe 3-87

De : Jean MARIMBERT
À : Anne-Carole.BENSADON@igas.gouv.fr; aquilino morelle; etienne.marie@iga...
Date : 14/01/2011 10:46
Objet : A l'attention de Madame et Messieurs les membres de la mission IGAS,
Pièces jointes : cour dc 28.04.06.pdf; cour c 13.06.07.pdf

A l'attention de Madame et Messieurs les membres de la mission IGAS,

Dans le prolongement de la conversation téléphonique que j'ai eu hier soir avec M. Morelle, j'ai fait ce matin avec les secrétariats et personnes concernées des recherches documentaires sur les observations transmises en 2006 et 2007 à la Cour des Comptes.

Il en ressort que :

- l'envoi des observations en date du 28 avril 2006 a été géré matériellement par le secrétariat général, où l'on n'a pu retrouver ce matin , en l'absence du secrétaire général depuis mercredi-qu'une trace informatique de l'existence de l'envoi, le document lui-même n'étant pas disponible au secrétariat (peut-être est-il rangé dans les dossiers du secrétaire général ou son coffre?
- en revanche le chef du service juridique avait gardé une copie du document, que j'ai donc pu consulter (cf en pièce joint la lettre de couverture et la page correspondante);
- la page du document susceptible de faire référence à Médiator, qui n'est pas expressément cité, mentionne effectivement que la commission a demandé une réévaluation du bénéfice risque avant d'ajouter que "le produit a en définitive cessé d'être commercialisé en avril 2006 (voir PV du 26 novembre 2006 ";
-cette précision était évidemment inexacte , et le caractère matériel de cette erreur est attestée par la date de commiission qui est mentionnée et qui est...postérieure de plusieurs mois à la date d'envoi des observations de l'agence;
-au demeurant, les observations que l'agence enverront à la Cour un peu plus d'un an après, dans le cadre d'une enquête sur la consommation et la prescription des médicaments, et dont l'envoi a été matériellement géré par le secrétariat du directeur général-ce qui a permis d'en retrouver trace plus facilement dès hier soir-comportent un passage sur benfluorex qui évoque le sujet en des termes conformes à la chronologie réelle de la réevaluation , cet envoi faisant référence notamment à l'avis de la commission d'AMM en date du 5 avril 2007 (cf en pièce jointe la lettre-chapeau de transmission et le passage des observations de l'agence qui abordait ce sujet);
En outre, comme convenu au téléphone il y a quelques minutes avec M.Morelle, je vous fais porter immédiatement la copie du document intégral du 28 avril 2006 , telle que conservée par le chef du service juridique qui me l'a remise ce matin.

Bien cordialement,
J.M.

Annexe 3-88

afssaps
Agence française de sécurité sanitaire
des produits de santé

Secrétariat général
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Saint Denis, le 04/01/2011

Note
relative aux vulnérabilités du management de la pharmacovigilance et de la surveillance du marché du médicament (affaire Mediator)

Dans le contexte du dossier Mediator, vous trouverez ci-après mes réflexions relatives à la qualité de la chaine décisionnelle en matière de pharmacovigilance et de surveillance des marchés du médicament à l'Afssaps.

Si l'analyse scientifique ne relève pas de ma compétence, le registre du management m'est en effet légitime compte tenu de ma position dans l'agence.

Ces réflexions pourront vous être utiles non seulement pour comprendre la possibilité de certaines défaillances dans la chaine décisionnelle, mais également et surtout pour préparer des décisions susceptibles de réduire les risques de rechute.

La chaine décisionnelle en matière de pharmacovigilance et de surveillance du marché des médicaments est composée comme suit :

- les chefs des unités pharmacovigilance, ces dernières comptant au total une vingtaine de personnes
- la chef du département de pharmacovigilance
- la chef du service de l'évaluation et de la surveillance du risque, et de l'information (SURBUM)
- le directeur de l'évaluation des médicaments et des produits biologiques (DEMEB)

Je n'ai rien à dire sur le premier niveau (les chefs d'unité) que je ne connais pas et avec qui je n'ai pas eu à traiter depuis mon arrivée à l'agence (2004).

Chacun des niveaux supérieurs présente depuis longtemps des failles managériales objectives et vérifiables dont le cumul peut expliquer pour partie la faiblesse d'une organisation qui n'a pas su capitaliser et exploiter les divers signaux remontés ces dernières années en ce qui concerne la dangerosité du Médiator.

1 – La chef du département de pharmacovigilance :

En l'occurrence, , la cher du département de pharmacovigilance a toujours systématiquement fait écran entre ses unités et la chef du SURBUM, et a constamment dénié à celle-ci le droit de s'immiscer dans la gestion de son département. Ce fait était connu de toute l'agence et reconnu et déploré par la chef du SURBUM.

2 – La chef du SURBUM :

Outre l'incapacité dans laquelle celle-ci était de pouvoir exercer correctement ses prérogatives managériales, elle présente également le grave inconvénient d'avoir été en charge de responsabilités dans le secteur de la pharmacovigilance pendant une période beaucoup trop longue.

Elle était déjà responsable de la pharmacovigilance en 1995 et l'était encore, si je ne me trompe, à l'époque des réexamens du Mediator à la fin des années 1990, puis a eu la responsabilité de la coordination des vigilances et de la surveillance du marché, puis a repris le secteur en direct comme chef du SURBUM.

C'est dire que la réévaluation du Médiator au cours des années 2000, à chaque fois qu'un signal est venu s'ajouter aux précédents, n'a pu bénéficier d'un regard neuf à son niveau de responsabilité.

3 – Le directeur de l'évaluation :

Pour remédier aux insuffisances de l'organisation qui lui était rattachée, il aurait fallu que celui-ci ait les moyens pleins et entiers attachés à sa fonction. Or la chef du Surbum a toujours bénéficié d'un statut de quasi directeur. Ainsi est-elle membre à part entière du comité de direction, et nombre de débats auxquels ce comité a pu assister ont montré que la chef du Surbum et le Demeb apparaissaient souvent comme des entités rivales plutôt que comme une chaine hiérarchique.

Un deuxième point de faiblesse du Demeb est qu'il est en déplacement à Londres une semaine par mois du fait de son assistance aux débats du CHMP.

Dans ces conditions, il est illusoire d'attendre de lui un management optimal d'une direction aussi complexe que la Demeb, qui compte plus de 300 personnes et opère sur des champs scientifiques et opérationnels aussi étendus.

Ce manque de proximité et de présence du directeur de la Demeb est une difficulté structurelle à laquelle il serait nécessaire de remédier, le choix devant lui être proposé d'opter clairement entre sa fonction managériale et une fonction d'expert européen. Une alternative pourrait consister à séparer clairement AMM et post AMM, en faisant du SURBUM une direction à part entière. La présence du directeur de l'AMM à l'Europe se justifierait donc mieux et aurait moins de conséquence sur le management.

*
* *

En conclusion de cette analyse, je recommande au nouveau directeur général, en liaison avec le Demeb :

- de renouveler prioritairement la responsable du SURBUM, puis la chef du département de pharmacovigilance, en insistant dans le recrutement sur le paramètre managérial de la fonction – l'agence ne manque pas d'experts ;
- de traiter avec le Demeb le problème de management que pose son absence de l'agence un quart de son temps pour cause d'assistance au CHMP
- d'engager sans tarder un chantier de revisitation des AMM susceptibles de poser problème parmi les 10 000 AMM de spécialités commercialisées, en priorisant leur examen en fonction de quelques critères à définir en liaison avec le Demeb et un groupe d'experts ad hoc (notamment, ancienneté de l'AMM, signaux connus par la littérature ou tous autres canaux tels ceux qui ont été négligés pour le Mediator : statut dans les autres pays développés, OMS, presse spécialisée. Un conseil des responsables des banques de données médicamenteuses - Vidal, Claude Bernard, Thesorimed- ne serait pas à négliger).

Outre ces sujets de personnel et d'organisation, je souhaite également évoquer deux aspects complémentaires :

- la question de la sécurisation juridique des décisions de l'agence ;
- la question des tutelles et des contrôles.

1/ La question de la sécurisation juridique des décisions de l'agence apparaît clairement dans les nombreuses interviews que la direction générale a données à l'occasion de l'affaire Mediator.

Ainsi dans l'interview parue dans le Journal du Dimanche du 28 novembre dernier : « *Les laboratoires peuvent engager des recours devant le conseil d'Etat, et si notre dossier n'est pas suffisamment étayé, la décision de l'Agence peut-être annulée* ».

Que la sécurité juridique des décisions de l'agence soit recherchée est de bonne administration. Mais quand sécurité juridique et sécurité sanitaire viennent à se contrarier, la priorité donnée à la sécurité juridique peut contribuer à affaiblir la sécurité sanitaire.

Cette question juridique soulève un problème plus général à l'agence : il est patent qu'il existe d'autres Mediator (à effets moins graves, il faut l'espérer) mais dont l'agence connaît les risques, tout en butant sur la difficulté que sauf effet nouveau et reconnu (« robuste », comme il est souvent dit), il lui serait impossible de demander le retrait de l'AMM au seul motif que celle-ci a été accordée dans des temps anciens où les préoccupations de sécurité sanitaire étaient moins pressantes, ou bien les connaissances générales sur le produit moins complètes qu'aujourd'hui.

Un exemple emblématique récent est celui du Ketum, suspendu par l'agence par une décision qui a été cassée par le Conseil d'Etat, parce que les motifs qu'elle invoquait étaient connus depuis longtemps, et accessoirement parce que le retrait nuisait aux intérêts économiques du laboratoire !

Il est dangereux que l'agence intériorise cette obsession de la sécurité juridique au détriment de la sécurité sanitaire. Si des considérations tenant à la loi, au règlement ou à la jurisprudence nuisent à la sécurité sanitaire, c'est au législateur, au ministre ou au juge d'en prendre la conscience et la responsabilité et, le cas échant, d'en tirer les conséquences. Mais il ne revient certainement pas à l'agence de s'autocensurer et de prendre sous son couvert les insuffisances éventuelles du dispositif juridique. Ce faisant, elle contribue à occulter celles-ci, et manque à sa mission.

2/ En dépit de la faible efficacité des tutelles et des contrôles externes portant sur l'agence, la Cour des comptes avait repéré la vulnérabilité de la pharmacovigilance et le sujet du Mediator.

En 2005, elle a en effet procédé à un audit des comptes et de la gestion de l'agence sur les années passées.

Dans son relevé d'observations définitives diffusé en novembre 2006, la Cour fait la constatation suivante (p. 27), à propos de l'action de l'Afssaps en matière de Pharmacovigilance :

« D. LA PHARMACOVIGILANCE

..... Par ailleurs, la réactivité de l'AFSSAPS dans le domaine de la pharmacovigilance pourrait être améliorée. Seules six études de pharmacovigilance ont été réalisées entre 1999 et juin 2005. Certains médicaments dont la balance bénéfices/risques était controversée ont continué d'être commercialisés, tandis que d'autres médicaments, retirés du marché de pays européens en raison d'une balance bénéfice/risque jugée défavorable, ont mis plusieurs années à être retirés du marché français.

La Cour recommande par conséquent d'accroître la transparence et la réactivité de l'AFSSAPS en matière de pharmacovigilance. *»*[1]

A ma connaissance, cette constatation de la Cour n'a donné lieu ni à audits complémentaires, ni à des investigations plus poussées de la part des tutelles. Le diagnostic était pourtant précisé dans le relevé de constatations provisoires que la Cour avait envoyé le 26 mars 2006 à l'Afssaps ainsi qu'à la direction générale de la Santé et à la direction du Budget, et la liste des spécialités pharmaceutiques en cause était donnée p. 123 :

- les coxibs
- les antidépresseurs
- les associations de dextropropoxyphène+paracétamol (de type Di-Antalvic)
- le benfluorex (Mediator)
- le veralipride (Agréal)
- le Réminyl.

Il est impressionnant de trouver sur cette courte liste non seulement le Médiator, retiré trois ans plus tard seulement, mais également le Di-Antalvic dont l'agence, après s'être battue contre toute l'Europe pendant un an, est actuellement conduite à accélérer le retrait.

Les tutelles ont manifestement des leçons à tirer elles aussi de l'affaire Mediator, en ce qui concerne la faible efficacité des contrôles et l'absence d'exploitation des signaux que ceux-ci remontent le cas échéant.

Michel POT

[1] En gras dans le texte

afssaps

Agence française de sécurité sanitaire des produits de santé

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Saint Denis, le 05/01/2011

Note
pour M. Didier Banquy

Directeur de cabinet du ministre du Budget, des Comptes publics, de la Fonction publique et de la Réforme de l'État

Objet : affaire Mediator – situation de l'Afssaps

Bonjour Didier,

N'ayant pas été auditionné par la mission IGAS mandatée par Xavier Bertrand sur l'affaire du Mediator[1], je tiens à ce qu'au moins Bercy ait un écho de ma vision des choses sur ce sujet (je te rappelle que je suis secrétaire général de l'Afssaps depuis sept ans, où j'ai mené la conception et la mise en œuvre de l'informatisation de l'agence, mais où malheureusement je n'ai pas été associé à sa marche opérationnelle).

Tu trouveras ci-joint la note que j'ai préparée dans la perspective de l'arrivée du futur directeur général de l'Agence, qui j'espère ne tardera plus.

S'il sera difficile de faire à plus de dix années de distance le procès d'une décision de non retrait du Médiator suite à l'interdiction de l'Isoméride en 1997 (un autre coupe-faim au principe actif proche de celui du Mediator), la presse n'a pas manqué en revanche de relever que de nombreux signaux se sont accumulés tout au long des années 1999-2006 pour confirmer et attester la dangerosité de ce médicament, signaux que l'Afssaps n'a pas su ou voulu exploiter.

Sans avoir besoin de rechercher je ne sais quelles compromissions des experts ou de l'agence avec les laboratoires (les discussions à l'agence sur les médicaments sont suffisamment ouvertes, collégiales et transparentes pour limiter les risques de « complots »), je pense que les défaillances du management suffisent largement à expliquer cette inertie.

En deux mots : la personne responsable de la surveillance des marchés du médicament est en poste depuis beaucoup trop longtemps. C'est elle qui était en charge de la pharmacovigilance au moment de la réévaluation du Mediator, et c'est donc la dernière à pouvoir avoir le réflexe de se repencher

[1] Je fais la supposition que tu n'as pas pu échapper au déferlement médiatique sur le sujet et que tu sais que ce médicament « coupe-faim », soupçonné d'avoir causé au moins 500 morts en 36 ans d'activité, n'a été interdit par l'agence qu'en 2009, celle-ci étant accusée d'avoir énormément tardé à le faire.

ultérieurement sur le dossier. Même si elle était une excellente manageuse (et ce n'est pas le cas), la laisser quinze ans ou plus sur un secteur aussi risqué est une faute lourde de gestion

Son incapacité managériale est notoire et désastreuse pour quelqu'un qui a la charge d'animer vingt évaluateurs et un réseau de 35 centres de pharmacovigilance. Quant à leur patron à toutes deux, il est arrivé plus récemment (2007) et n'est pas là une bonne partie du temps pour cause de réunions à Londres.

Tu me diras que le directeur général de l'Afssaps en place depuis sept ans aurait pu s'en apercevoir et y remédier : le seul fait qu'il ne l'ait pas fait suffit à mon sens à objectiver son incompétence en matière de management, incompétence que je pourrais attester par vingt autres exemples

Tout ceci non pour « dénoncer » mon chef – je pense que X. Bertrand n'est pas aveugle et va lui réserver le sort qu'il mérite – mais pour que tu saches qu'il y a bien une réponse aux questions que l'on se pose sur Mediator – c'est bien d'une banale incompétence du service public qu'il s'agit et qui a permis à Servier de rouler l'agence dans la farine – et que tu jettes le cas échéant un coup d'œil sur mes –courtes- suggestions en matière de recrutement des hauts dirigeants du secteur public. En trente ans de carrière dans l'administration (Agriculture, Finances) et le management public (Monnaie, DCN, Afssaps), ce n'est pas le premier manager incompétent que je rencontre, et j'espère que tu es conscient comme moi que cette incompétence est à la source des principaux problèmes que rencontre le service public. Je pense qu'un filtrage obligatoire par un cabinet de recrutement, sans que l'avis soit liant pour le politique, serait rapide à mettre en place et améliorerait considérablement les choses.

Je te demande par ailleurs de porter une attention particulière au dernier paragraphe de ma note sur Mediator : la Cour des comptes avait vu la faiblesse de la pharmacovigilance et le sujet Mediator, et les tutelles –dont Bercy- en étaient informées depuis 2006 et n'ont pas bougé.

Il ne serait pas inutile que les Finances préparent préventivement des éléments de langage – même si elles ne sont pas en première ligne sur le sujet- avant que cette information ne finisse par sortir (ce n'est pas le cas actuellement à ma connaissance) et travaillent accessoirement à une meilleure exploitation des rapports de la Cour.

Je suis bien sûr à la disposition de Bercy pour toute information complémentaire sur le sujet si besoin. Je profite de ce courrier pour te présenter mes meilleurs vœux pour cette nouvelle année. Il est en outre vraisemblable que je te demanderai un entretien dans les mois qui viennent car mes chantiers informatiques se terminent, et je m'applique à moi-même le principe que sept années au même endroit sont largement suffisantes !

Amitié

Michel POT

Annexe 3-89

REUNION DE SECURITE SANITAIRE DU 28 OCTOBRE 2009 (SEMAINE 44)

Participants : Mmes F. BARTOLI (AFSSAPS), J. CARMES (DGS), M. FAVROT (AFSSA), C. MARCHAL (ASN), E. PRADA-BORDENAVE (ABM), Ch. SAURA (InVS), F. SIMON-DELAVELLE (cabinet) et M. VALTIER (DGS).
MM. B. BASSET (INPES), J-J. BERGER (DGCCRF), G. BRÉART (INSERM), G. CZERWINSKI (DGAl), Cl. FUILLA (DSC), M. GUESPEREAU (AFSSET), E. HERGON (EFS), D. HOUSSIN (DGS), Ph. MAGNE (DGS), G. NICOLAS (DHOS) et J. REPUSSARD (IRSN).

1. Epidémie de grippe H1N1 :

1.1. Épidémiologie

En métropole, nette augmentation de l'activité au travers des réseaux Sentinelles (incidence estimée à 216/100.000 [seuil épidémique à 122/100.000], +38% par rapport à la semaine précédente) et GROG (taux de positivité H1N1 passant de 9 à 16%), en particulier avec une nette augmentation du recours aux soins et aux urgences pour les moins de quinze ans en Île-de-France (activité x 2) et début d'évolution identique dans les grands centres urbains. Depuis le début d'épidémie, 70 hospitalisations dont 22 en SI). Au total 17 décès en métropole dont 4 en semaine 43.

Poursuite de décroissance d'incidence et d'activité dans les départements français d'outremer.

Continent Nord-américain : augmentation d'incidence au Mexique, Canada et USA où le taux de positivité est de 37% pour les virus *influenzae* dont 70% de A(H1N1), indiquant une co-circulation virale (74%).

En Europe, augmentation des incidences en Islande, République d'Irlande et Irlande du Nord, Royaume-Uni, Norvège, Suède, Roumanie. Stabilité en Espagne.

1.2. Gestion

Vaccination en cours dans les établissements de santé avec une faible adhésion. La circulaire sur les centres de vaccination pour la population générale a été signée par les ministres le 27/10 et est diffusée aux préfets. L'ouverture des centres est fixée au 12 novembre. Les vaccins Pandemrix® (GSK) ont été reçus, et Focetria® (Novartis) seront livrés en semaine 47. Les vaccins sans adjuvants devraient être disponibles à partir du 15-20 novembre (semaine 47). L'Inpes commence les tournages des spots pour la vaccination grand public, en vue d'une diffusion dès le 6 novembre.

1.3. Foyers animaux H1N1 : Vingt-et-un élevages touchés en Norvège (Cf. CR du 21/10/09). La République d'Irlande ne déclare plus les foyers. Premier foyer au Japon. Un foyer au Minnesota (USA) à l'occasion d'une foire. Contamination d'un élevage de dindes en Ontario (Canada) dont l'origine humaine (jamais décrite) est en cours d'analyse. Avis de l'Afssa sur les risques de recombinaison virale, l'absence d'impact sur les viandes et la possibilité de transmission virale entre homme et dinde.

En matière de grippe aviaire (H5N1), pas de nouveau signalement.

2. Points évoqués par l'**InVS** :

- **Surveillance aspécifique Sursaud® :** poursuite de l'augmentation modérée d'incidence des bronchiolites.
- **Dengue (type 3)** au Cap Vert (1ère épidémie, touchant 3400 personnes), probablement en lien avec l'épisode du Sénégal.
- **Chikungunya** au Vietnam : 6700 hospitalisations. Mission OMS sur place. Première circulation depuis 1970.
- **Légionellose :** deux cas (19/9 et 12/10) ayant séjourné au village de vacances « Cap Estérel » au lieu-dit d'Agay (Saint-Raphaël, 83), d'une capacité d'accueil de 8000 places. Dysfonctionnements de ballons d'eau chaude, du système de chloration en continu et

interconnexions entre les circuits d'eaux froide et chaude. Mesures de gestion locale suivies par le service communal d'hygiène et de santé et la DDASS, et information des personnes potentiellement exposées.

- **Contaminations de duodénoscopes par des souches de *Klebsiella pneumoniae*** (cf. CR du 7/10/09 et suivants) : deux nouveaux patients dépistés aux CH de Poissy et de Blois. L'Afssaps précise que sur trois endoscopes TJF-145 envoyés en expertise chez le fabricant, deux avaient pu être décontaminés après désinfection manuelle classique. L'enquête nationale mise en place a retrouvé une contamination d'endoscope par *Klebsiella spp.* et *Pseudomonas spp.* au CH d'Alençon (61). Poursuite de l'expertise en cours.

3. Points évoqués par l'**AFSSA** :

- **Foyer animal A(H3N2)** dans un élevage de visons d'Amérique (*Mustela ou Neovison vison*) à Holstebro (Danemark).
- **Trois foyers de TIAC dans le sud de la France** dues à des œufs importés d'Espagne, contaminés par *Salmonella enteritidis* et *S. typhymurium*. Retrait des produits.
- **Compléments alimentaires :** campagne de communication visant à développer la vigilance des consommateurs sur ces produits.

4. Points évoqués par l'**AFSSAPS** :

- **Matériovigilance : retrait immédiat de cryosondes à CO2 Wallach Surgical** dont la température n'est pas assez froide et pourrait entrainer des nécroses trop superficielles, inefficaces pour le traitement de dysplasies du col utérin.
- **Pharmacovigilance :** Nouvelles publications et étude cas-témoin démontrant un **risque accru de valvulopathies dues au benfluorex[1] (Médiator®**, laboratoires Servier). Vote unanime de la commission nationale de pharmacovigilance pour le retrait du produit. Procédure contradictoire en cours avec le laboratoire. La commission d'AMM examinera ce dossier le 12 novembre.
- **Communication sur les produits cosmétiques destinés aux enfants de moins de trois ans,** avec la DGCCRF : Absence d'éléments en faveur d'un risque immédiat de santé publique (conformité microbiologique et de l'étiquetage), mais besoin d'une évaluation toxicologique, en l'absence d'AMM pour ces produits dans la réglementation européenne.

5. Points évoqués par l'**EFS** :

- **Point d'étape sur l'enquête EIGD de Lyon** (Cf. CR du 30/09/09 et suivants) **:** L'IGAS organise une première restitution le 4 novembre. L'Afssaps s'étonne de ne pas en être informée.
- **Production retardée des PVA-SD** (Cf. CR du 14/10/09 et suivants) : poursuite du retard de production sur le site de Bordeaux. Un plan de substitution sera proposé en cas de persistance.
- **Panne de réfrigération** avec absence d'alarme ayant conduit à la destruction de stock de culots de globules rouges en Martinique. Révision de processus en cours.

6. Points évoqués par l'**IRSN** :

- **Evaluation de risque relative aux incidents de radiologie interventionnelle au CHU de Strasbourg** (Cf. CR du 23/09/09 et suivants) **:** L'IRSN demande une révision du projet de saisine conjointe ASN/DGS en vue de pouvoir accéder aux informations médicales des patients pour la réalisation de son expertise.

7. Points évoqués par la **DSC** :

- **Nombreuses intoxications au monoxyde de carbone (CO) ayant entrainé des décès.** DH demande de vérifier la coordination des actions de communication et les rappels des dispositifs préventifs saisonniers par voie de circulaires.

[1] Le benfluorex est un amphétaminique anorexigène dérivé de la fenfluramine, retirée du marché en raison d'hypertensions artérielles pulmonaires graves. Médicament prescrit dans les diabètes de type 2, à visée hypoglycémiante complémentaire, hypolipidémiante et hypouricémiante. SMR insuffisant (10/05/2006).

8. Points évoqués par l'**ASN** :

- **Réouverture du site de médecine nucléaire** du CH du Sud Francilien (Corbeil, 91) (Cf. CR du 7/10/09).
- **Suspension d'autorisation d'activité de radiothérapie** du CH de Poissy- Saint-Germain (78) en raison d'un manque d'effectif de radiophysiciens et de l'absence de correction d'un dispositif d'imagerie portale défectueux. L'ARH a également suspendu l'autorisation d'activité.
- **Perte d'une source radioactive d'entrainement** (Cf. CR du 21/10/09) : Procès-verbal établi par l'ASN à l'encontre de l'Unité d'instruction et d'intervention de la sécurité civile (UIISC n°1) de Nogent-le-Rotrou (28).

9. Points évoqués par la **DGCCRF** :

- **Champignons importés de Roumanie contaminés par du Césium 137 :** contamination alimentaire d'un employé de la CNPE de Paluel (76) détectée par la médecine du travail lors d'un examen d'anthropogammamétrie. Distribution régionale en Normandie. Enquête de traçabilité en cours au MIN de Rungis. L'activité massique de ces champignons, estimée par l'IRSN à partir de la charge corporelle mesurée (environ 1000Bq) et sur la base de 600g consommés, serait grossièrement de l'ordre de 1500 à 2000 Bq/kg frais, et la dose efficace engagée est estimée de l'ordre de 10µSv.
- **Graines de lin génétiquement modifié** provenant du Canada (où elles sont autorisées) incorporées dans des pains spéciaux. (Cf. CR du 7/10/09). Ces graines ne sont pas autorisées dans l'UE. Pour les produits transformés incorporant du lin issu des lots en cause, la France demande à la Commission européenne des mesures harmonisées de gestion.

10. Points évoqués par l'**INSERM** :

- **Thérapie génique :** communication prévue en semaine 45 à propos de traitements efficaces d'adrénoleucodystrophies par thérapie génique à vecteur rétroviral (équipe du Pr Aubourg, Saint-Vincent de Paul, Paris).

11. Points divers :

- DH demande qu'un point soit préparé pour la prochaine réunion de sécurité sanitaire, après la fin du procès de la clinique du sport, sur la **survenue tardive d'infections ostéoarticulaires dues à *Mycobacterium Xenopi*** chez des patients n'ayant pas présenté de lésion suspecte au cours de la campagne de dépistage organisée pour les personnes exposées.
- *Calendrier* : la réunion de sécurité sanitaire de la semaine 46 aura lieu le **jeudi 12 novembre** 2009 à 8h30.

☞ **Prochaine réunion le mercredi 4 novembre à 8 heures 30**

Annexe 3-89

REUNION DE SECURITE SANITAIRE DU 2 DECEMBRE 2009 (SEMAINE 49)

Participants : Mmes J. CARMES (DGS), Th. LE LUONG (INPES), E. PRADA-BORDENAVE (ABM) et F. SIMON-DELAVELLE (cabinet).
MM. J-L. ANGOT (DGAL), J-J. BERGER (DGCCRF), P. BRASSEUR (DGS), J-Cl. DESENCLOS (InVS), Cl. FUILLA (DSC), M. GUESPEREAU (AFSSET), D. HOUSSIN (DGS), Ph. MAGNE (DGS), J. MARIMBERT (AFSSAPS), M. MORTUREUX (AFSSA), J. REPUSSARD (IRSN) P. TIBERGHIEN (EFS), et D. VUILLAUME (INSERM).

1. Epidémie de grippe H1N1 :

1.1. Épidémiologie

En métropole, poursuite de la progression épidémique. Activité estimée par le réseau Sentinelles à 461.000 consultations (+20%). Réseau GROG (infections respiratoires aiguës – IRA) : 952.000 consultations estimées (+36%). Taux de positivité pour les virus influenza de 50%. Environ 3 millions de cas cumulés. Les résultats d'une étude de séro-épidémiologie seront disponibles en semaine 50.

Cinquante-six nouveaux cas graves hospitalisés en SI. Au total, 481 hospitalisations dont 21% de patients sans facteurs de risque, 18% de mineurs de quinze ans, 6% de femmes enceintes. Vingt-deux décès en semaine 48 dont 9 mineurs de quinze ans et 14 patients sans facteurs de risque.

Diminution d'incidence dans tous les départements et collectivités d'outre-mer sauf à St-Pierre-et-Miquelon où l'incidence augmente nettement.

1.2. Virologie

Sur 1400 virus analysés en France, un seul présentait la mutation H275Y[1] observée en Norvège (Cf. CR du 25/11/09).

1.3. Gestion

Une circulaire à l'attention des préfets, relative à la permanence des soins en milieu ambulatoire est en cours de signature. Par ailleurs la circulaire interministérielle du 30 novembre 2009 précisant les actions à mettre en œuvre au niveau local pour prévenir et faire face aux conséquences sanitaires propres à la période hivernale est en cours de diffusion.

1.4. Foyers animaux H1N1 : Deux cas chez des chiens en Chine. Plusieurs foyers porcins disséminés en Norvège, et un à Teuva (province de Finlande-Occidentale, *Länsi-Suomen lääni*, Finlande).

En matière de grippe aviaire hautement pathogène (H5N1), un nouveau cas humain en Egypte (enfant de trois ans, en état stable), un décès au Vietnam (homme de 23 ans) et une suspicion de cas en Indonésie. Ces trois cas ont été contaminés au contact de volailles.

2. Points évoqués par l'**InVS** :

- **Dengue à St-Barthélémy :** phase de circulation active du virus (niveau 2 du plan de surveillance, alerte et gestion des épidémies) avec nette augmentation d'incidence depuis la semaine 45.

3. Points évoqués par l'**AFSSA** :

- **Contamination de tomates séchées par du virus de l'hépatite A (VHA),** signalée par l'Australie. Enquête en cours par la DGCCRF.

[1] Substitution de l'histidine par une tyrosine en position 275 de la neuraminidase N1. Cette mutation est parfois notée H274Y par référence à la neuraminidase N2. Elle confère une résistance à l'oseltamivir mais pas au zanamivir, et ne modifie pas les caractères antigéniques.

4. Points évoqués par l'AFSSAPS :

- **Vaccination H1N1 et pharmacovigilance :** prochain bilan France le 3/12. Pour plus d'un million de personnes vaccinées (en semaine 48), l'incidence des déclarations d'EIG ne connaît pas d'augmentation sensible. Les retours sur les analyses d'imputabilité des précédents EIG feront l'objet de communication.
- **Erreurs de procédure pour la vaccination** concernant en particulier l'utilisation de doses adultes pour des enfants en Bretagne : l'Afssaps envisage une communication de rappel sur les indications et bonnes pratiques.
- **Benfluorex** (Cf. CR du 28/10/09 et suivants) : suspension effective avec rappel du produit.

Hémovigilance :

- **EIG receveur :** allergie après transfusion de plasmas viro-atténués par le bleu de méthylène (PVA- BM) chez un enfant de 7 ans. Analyse en cours (ETS de Rhône-Alpes).
- **Séroconversion VHB receveur** survenue chez un patient de 82 ans après transfusion de CGR. Le patient était suivi en hémodialyse au Maroc. Enquête d'imputabilité en cours.
- **EIG donneur après don de sang total :** malaise ayant entrainé une chute chez un homme de 36 ans, survenu 45 minutes après don. ECG normal. Analyse en cours (ETS de Bourgogne).

5. Points évoqués par l'AFSSET :

- **Rapport sur les nanoparticules** qui sera présenté le 10/12 à l'occasion d'une journée publique de rencontres parlementaires sur le thème « Le développement des nanomatériaux entre perspectives d'innovations et évaluation des risques ? », co-organisée par l'Afsset et le Groupe d'étude sur la santé environnementale de l'Assemblée Nationale.
- **Canapés contaminés par le diméthylfumarate (DMFu)** (Cf. CR du 25/11/09) : le collectif de victimes se déclare surpris par l'inhomogénéité de ces résultats, demande des investigations complémentaires, prévoit de saisir la justice et saisirait la ministre de la santé en vue de mesures de décontamination environnementale.
- **Un rapport sur la qualité de blouses de protection des travailleurs** sera rendu en semaine 50, qui retrouve 90% de produits non-conformes.

6. Points évoqués par l'ABM :

- **Prélèvement et greffe de face** au CHU d'Amiens réalisée par les équipes des Pr B. Devauchelle (CHU d'Amiens) et J.-M. Dubernard (Hospices civils de Lyon) à partir d'un donneur décédé d'un accident vasculaire cérébral. Le receveur est un sapeur-pompier de Montpellier présentant un délabrement facial et mandibulaire provoqué par une fusée d'artifice. Infusion *in situ* de cellules souches hématopoïétiques (CSH) du donneur, HLA non compatible, dans le but d'obtenir une chimère hématopoïétique. Le patient est suivi à Lyon. Pas de communication de la part de l'ABM.

7. Points évoqués par l'EFS :

- **Stocks :** le niveau baisse à 95.000 CGR avec un impact probable de la grippe A. La cible est de 100.000 avec l'objectif de 120.000 avant les fêtes pour aborder le début d'année dans de bonnes conditions. Des actions pour accroître la fréquentation des sites de collectes sont programmées.
- **Production de plasma viro-atténués** (Cf. CR du 14/10/09 et suivants) : la reprise de production de PVA-SD sur le site Bordeaux reste retardée avec pour conséquence la poursuite de la mesure transitoire d'acceptation au don de plasma monodonneur (PVA-BM ou PVA Amotosalen) de femmes non-nullipares, prise en juin dernier pour assurer l'autosuffisance pendant la période d'arrêt de production du PVA-SD (initialement estimée à 2 mois). L'utilisation de plasma monodonneur, incluant les femmes donneuses ayant eu une grossesse, est associée à une augmentation du risque de TRALI[2]. L'EFS va mettre en œuvre des mesures pour maîtriser autant que possible ce risque.

[2] Les grossesses sont une des causes de production d'anticorps pouvant être à l'origine du syndrome de détresse respiratoire aigu post-transfusionnel (*transfusion related acute lung injury – TRALI*).

8. Points évoqués par l'**IRSN** :

- **Incident classé par l'ASN niveau 2 de l'INES à la CNPE de Cruas-Meysse (07) :** le plan d'urgence interne (PUI) a été déclenché dans la nuit du 1 au 2/12/09 par EDF sur le réacteur n°4 de la centrale en raison de l'obturation de la prise d'eau alimentant le système de refroidissement par des débris végétaux charriés par le Rhône. Le PUI a été levé à 6h30. Pas de rejet dans l'environnement.
- L'IRSN souhaite être informé de l'état d'avancement de l'homologation[3] de la décision n°2009-DC-0153 de l'Autorité de sûreté nucléaire du 18 août 2009 relative aux niveaux d'intervention en situation d'urgence radiologique (Cf. CR du 9/09/09) : le dossier est à la validation du directeur de cabinet de la ministre.

8. Points évoqués par la **DSC** :

- **Vaccination H1N1 :** mise en place du dispositif de remontées d'informations entre les équipes opérationnelles départementales via les préfets et le COGIC, et participation des services de santé et de secours médical (3SM) pour armer des centres de vaccination, en activité partagée avec la vaccination spécifique des personnels des SDIS.

9. Points évoqués par la **DGAl** :

- **Foyers de toxi-infections alimentaires à staphylocoque producteur d'entérotoxine** liés à du vacherin de Mont-d'or (Cf. CR du 12/11/09 & suivants) : pas de nouveau signalement de TIAC.
- **Contamination par *Listeria Monocytogenes* de langue de porc en gelée** (Cf. CR du 25/11/09), terrines et andouillettes. Rappel élargi des produits. Pas de cas clinique signalé.

10. Points évoqués par la **DGCCRF** :

- **Contamination par de l'huile minérale d'une huile de noix** importée des USA en France et réexportée dans plusieurs Etats membres de l'UE, mise en évidence par autocontrôle. Cinq lots de bouteilles contaminés (jusqu'à 369 ppm) et six suspectés. Après mélanges, jusqu'à 500 tonnes de produits finis seraient concernés. Retrait sans rappel, dans l'attente de l'analyse de risque en cours par l'Afssa. Signalement RASFF prévu. Enquête complémentaire en lien avec la DGDDI sur la possibilité d'une telle contamination d'autres huiles de même provenance.
- **Retrait et rappel de plats à gratin en céramique** « terra toscana Italian style ceramics » et « rustica » en raison d'une migration de plomb dépassant la limite maximale autorisée.
- « **Boisson minérale Fangocur** » présentant des teneurs en métaux lourds (plomb, thallium et arsenic) élevées, assortie d'allégations thérapeutiques[4]. Saisine de la DGS qui examine l'alerte avec Afssa et Afssaps.

11. Points évoqués par l'**INSERM** :

- **Retard de l'étude SentiVir** (suivi virologique des syndromes grippaux, H1N1 et autres virus, Cf. CR du 21/10/09) conduite par l'unité 707 qui pourrait ne débuter qu'après le pic épidémique.

12. Points divers :

- Le DUS/DGS indique que le bulletin national des activités et capacités hospitalières du 1/12/09 ne montre **aucune région classée en fortes tensions** mais que l'évolution dans les régions Haute-Normandie et Bretagne est à surveiller.

☞ **Prochaine réunion le mercredi 9 décembre à 8 heures 30**

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[3] L'article R.1333-112 du CSP prévoit qu'à réception de ladite décision par le ministre chargé de la santé l'homologation doit être notifiée ou refusée sous trois mois et est réputée acquise en l'absence de réponse dans ce délai.

[4] « La boue curative naturelle de fangocur purifie et désinfecte, (...) combat efficacement les gastrites chroniques, maladies inflammatoires de l'intestin et les ulcères gastroduodénaux ». [Source : site Internet fangocur.fr]. Ce produit, fabriqué en Autriche et vendu via Internet, a fait l'objet d'alertes au Royaume-Uni en janvier 2009 et au Canada en juin 2009.

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoires SERVIER

Demande déposée le 29 Mai 1998

Principe actif :	Chlorhydrate de benfluorex
Caractère d'originalité :	Modifications de la rubrique 4.8. Effets indésirables
Classe ATC :	Système cardio-vasculaire/ Hypolipidémiants (C10A : hypocholestérolémiants et hypotriglycéridémiants)

TYPE DE DEMANDE :

La demande actuelle concerne l'ajout d'effets indésirables au sein de la rubrique 4.8. « Effets indésirables » du RCP (nouveau texte proposé en gras) :

- *digestifs (nausées, vomissements, gastralgies, diarrhées), asthénie,* ***confusion,*** *somnolence ou états vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.*
- *très rares cas de réactions anaphylactiques, hypotension,* ***choc****, rash cutané, urticaire, œdème de Quincke ;*
- ***élévation des enzymes hépatiques, hépatite (très rare).***

Il s'agit d'une demande complémentaire de celle déposée en mars 2000 qui portait sur l'ajout d'effets indésirables de type cutanés et/ou allergiques) au sein de la rubrique 4.8., validée en GTI n° 113 du 30 juin 2000, en même temps qu'une modification de la rubrique 4.2 (ajout d'une contre-indication en cas d'hypersensibilité au benfluorex).

Pour rappel, cette modification de l'information scientifique fait suite à la demande des autorités italiennes auprès du CSP en septembre 1998 de revoir le profil de sécurité d'emploi du benfluorex.

La réévaluation avait été conduite par l'Italie et la France sur la base des données déposées par la firme (PSUR : période de janvier 1995 à décembre 1999). La demande complémentaire actuelle est également basée sur les données du même PSUR et est effectuée à la demande de l'Italie.

Note interne d'évaluation :

RÉPUBLIQUE FRANÇAISE

Annexe 4-1

AGENCE
DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ

Direction de l'Evaluation des
Médicaments et des
Produits Biologiques

www.afssaps.sante.fr

SAINT DENIS, le 02 SEP. 2002

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
Les Laboratoires SERVIER
22 rue Garnier
92200 NEUILLY SUR SEINE Cedex

Dossier suivi par : Madame le Dr. Catherine REY QUINIO

Réf. à rappeler : VNL10008
GTI 120 - COM 315
CRQ/DN

Monsieur,

J'ai l'honneur de vous faire parvenir, ci-joint, l'ampliation de la décision portant modification de l'autorisation de mise sur le marché du médicament :

- MEDIATOR 150 mg, comprimé enrobé

que vous avez sollicité le 29 mai 1998.

Je vous informe que le pictogramme mentionné à l'avant dernier alinéa de l'article R 5143 du code de la santé publique tel qu'issu du décret N°99-338 du 3 mai 1999 doit être apposé sur le conditionnement extérieur de votre spécialité, celle-ci ayant des effets sur la capacité de conduire des véhicules ou d'utiliser des machines mentionnés dans la rubrique du résumé des caractéristiques du produit prévue à cet effet.

Le modèle de pictogramme devant être utilisé et libre de droit, est disponible sur le site internet de l'Agence Française de Sécurité Sanitaire des Produits de Santé : www.afssaps.sante.fr

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

02 OCT. 2002

Pour le Directeur Général
et par délégation
Par empêchement du Directeur de l'Évaluation des
Médicaments et des Produits Biologiques
Adjointe au Directeur Chargée des Affaires Réglementaires

[illegible]:\AMM\CRQ\rectif\10000\vnl10008.a03.wpd

France ROUSSELLE

Annexe 4-1

A G E N C E
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ

Direction de l'Evaluation des
Médicaments et des
Produits Biologiques

www.afssaps.sante.fr

Références à rappeler : VNL10008
GTI 120 - COM 315
CRQ/DN

DÉCISION DU DIRECTEUR GÉNÉRAL DE L'AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES PRODUITS DE SANTÉ

du 02 OCT. 2002

portant modification
de l'autorisation de mise sur le marché du médicament

MEDIATOR 150 mg, comprimé enrobé

VU le code de la santé publique, cinquième partie, notamment les articles L.5121-8, L5121-9, L.5121-20 et R.5128 à R.5140 ;

VU l'autorisation de mise sur le marché validée octroyée le **22 avril 1987** modifiée ;

Vu la demande de modification de l'autorisation de mise sur le marché présentée par LES LABORATOIRES SERVIER ;

le 29 mai 1998 ;

pour le médicament :

MEDIATOR 150 mg, comprimé enrobé

et concernant :

- la rubrique de l'annexe I (résumé des caractéristiques du produit)
  4.8. Effets indésirables

Les annexes I (RCP) et IIIB (Notice)sont modifiées en conséquence ;

Annexe 4-1

DÉCIDE

Article 1er

La demande de modification du dossier d'autorisation de mise sur le marché est acceptée et les annexes I, II, III_A, et III_B de la présente décision remplacent les dispositions prévues par les annexes I, II, IIIA et IIIB de l'Autorisation de Mise sur le Marché susvisée modifiée.

Article 2

Les Laboratoires SERVIER
22 rue Garnier
92200 NEUILLY SUR SEINE Cedex
sont destinataires de la présente décision.

FAIT A SAINT DENIS, le 02 SEP. 2002

LE DIRECTEUR GENERAL DE L'AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Pour le Directeur Général
et par délégation
Par empêchement du Directeur de l'Évaluation des Médicaments et des Produits Biologiques
L'Adjointe au Directeur Chargée des Affaires Réglementaires

France ROUSSELLE

Pièces Jointes : 4 annexes

ANNEXE I

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION

02 OCT. 2002

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé de 700 mg

Pour les excipients, voir rubrique 6.1..

3. FORME PHARMACEUTIQUE

Comprimé enrobé

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

- Adjuvant du régime adapté dans les hypertriglycéridémies;
- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque : L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

4.2 Posologie et mode d'administration

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:
- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.

En association à un régime adapté, Médiator constitue un traitement *adjuvant* : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

4.3. Contre-indications

- Hypersensibilité au chlorhydrate de benfluorex ou à l'un des constituants ;
- Pancréatites chroniques avérées.

4.4. Mises en garde et précautions particulières d'emploi

Les troubles métaboliques relevant d'un traitement par Médiator sont essentiellement observés chez l'adulte. La prescription de Médiator n'est donc pas justifiée chez l'enfant.

Si, après une période d'administration de quelques mois (3 à 6 mois), une diminution satisfaisante de concentrations sériques de lipides ou de glucose n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

4.6. Grossesse et allaitement

Grossesse:
Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.
En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.
En conséquence, par mesure de prudence, il est préférable de ne pas utiliser ce médicament pendant la grossesse. En cas d'exposition fortuite, il conviendra d'interrompre ce traitement.

Allaitement
En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

L'attention des conducteurs est attirée sur la somnolence pouvant survenir lors de l'utilisation de ce médicament.

4.8. Effets indésirables

Les effets secondaires suivants ont été observés :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, confusion, somnolence ou états vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles.
- très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, oedème de Quincke,
- élévation des enzymes hépatiques, hépatite (très rare).

4.9. Surdosage

En cas d'absorption massive, le traitement sera uniquement symptomatique: lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience ainsi que des fonctions respiratoire et cardiaque.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

HYPOCHOLESTROLEMIANT ET HYPOTRIGLYCERIDEMIANT
Code ATC : C10AX04

Actions de Médiator sur le métabolisme lipidique:
Chez l'animal (rat), Médiator diminue l'absorption intestinale des triglycérides.
Cet effet a été également observé chez l'homme en pharmacologie clinique et serait dû à une diminution de l'activité de la lipase pancréatique.

Les effets suivants ont été également observés chez l'animal:
- diminution de la synthèse hépatique des triglycérides et du cholestérol, *in vitro* et *in vivo* (rat);
- diminution de la stéatose hépatique induite par des régimes riches en lipides, riches en glucides (rat obèse) ainsi qu'au cours du diabète expérimental (rat);
- limitation de l'incorporation du cholestérol dans la paroi artérielle (lapin).
Ces différents mécanismes pourraient expliquer en partie la diminution du cholestérol et des triglycérides observée chez l'homme.

Actions de Médiator sur le métabolisme glucidique:
Chez l'animal, les effets suivants ont été observés:
- facilitation de la pénétration et de l'utilisation cellulaire du glucose (rat);
- diminution de l'hyperglycémie chez le rat diabétique (insulinoprive ou non), diminution de l'hyperglycémie (mesurée par l'aire d'HPO) chez le lapin.

Médiator n'a pas d'action sur l'insulino-sécrétion; la survenue d'hypoglycémie est peu probable.

Effet complémentaire de Médiator:
Une baisse de l'uricémie d'environ 14 % a été observée chez des patients obèses hyperuricémiques traités par Médiator en association à un régime adapté.

Annexe 4-1

5.2 Propriétés pharmacocinétiques

L'absorption gastro-intestinale est rapide et totale.
Après administration orale, le pic de concentration plasmatique est maximal entre 1 et 2 heures.

L'élimination est rapide et totale par voie urinaire. Huit heures après l'absorption, 74 % de la dose administrée est éliminée dans les urines.

L'élimination se fait en 2 phases :
- une première phase rapide (60 % en 3 ou 4 heures);
- une seconde phase lente, de 36 heures environ.

5.3 Données de sécurité précliniques

Sans objet.

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane (E 171), éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

6.2. Incompatibilités

Sans objet.

6.3. Durée de conservation

3 ans

6.4. Précautions particulières de conservation

Pas de précautions particulières de conservation.

6.5. Nature et contenu de l'emballage extérieur

Plaquettes thermoformées (PVC-Aluminium)

6.6. Instructions pour l'utilisation et la manipulation

(Cf. 4.2.Posologie et mode d'administration)

Annexe 4-1

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE Cedex

8. PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE

317 553-3 :10 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 555-6 : 20 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 556-2 : 24 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 557-9 : 30 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 558-5 : 60 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
317 559-1 : 100 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

10. DATE DE MISE A JOUR DU TEXTE

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Liste I

ANNEXE II

A- TITULAIRE DE L'AUTORISATION(S) DE FABRICATION RESPONSABLE DE LA LIBERATION DES LOTS ET NOM ET ADRESSE DU PRODUCTEUR DE SUBSTANCE ACTIVE BIOLOGIQUE

LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

B- CONDITIONS LIEES A L'AUTORISATION DE MISE SUR LE MARCHE

CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I

AUTRES CONDITIONS

Sans objet.

C- ENGAGEMENTS DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

Sans objet.

ANNEXE IIIA
ETIQUETAGE

MENTIONS DEVANT FIGURER SUR L'EMBALLAGE EXTÉRIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTÉRIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION EN SUBSTANCES ACTIVES

Chlorhydrate de benfluorex ..... 150,00 mg

pour un comprimé enrobé

3. LISTE DES EXCIPIENTS

Excipient à effet notoire : saccharose

4. FORME PHARMACEUTIQUE ET CONTENU

Comprimé enrobé.
Boîte de 10, 20, 24, 30, 60 et 100 comprimés.

5. MODE ET VOIE(S) D'ADMINISTRATION, SI NÉCESSAIRE

Voie orale.

6. MISE EN GARDE SPÉCIALE INDIQUANT QUE LE MÉDICAMENT DOIT ÊTRE CONSERVÉ HORS DE PORTÉE ET DE VUE DES ENFANTS

Ne laisser ni à la portée, ni à la vue des enfants.

7. AUTRE(S) MISE(S) EN GARDE SPÉCIALE(S)

Lire attentivement la notice avant utilisation.

8. DATE DE PÉREMPTION

9. PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

Pas de précautions particulières de conservation.

Annexe 4-1

10. PRÉCAUTIONS PARTICULIÈRES D'ÉLIMINATION DES MÉDICAMENTS NON UTILISÉS OU DES DÉCHETS PROVENANT DE CES MÉDICAMENTS S'IL Y A LIEU

Sans objet

11. NOM ET ADRESSE DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

Titulaire/Exploitant :
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Fabricant :
LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

12. NUMÉRO D'IDENTIFICATION ADMINISTRATIVE

13. NUMÉRO DU LOT DE FABRICATION

14. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I

15. INDICATIONS THÉRAPEUTIQUES

Sans objet

PICTOGRAMME DEVANT FIGURER SUR L'EMBALLAGE EXTERIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTERIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

Le pictogramme doit être conforme à l'arrêté du 3 mai 1999 pris en application de l'article R 5143 du code de la santé publique et relatif à l'apposition d'un pictogramme. Celui-ci précise que le pictogramme a la forme d'un triangle équilatéral rouge sur fond blanc dans lequel se trouve une voiture noire. Ses dimensions sont adaptées à la taille du conditionnement extérieur.

Annexe 4-1

MENTIONS DEVANT FIGURER À TITRE MINIMAL SUR LES PLAQUETTES THERMOFORMEES OU LES FILMS THERMOSOUDEES

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. NOM DU TITULAIRE DE L'A.M.M

Les Laboratoires SERVIER

3. DATE DE PÉREMPTION

4. NUMÉRO DE LOT

Annexe 4-1

ANNEXE III B

NOTICE

Lisez attentivement l'intégralité de cette notice avant de prendre ce médicament.
Elle contient des informations importantes sur votre traitement.
Si vous avez d'autres questions, si vous avez un doute, demandez plus d'informations à votre médecin ou à votre pharmacien.
Ce médicament vous a été personnellement prescrit. Ne le donnez jamais à quelqu'un d'autre, même en cas de symptômes identiques, car cela pourrait lui être nocif.
Gardez cette notice, vous pourriez avoir besoin de la relire.

MEDIATOR 150 mg, comprimé enrobé

La substance active est :
Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé

Les autres composants sont : amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane (E 171), éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

Titulaire/Exploitant :
LES LABORATOIRES SERVIER
22, rue Garnier
92200 NEUILLY SUR SEINE

Fabricant :
LES LABORATOIRES SERVIER INDUSTRIE
905, route de Saran
45520 GIDY

1. QU'EST-CE QUE MEDIATOR 150 mg, comprimé enrobé ET DANS QUEL CAS EST-IL UTILISÉ ?

MEDIATOR 150 mg, comprimé enrobé contient du chlorhydrate de benfluorex.
MEDIATOR 150 mg se présente sous la forme de comprimés enrobés.
Boîtes de 10, 20, 24, 30, 60 et 100 comprimés.

Ce traitement est en préconisé comme adjuvant à un régime adapté :
- dans les hypertriglycéridémies *(taux de lipides élevés dans le sang)* ;
- chez les diabétiques avec surcharge pondérale *(taux de sucre élevé dans le sang)*.

Annexe 4-1

2. INFORMATIONS NÉCESSAIRES AVANT D'UTILISER MEDIATOR 150 mg, comprimé enrobé

MEDIATOR 150 mg, comprimé enrobé NE DOIT JAMAIS ETRE UTILISE dans les cas suivants :

- allergie au chlorhydrate de benfluorex ou à l'un des composants du produit;
- en cas de pancréatite chronique *(insuffisance de fonctionnement chronique du pancréas)*.

MISES en GARDE et PRECAUTIONS PARTICULIERES D'EMPLOI avec MEDIATOR 150 mg, comprimé enrobé :

Un régime alimentaire adapté doit être poursuivi pendant toute la durée du traitement.

Si après une période de plusieurs mois (3 à 6 mois), une diminution des concentrations de lipides ou de glucose (sucre) dans le sang n'est pas obtenue, votre médecin pourra envisager d'autres moyens thérapeutiques adaptés à votre cas.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase *(maladies métaboliques rares)*.

Grossesse/Allaitement:
Il est préférable de ne pas utiliser ce médicament pendant la grossesse ou au cours de l'allaitement.
Si vous découvrez que vous êtes enceinte pendant le traitement, consultez votre médecin car lui seul peut juger de la nécessité de le poursuivre.

Conduite de véhicules et utilisation de machines:
L'attention est attirée sur le risque de somnolence pouvant survenir avec ce médicament.

Sportifs:
Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

Liste des excipients à effet notoire:
Saccharose.

Prise ou utilisation d'autres médicaments:
Sans objet.

3. COMMENT PRENDRE MEDIATOR 150 mg, comprimé enrobé ?

Posologie:
RESERVE A L'ADULTE

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:
- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

La posologie peut-être ramenée à 2 comprimés par jour, voire 1 comprimé par jour, en fonction des résultats biologiques.

DANS TOUS LES CAS, SE CONFORMER STRICTEMENT A L'ORDONNANCE DE VOTRE MEDECIN.

Si vous avez pris plus de MEDIATOR 150 mg, comprimé enrobé que vous n'auriez dû:
Les signes de surdosage peuvent être des troubles digestifs (nausées, vomissements, diarrhée), une sensation vertigineuse voire une somnolence. En cas d'apparition de ces troubles, consultez votre médecin ou votre pharmacien.

Si vous oubliez de prendre MEDIATOR 150 mg, comprimé enrobé:
Ne prenez pas de double dose pour compenser la dose simple que vous avez oubliée de prendre.

Effets pouvant apparaître lorsque le traitement par MEDIATOR 150 mg, comprimé enrobé est arrêté :
Sans objet.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS avec MEDIATOR 150 mg, comprimé enrobé ?

Comme tous les médicaments, MEDIATOR 150 mg, comprimé enrobé est susceptible d'avoir des effets indésirables :
- troubles digestifs: nausées, vomissements, diarrhée, maux d'estomac ;
- sensation de fatigue, voire somnolence ;
- confusion ;
- sensations vertigineuses.

Ces effets ont été observés à des posologies supérieures à 3 comprimés par jour et varient en fonction de la susceptibilité individuelle des patients.

- très rares cas de manifestations allergiques : éruptions cutanées soudaines, urticaire, malaise brutal avec hypotension (diminution de la pression artérielle), oedème de Quincke (brusque gonflement du visage et du cou). Dans ce cas, le traitement devra immédiatement être interrompu.

- élévation des enzymes hépatiques (anomalies biologiques au niveau du foie). Très rares cas d'hépatite.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

5. COMMENT CONSERVER MEDIATOR 150 mg, comprimé enrobé ?

Pas de précautions particulières de conservation.

Ne laisser ni à la portée ni à la vue des enfants.

Ne pas utiliser après la date de péremption figurant sur la boîte.

La dernière date à laquelle cette notice a été approuvée est le (date).

Annexe 4-2

REUNION GROUPE DE TRAVAIL AD HOC SUR LES MEDICAMENTS UTILISES EN DIABETOLOGIE, ENDOCRINOLOGIE, UROLOGIE ET GYNECOLOGIE N° 6 DU 21 DECEMBRE 2006

PROCEDURE NATIONALE

- **MEDIATOR 150**, comprimé

Dossier n° VNL 10008

Laboratoire SERVIER

Demande déposée le

Principe actif:	**Benfluorex**
Caractère d'originalité	**Réévaluation de Bénéfice Risque**
Classe ATC:	**Système cardio-vasculaire/Hypolipémiants (C10A: hypocholestérolémiants et hypotriglycéridémiants**

TYPE DE DEMANDE:

Faisant suite à la demande de réévaluation de bénéfice Risque de la Commission Nationale de Pharmacovigilance de Juin 2006, une revue des études d'efficacité dans les deux indications actuelles de l'AMM a été déposée par la firme.

Pour rappel, MEDIATOR (chlhorydrate de benfuorex) est commercialisé depuis 1987 dans les indications suivantes:

- *« Adjuvant au régime adapté dans les hypertryglycéridémies. La poursuite du traitement est toujours nécessaire.*
- *Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.*

Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée».

HISTORIQUE DE L'EVALUATION DES DONNEES RELATIVES AU MEDIATOR

- Date d'AMM : 16-07-1976

- 1995. Inscription sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes. Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables de ces produits et étant donné les restrictions de leur délivrance, le CTPV a craint une dérive de l'utilisation du benfluorex comme anorexigène.

- 1998: 1ère enquête de Pharmacovigilance. Présentation des effets indésirables en CTPV (plusieurs séances) en 1998 ainsi qu'au groupe Européen de PV le 30-11-2000, entraînant des modifications de la rubrique 4.8. du RCP (ajout de « confusion » comme effet indésirable».

- 1987: validation de la 1ère tranche dans l'indication « hypertriglycéridémies »

- **1990 :** dépôt du dossier de la 8ème tranche de validation dans l'indication en « diabétologie » ; nombreux échanges entre l'Afssaps et la firme entre 1990 et 1995 sur la nature des données à soumettre afin de valider cette indication (type d'étude, population cible, etc.), aboutissant finalement en 1998 au dépôt de l'étude Del Prato (étude de l'efficacité du benfluorex versus placebo et metformine sur les paramètres glucidiques (voir ci-dessous données cliniques). En attente de cette étude, l'indication telle que libellée lors de l'octroi de l'AMM a été maintenue.

- **Septembre 2000:** demande d'extension d'indication au «*Diabète de type II insulino-dépendant, en association au régime adapté, lorsque ce régime n'est pas suffisamment suffisant pour rétablir à lui seul l'équilibre glycémique* ». Une seule étude de phase III **(Etude Del Prato)**, randomisée, en double insu, benfluorex versus placebo et metformine a été soumise à l'appui de cette demande (A noter, cette étude réalisée a été réalisée à la demande de l'Afssaps; protocole revu en concertation avec l'Afssaps). Un avis défavorable a été émis par le Groupe de Travail PTC2 ainsi que par la COM d'AMM. Après recours de la firme de cette décision, cet avis a été maintenu par la COM d'AMM. En effet, compte tenu des défauts de la qualité méthodologique de cet essai (ayant l'objet par ailleurs d'une inspection), aucune conclusion n'a pu être formulée sur la taille de l'effet: i) du benfluorex versus placebo; ii) du benfluorex versus metformine (non-infériorité non démontrée : déséquilibre des taux d'HbA1c entre les groupes à l'inclusion, 68% seulement inclus dans l'analyse per protocole, 25% de patients inclus à tort). A noter également, aucune efficacité sur les paramètres lipidiques n'a été mise en évidence dans cette étude. En conclusion, la COM d'AMM (20-09-2002) a demandé qu'une étude évaluant l'efficacité du benfulorex en monothérapie et en association avec d'autres antidiabétiques oraux soit effectuée; l'association devant être également étudiée chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisants rénaux, sujets âgés)

- **2004-2005/Seconde enquête de Pharmacovigilance**

Cette 2nd enquête fait suite à plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique rapportés avec le benfluorex. De ce fait, une actualisation des données relatives aux troubles neuro-psychiatriques observés avec cette spécialité a été décidée. L'enquête a ensuite été étendue aux hypertensions artérielles pulmonaires du fait de la notification d'un cas d'HTAP associé à la prise de benfluorex. Les conclusions de la CNPV sont les suivantes:

- en ce qui concerne les troubles neuro-psychiatriques: « *cette enquête confirme la réalité du risque de survenue de « confusions » en présence de Médiator. Il est proposé que cet effet, déjà mentionné dans le RCP soit détaillé comme suit :* ***« troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) ».***
- en ce qui concerne l'HTAP: « *compte tenu de l'incidence des HTAP idiopathiques (1 à 2 millions et par an), le nombre de cas d'HTAP idiopathique rapportés dans l'enquête ne constitue pas un signal significatif de toxicité du Mediator dans la classe organe cardio-vasculaire* ».

La discussion en CNPV (29-11-2005, adoptée le 16-06-2006) a par ailleurs porté sur les éléments suivants (extrait):

Les ventes de Médiator en Europe sont réalisées en quasi totalité en France. Les données DOREMA d'avril 2005 montrent une utilisation dans 46,3% dans les dylipidémies et dans 8,3% dans d'autres indications. L'effet anorexigène du benfluorex n'a pas été démontré. Toutefois, les membres de la CNPV craignent un mésusage, en particulier dans l'obésité. Dans ce contexte, une étude d'utilisation de prescription serait utile.

Il est à noter que le renouvellement quinquennal du produit intervient dans 2 ans en

France et que des données d'efficacité dans le diabète existent mais restent limitées et mériteraient d'être réévaluées.

Le bilan de pharmacovigilance confirme les données de sécurité d'emploi du Médiator déjà connues. Les effets neuro-psychiatriques décrits actuellement dans le RCP sous le terme « confusion » doivent être détaillés. Il n'y a pas actuellement assez de données pour affirmer l'existence de syndrome de sevrage. Le faible nombre de cas décrits d'HTAP idiopathique associés au Médiator doit être relativisé par rapport à la sous-notification habituelle en pharmacovigilance. Afin d'évaluer au mieux les risques potentiels de l'utilisation de Médiator, il conviendrait de réaliser:
i) une étude d'utilisation/prescription de Médiator;
ii) une étude expérimentale sur un modèle animal permettant d'évaluer le potentiel de Médiator à engendrer des HTAP;
iii) une étude au niveau des Centres d'évaluation et d'information sur la pharmacodépendance (CEIP) afin d'évaluer un éventuel problème de pharmacodépendance. A ce titre, une saisine de la Commission Nationale des stupéfiants et psychotropes sera effectuée.
Enfin, il a été proposé d'étudier la possibilité d'interroger les registres d'HTAP existant dans 17 centres, afin de rechercher, dans une étude rétrospective cas-témoins, le rôle éventuel du benfluorex.
Au vue des résultats présentés et des discussions, la CNPV a décidé une réévaluation de la balance Bénéfice-Risque de Médiator.

13 Octobre 2006/Réunion firme/Afssaps (PV, SURBOUM, PTC2/CRPV de Besançon)/Discussion des modalités de mise en oeuvre des études demandées par la CNPV, en particulier : i) étude sur un modèle animal d'HTAP; ii) étude d'utilisation-Prescription de Médiator.

=> Lors de cette réunion ont été présentés les types de modèle expérimentaux in vivo existants d'HTAP (modèle de stimuli patho-physiologique comme l'hypoxie aïgue ou chronique chez le rat ou la souris, stimulis chimiques comme la manocrotaline chez le rat, les modèles dits génétiques comme le rat Fawn-Hooded)

La firme retiendrait plus particulièrement un modèle d'étude de l'effet du benfluorex en conditions d'hypoxie ou de normoxie avec études des paramètres hémodynamiques, de l'index d'hypertrophie ventriculaire droit et du « remoduling » vasculaire pulmonaire (ou analyse histologique de la muscularisation des artérioles.

=> Données relatives à la commercialisation. A ce jour, le produit reste commercialisé dans 6 pays : Grèce, France, Pologne, Malte, Luxembourg et Chypre. L'Espagne et l'Italie n'ont pas demandé de renouvellement de l'AMM lors du dernier RQ dans ces deux pays.

=> Données de prescription. La firme a présenté des données de prescription issues de l'observatoire de prescriptions Thalès. 5 groupes ou populations pour lesquels Mediator est prescrit ont été identifiés (deux périodes d'observation: de 05/04 à 04/05 et de 05/05 à 04/05).
A - Patients dyslipidémiques +/- 50% des patients traités
B – Patients diabétiques de type 2 soit 1,8% (à confirmer)
C (A+B) - soit 15,2%
D – Ni A ni B (patients en **surpoids ou obèses, soit 14,3%)**
E – Ni A ni B + autre diagnostic (non précisé, HTA? Rapport Taille/Hanche élevé ?), **soit 8,1%.**
A noter, les chiffres de prescription sont stables pour les deux périodes étudiées.
Au total, +/- 20% de patients reçoivent du Médiator hors indications de l'AMM (14,3% + 8,1%). Des précisions seraient à apporter sur cette population de patients traités (leur

poids?, sont-ils obèses ou non?, Quelles sont les raisons de la prescription de Médiator (prescription saisonnière à l'automne ou non?). D'autres réunions sont envisagées avec la firme afin d'étayer les différents points discutés lors de cette réunion.

CONTENU DU DOSSIER:

En vue de la réévaluation de bénéfice Risque, le dossier déposé par la firme repose essentiellement sur des données d'études anciennes et ayant déjà l'objet d'expertise depuis la commercialisation du produit. Seule une nouvelle étude clinique : l'étude MOULIN apporte de nouvelles données dans l'indication en « diabétologie ».

Le rapport est structuré en 3 parties:

1. Un rappel du mécanisme d'action supposé de la molécule;
2. Des données d'efficacité dans chacune des 2 indications actuelles, avec une analyse plus particulière des données de l'étude MOULIN (indication « diabétologie »).
3. Une synthèse des données de sécurité d'emploi issues des études cliniques et de la pharmacovigilance.

1. MECANISME D'ACTION DE MEDIATOR

1. Activité hypoglycémiante

La firme met en avant des propriétés insulino-sensibilisatrices chez l'Homme avec un effet sur les transporteurs de glucose, un effet direct sur le foie avec augmentation de la synthèse du glycogène et inhibition de la néoglucogenèse et enfin une réduction du contenu musculaire en triglycérides. Les données suivantes sont soumises:

=> Etude in vitro sur modèles cellulaires chez le rat => action sur le métabolisme du glycogène : augmentation de la synthèse du glycogène et diminution de la glycogénolyse stimulée par le glucagon (Melin, 1991).

=> Diminution de la production hépatique de glucose et effet sur la néoglucogenèse (Tielens 1993 et Zorzano 1996 et Kohl 2002

=> 4 études sur l'amélioration de l'insulinosensibilité (Brindley 1991, Portha 1993, Serrasas 1993 et Storlien 1993).

=> 4 études sur l'amélioration de l'insulino-résistance musculaire avec effet de majoration du transporteur GLUT-4 (Sevilla 1999, Storlien 1993, Zorzano 1996) et l'oxydation du glucose (Bailey 1992)

=> Pas d'effet sur le sécrétion basale d'insuline (chez le rat normal ou diabétique (Portha 1993 et Serradas 1993). Voir Note interne ci-dessous.

Note interne:

D'après la firme, ces données permettent de conclure que le benfluorex a un effet insulino-sensibilisateur chez l'Homme démontré par les 3 études citées de clamp hypersinsulinique. Un effet direct sur le foie avec augmentation de la synthèse du glycogène et inhibition de la néoglucogenèse aurait également été mis en évidence.

Annexe 4-2

Le benfluorex améliorerait l'insulino-sensibilité musculaire avec un effet sur les transporteurs de glucose. Enfin, la firme souligne que le mécanisme d'action du benfluorex diffère de celui des autres insulino-sensibilisateurs comme la metformine et les glitazones.

En effet, la mesure de l'expression des enzymes clés contrôlant le métabolisme du glucose et des acides gras libres après 48 heures d'incubation aurait montré une diminution franche de la CPT1, enzyme responsable de l'entrée des acides gras dans la mitochondrie, et de la PEPCK impliquée dans l'activation de gluconéogenèse. Cet effet serait propre à Médiator (déjà mis en exergue en 2000) puisque dans les mêmes conditions expérimentales, l'action inhibitrice de la metformine est indépendante de l'oxydation des acides gras et semble être en rapport avec une augmentation du potentiel redox de la cellule hépatique, les glitazones (étude avec la troglitazone) freine l'activation des acides gras en inhibant l'acyl-CoA synthase, réaction préalable à leur oxydation.

Il est noter qu'en 2000 (lors de la soumission de l'étude versus placebo et metformine, des données relatives à l'activité hypoglycémiante avaient déjà été soumises. D'après les experts mandatés, les données du dossier ne permettaient pas à l'époque de conclure à une augmentation de la sensibilité à l'insuline sous benfluorex Les conclusions suivantes avaient été émises:

- l'absence d'effet direct de Médiator sur la sécrétion d'insuline induite par le glucose ou l'arginine avait été confirmée in vitro à partir de cellules de pancréas isolées perfusées de rats témoins et de rats diabétiques (Serradas, Portha 1993);

- 3 études de pharmacodynamie contrôlées en double aveugle utilisant des techniques de clamp hyperinsulinique euglycémique (Biancchi 1993, Ricchio 1993) et isoglycémique (De Feo 1993 ont étudié l'utilisation périphérique de glucose. Deux de ces études ont étudié la production hépatique de glucose; une (De Feo) a montré une diminution de cette production; l'autre étude (De Ricchio) n'a pas mis en évidence de variation. Une étude complémentaire de Bianchi réalisée en 1996 n'avait pas montré d'amélioration de la consommation de glucose sous benfluorex. Sur la base de ces éléments, aucune certitude

Tableau 1 Evolution de la sensibilité à l'insuline

	Nb patients	Traitt	Valeurs basales	Valeurs finales	p**
Riccio **Captation du glucose** (µmol/kg/min) (40 dernières minutes du clamp., perfusion d'insuline qsp insulinémies=480 pmol/L au dessus de la valeur basale)	14	Med Pla p*	26.8±1.4 29.7±3.4	34.5±1.3 27.2±4.0	<0.05 NS
Bianchi§ **Taux de perfusion de glucose** (µmol/kg/min) (30dernières minutes du clamp., perfusion d'insuline 0.1 U/kg/h)	10	Med Pla	- -	5.36±0.49 3.87±0.83	- -
De Feo **Taux de perfusion de glucose** (µmol/kg/min) (2 dernières heures du clamp, perfusion d'insuline 1 mU/kg/min, *soit0.06U/kg/h*)	20	Med Pla p*	28.5±0.93 27.6±2.00 0.847	32.2±0.62 27.2±2.00 <0.001	0.004 0.307

*MEDIATOR® vs placebo ; ** valeurs finales vs valeurs basales
§ Etude croisée, clamps réalisé en fin de période, pas de valeurs basales

sur le mécanisme d'action de cette molécule n'avait pu être mis en évidence.

Dans le présent argumentaire déposé, la firme s'appuie sur ces 3 mêmes études et conclut que ces études permettent de confirmer l'action de benfluorex sur le métabolisme glucidique et le situe clairement dans la classe des insulino-sensibilisateurs. L'ensemble

des résultats et leur cohérence ont conduit à mettre en place deux études pivot visant à confirmer l'efficacité hypoglycémiante du benfluorex chez les patients diabétiques de type 2 (Moulin 2006, Del Prato 2003). Voir données d'efficacité plus loin.

Un avis d'expert sur le mécanisme d'action de cette molécule est requis.

2. Activité hypolipémiante

Une action sur les différentes étapes enzymatiques régulant le métabolisme des acides gras, des triglycérides et du cholestérol aurait été mise en évidence in vitro. Aucune donnée dynamique ou clinique n'est fournie par la firme afin d'étayer le mécanisme d'action annoncé.

Note interne:
A noter qu'en 2000 lors de l'analyse des données de l'étude clinique versus placebo et versus metformine (Del Prato) les experts mandatés avaient tous souligné l'absence d'effet du benfluorex sur les paramètres lipidiques.

Extrait du rapport d'expertise sur le mécanisme d'action de l'activité hypolipémiante:

Benfluorex exerce une action sur différentes étapes enzymatiques regulant le métabolisme des acides gras, des triglycérides et du cholestérol.

In vitro, les données expérimentales sur hépatocytes isolés et homogénats de foie montrent que benfluorex diminue l'incorporation de C^{14} acétate dans les acides gras (Melin, 1991 ; Beynen 1992) et réduit l'activité de la phosphatidate-phosphorylase (Geelen,1977), enzyme responsable de la conversion du phosphatidate en diglycérides. Benfluorex et son principal métabolite (S 422) provoquent une inhibition dose dépendante d'une enzyme microsomiale, l'Acyl CoA cholestérol acyltransférase, augmentant le catabolisme des LDL (Low Density Lipoprotein) (Mazière,1991 ; Orsière, 1995).

Les effets inhibiteurs sur la synthèse des triglycérides sont confirmés *in vivo* sur différents modèles d'insulino-résistance chez le rongeur. L'administration de benfluorex (50 mg/kg) pendant un mois améliore l'action de l'insuline et réduit l'accumulation de triglycérides dans les muscles squelettiques (Storlien, 1993). L'administration à court terme de benfluorex diminue la triglycéridémie et la cholestérolémie chez le rat hyperphagique (Brindley, 1991). L'administration de benfluorex (10 mg/kg), à long terme (9 mois) entraîne une diminution des taux circulants de triglycérides et de cholestérol, ainsi que de l'insulinémie et de la glycémie post prandiale chez le rat obèse (Marquié, 1998).

En résumé, un effet hypolipémiant, portant sur les triglycérides et sur le cholestérol total, est observé sur de nombreux modèles animaux, après une administration courte ou prolongée de benfluorex.

2. DONNES D'EFFICACITE DE MEDIATOR

Présentation et analyse des données soumises par indication

=> Traitement adjuvant du régime adapté dans les hypertriglycéridémies.

Dix études sont soumises par la firme pour soutenir cette indication: i) versus placebo (chez 394 patients) ;ii) 4 études versus fibrates (chez 163 patients) chez des patients présentant une hyperlipidémie associée ou non à un diabète de type 2.

Etudes versus placebo (réalisées entre 1978 et 2006). Il s'agit d'études anciennes à l'exception de l'étude MOULIN (soumise 2006).

Annexe 4-2

Quand les mesures ont été effectuées sur les différentes fractions du cholestérol total, on observe une réduction significative du taux de LDL-cholestérol après traitement par benfluorex de 29.3%, ($p<0.05$) (Soltero, 1988) et de 5 % ($p < 0.05$) en comparaison au placebo (Moulin, 2006). Par ailleurs une augmentation significative du taux de HDL-cholestérol de l'ordre de 7.8 à 44.3% a été rapportée dans les études Mazzi et Di Martino.

Ces études ont inclus des patients de pathologies diverses (anomalies polymétaboliques, hyperlipidémie, diabète ou intolérance au glucose). Elles ont été menées selon un schéma croisé, parallèle ou séquentiel durant une période de 15 à 180 jours. A noter que dans l'étude Di Martino, le comparateur est le régime seul et que dans les études Del Prato et Moulin chez le diabétique de type 2, il s'agit de sous-groupes de 87 et 112 patients respectivement dont le taux de triglycérides à l'inclusion est >2.2mmol/L.
Les résultats figurent dans le tableau 8.

L'analyse de ces études a montré qu'un traitement par benfluorex diminue le taux de triglycérides (-8.3% à -56.1%) et du cholestérol total (-4.8% à -36.6%). L'importance de la diminution est dépendante de la valeur initiale ce qui explique la large fourchette des variations observées. Cet effet hypolipémiant, à la fois sur les triglycérides et le cholestérol, est démontré dans chaque catégorie de patients (hyperlipidémiques, diabétiques et polymétaboliques).

Mazzi 1985	[illegible] hyperlipidémie IIb ou IV*	cross-over	[illegible] 7 (IV)	120	Bf : -39.0* Pl : -17.2		Bf : -56.1% Pl : -27.9*	-
Ranquin 1987	hyperlipidémie IV*	cross-over	22	40	Bf : -4.9 Pl : + 0.02		Bf : -32.7 Pl : - 11.7	+
Soltero 1988	hyperlipidémie IIa IIb*	séquen-tielle	20	56	Bf : -20.7* Pl : 1.7	ND	Bf : -10.8* Pl : -0.5	
Di Martino 1989	obésité-anomalie métabolique	groupe parallele	50	180	Bf : -6.9 * Contrôle : - 2.6	ND	Bf : -24.7* Contrôle : - 13.8*	ND
Bianchi, 1993	diabete type 2 + obesite	cross-over	10	35	Bf : -10** Pl : -8%,	-	Bf : -36 Pl : -25%	
Del Prato, 2003 (Analyse complémentaire en annexe 8)	diabete type 2 + hypertriglyceridémie	groupe parallele	72	189	ND		Bf : -24 * Pl : +24	-
Moulin, 2006	diabete type 2 + hypertriglyceridémie	groupe parallele	112	125	Bf : -6* Pl : 0.0	-	Bf : -12* Pl : - 5	

a=classification de Fredrickson
ND=non déterminé
**=effet significatif valeur finale versus valeur initiale*
+ = différence intergroupe significative

Etudes versus produit de référence (fibrates), réalisées entre 1980 et 1986 => 5 études dont les conclusions apportées par la firme sont le suivantes.

Quatre études ont comparé l'activité hypolipémiante de MEDIATOR® à celle du clofibrate selon un schéma croisé (Graisely, 1980) ou en groupes parallèles (Di Perri, 1981 ; Nathan, 1981 ; Balestreri, 1982) et une étude en groupes parallèles au fénofibrate et au bézafibrate (Sommariva, 1986b). Ces études ont inclus des patients présentant une hyperlipidémie (IIa, IIb, IV) associée ou non à un diabète de type 2. Le traitement durait de 30 à 112 jours selon les études (tableau 9).

L'ensemble des résultats démontrent qu'un traitement par benfluorex entraîne une diminution des triglycérides (-20.5% à -52.7%) et du cholestérol (-9.6% à -20.9%). L'amplitude de l'effet hypolipémiant est comparable à celui obtenu avec les fibrates (-19.0% à -49.7% et -4.9% à -22.7% respectivement).

Annexe 4-2

La dyslipidémie des patients inclus est fréquemment associée à une intolérance au glucose et à une hyperuricémie dans le cadre d'un syndrome plurimétabolique. Dans ces études, on observe une diminution significative de l'uricémie sous benfluorex (-11.3%) (Graisely, Balestreri, Nathan) tandis que les fibrates ne la modifient pas (−1.4%), à l'exception du fénofibrate (Sommariva). Chez les patients non diabétiques, une amélioration de la tolérance au glucose est rapportée, et chez les patients diabétiques une réduction de l'hémoglobine glyquées qui ne sont pas observées sous fibrates (Graisely, di Perri, Balestreri, Sommariva).

=> Traitement adjuvant au régime adapté chez les diabétiques avec surcharge pondérale

Pour rappel, en réponse à la demande de l'Afssaps de validation de l'indication «en « diabétologie » en 1990, la firme avait mis en place un programme d'études de l'efficacité du benfluorex dans différentes populations. Le programme d'étude avait pour but d'explorer l'efficacité et la sécurité d'emploi du benfluorex dans différentes populations (extrait relevé d'avis GT PTC2 N°1 du 21-09-2000)

- Patients insuffisamment contrôlés par régime seul (**Velussi**, 1996) => comparaison à un placebo en monothérapie;
- Patients insuffisamment contrôlés par un SU en monothérapie
  Deux anciennes études : Stucci 1996, **Louvet** 1995) => comparaison de Médiator à un placebo en association à un traitement par SU à dose maintenue constante pendant l'étude.
- Patients insuffisamment contrôlés par une insulinothérapie (Bianchi et Pontiroli 1996);
- Patients insuffisamment contrôlés par metformine en monothérapie (Pr Roger) => comparaison de Médiator à un placebo en association à la metformine à dose maintenue constante pendant l'étude, après une période de pré-inclusion de 2 mois sous metformine seule,
- Patients insulino-requérants (Pr Leutenegger) => comparaison de Médiator au placebo en association à l'insuline, dont la dose pouvait être modifiée en cours d'étude.

Seules trois de ces études (Velussi, Tomassi et Louvet) sont reprises par la firme dans le présent rapport soumis (noms des auteurs en gras dans le texte ci-dessous).

Etude	N	Durée (mois)	Comparateur	Cholestérol total mmol/l		Triglycéride mmol/l	
				Benfluorex Δ (%) p* p**	Fibrate Δ (%) p* p**	Benfluorex Δ (%) p* p**	Fibrate Δ (%) p* p**
Graisely, 1980	24	2	Clofibrate	-9.1% <0.001	-7.7% <0.001 NS	-35.5% <0.05	-31.5% <0.05 NS
Di Perri, 1981	28	2	Clofibrate	-17.8%	-10.1% <0.05	-40.5%	-19.0% <0.05
Nathan, 1981	43	4	Clofibrate	-10.4% <0.05	-17.7% <0.001 NS	-20.5% <0.05	-28.6% <0.01 NS
Balestreri, 1982	40	2	Clofibrate	-20.9% <0.001	-22.7% <0.001 NS	-52.7% <0.001	-38.5% <0.001 S
Sommariva, 1986b	28	1	fénofibrate bézafibrate	-16.7% <0.001	-8.7% NS -4.9% NS	-33.1% <0.005	-49.7% <0.02 -44.3% <0.005

p : valeurs finales vs valeurs basales ; p** : différence entre groupes (benfluorex vs référence) ; NS=non significatif*

Annexe 4-2

Etudes versus placebo

=> La firme fait référence à trois anciennes études versus placebo dont les résultats sont présentés dans le tableau ci-dessous

Auteurs (réf)	Durée	Effectif	Traitement associé	HbA1c initiale (SD)	HbA1c différence versus placebo
Velussi 1996 (rapport en annexe 5)	3 mois	32	Regime seul	6.7 % (± 0.8)	-0.9 % p = 0.024
Tomasi 1996 (rapport en annexe 6)	3 mois	68	Regime + sulfamide hypoglycemiant	8.7 % (± 0.9)	-0.8 % p = 0.007
Louvet 1996 (rapport en annexe 7)	3 mois	35	Regime + sulfamide hypoglycemiant	8.5 % (± 1.7)	-1.7 % p = 0.023

=> la firme présente de manière détaillée les résultats du bras placebo de l'**étude Del Prato** (1998, publiés dans Acta Diabetologica en 2003) déposée dans le cadre de la validation de l'indication en « diabétologie ». Cette étude avait fait l'objet d'une expertise en plusieurs étapes.

Rappel de la méthodologie de l'étude:

Cette etude internationale multicentrique, conduite en double aveugle et groupes parallèles, a porté sur 438 patients diabétiques de type 2 insuffisamment contrôlés par régime seul. L'étude comportait une période de pré-inclusion de 2 mois pendant laquelle les patients recevaient du placebo (en simple insu) et des conseils diététiques. Les traitements ont été randomisés, soit benfluorex soit placebo, selon une répartition non équilibrée (2:1). Le traitement de 6 mois a été administré en trois prises quotidiennes, la dose passant de 1 cp/j (benfluorex 150 mg) à 2 cp/j au bout de 2 semaines et à 3 cp/j si la glycémie à jeun restait ≥ 7.8 mmol/L.

Critères d'inclusion

Patients diabétiques de type 2, en surpoids (IMC compris entre 25 et 40Kg/m^2), insuffisamment contrôlés par régime seul (HbA1c initiale comprise entre 7.5 et 10 % ou glycémie à jeun comprise entre 7.8 et 13.9 mmol/L).

Critères d'évaluation

Le critère principal d'efficacité était l' HbA1c (dosage centralisé, méthode HPLC).
Les critères secondaires d'efficacité étaient : glycémie à jeun, insulinémie, bilan lipidique.
Les critères de tolérance étaient : données de l'examen clinique (poids, fréquence cardiaque, PA), créatininémie et recueil des événements indésirables reportés spontanément.

Analyse statistique

L'analyse principale a été réalisée selon une approche en ITT dans la population FAS définie par l'ensemble des patients inclus ayant au moins une valeur du critère principal sous traitement.

La population FAS est constituée de 259 patients et 128 patients respectivement pour le groupe benfluorex et pour le groupe placebo, soit 88 % et 89 % de la population incluse (répartition : 2:1).
Les groupes sont comparables à l'inclusion. La moyenne d'âge est de 56 ± 9 ans, le diabète connu depuis 5 ± 5.5 ans. Les valeurs basales d'HbA1c sont de 7.7 % ± 1.6 dans le groupe benfluorex et de 7.4 % ± 1.5 % dans le groupe placebo, traduisant une sévérité modérée du diabète comme attendu dans cette population.

Conclusions de la firme:

L'HbA1c est significativement améliorée sous benfluorex et s'altère sous placebo ce qui conduit à une différence entre les groupes de 0.86% (p<0.001) et de 1.01 % (p < 0.001) après ajustement sur la valeur basale d'HbA1c. L'analyse en per protocole confirme ces résultats.
Des résultats identiques sont observés pour la glycémie à jeun avec une différence entre les groupes de 1.33mmol/L (p<0.001) (tableau 6). Le nombre d'arrêts de traitement pour inefficacité thérapeutique est plus important sous placebo (10.4 %) que sous benfluorex (6.8 %) (p = 0.19).

variables	benfluorex (DS)		placebo (DS)		différence [95 % IC]
	n	moyenne (ES)		n	
HbA1c (%)					
M0		7.7 (± 1.6)	7.4 (± 1.5)		
M6		7.1 (± 1.5)	7.9 (± 1.9)		
Différence entre les groupes	258	-0.86 (0.17)		127	[-1.20; -0.52]***
Différence entre les groupes ajustée sur la valeur basale		-1.01 (0.14)			[-1.28; -0.74]***
Glycémie à jeun (mmol/L)					
M0		10.0 (± 2.9)	9.7 (± 2.3)		
M6		8.8 (± 2.3)	10.1 (± 3.1)		
Différence entre les groupes	253	-1.33 (0.28)		123	[-1.89; -0.77]***

***p <0.001

Note interne :

Pour rappel, les conclusions de la COM d'AMM du 09-12-1999 avaient été les suivantes: « ... Il est noté une efficacité du benfluorex versus placebo. Néanmoins, il n'est pas possible d'évaluer sur la taille de l'effet compte tenu des défauts de qualité des données. ... En effet, compte tenu des défauts de la qualité méthodologique de cet essai, aucune conclusion n'avait pu être formulée sur la taille de l'effet; i) du benfluorex versus placebo; ii) du benfluorex versus metformine. L'octroi d'une AMM dans le diabète de type 2 avait été rejetée. De manière plus précise, le groupe placebo de cette étude avait également soulevé de nombreuses remarques sur la qualité des analyses et résultats.

=> Etude MOULIN

An 18-week multinational, randomised double-blind study of the effect of benfluorex versus placebo in combination with SU for the treatment of type 2 diabetes, followed by a 16-week open label period with benfluorex given as combination with SU or in multiple combination.

Annexe 4-2

Méthodologie

Etudes comportant 2 périodes ii) période en ouvert de 16 semaines.

i) période en double aveugle (DA) de 18 semaines dont l'objectif principal était de démontrer la supériorité du benfluorex versus placebo, en association à un SU, sur l'évolution de l'HbA1c sur une période de 18 semaines chez des patients diabétiques de type 2 mal contrôlés par SU en monothérapie et chez qui l'utilisation de la metfomrine est contre-indiquée ou non recommandée. Etude multicentrique, en double aveugle, en groupes parallèles, comparative versus placebo.

ii) période en ouvert 16 semaines ayant pour objectif d'obtenir des données d'efficacité et de sécurité d'emploi à long terme du benfluorex en association avec un SU et, si nécessaire, à l'acarbose (3ème ADO pouvant être prescrit).

Période 1 : étude en double aveugle de 18 semaines

Population : 325 patients diabétiques de type 2 avec HbA1c entre 7 et 10% à l'inclusion insuffisamment équilibrés par SU (pendant 4 mois avant l'inclusion ou 2 mois à dose maximale tolérée, en surpoids (IMC entre 25 et 40 kg/m²).

Objectifs : principal : démontrer la supériorité du benfluorex versus placebo, en association à une SU, sur l'évolution de l'HbA1c pendant une période de 18 semaines chez des patients diabétiques de type 2 mal contrôlés par SU en monothérapie, et chez qui l'utilisation de la metformine n'est pas recommandée (problèmes de tolérance) ou est contre indiquée. L'objectif de la phase d'extension en ouvert est d'obtenir des données d'efficacité et de tolérance du benfluorex en association aux SU et si nécessaire à un 3 ème agent l'acarbose.

Méthodologie: étude multicentrique (63 centres et 7 pays), randomisée, stratifiée à « baseline » sur le taux d'HbA1c et le pays.

Critères d'efficacité. Principal : HbA1c à chaque visite. Secondaires :glycémie à jeun, insulinémie à jeun, paramètres lipidiques (TG, Hdl, LDL cholestérol). Analyse de la sécurité d'emploi : poids, tension artérielle, recueil des événements indésirables, etc.).

Résultats (phase en double aveugle seulement)

1 Caractéristiques démographiques des patients inclus

	benfluorex (n = 165)	placebo (n = 160)
Age (années)	62.9 ± 10.8	64.8 ± 10.3
Sexe (hommes/femmes)	86 79	68 92
Durée du diabète (années)	6.8 ± 5.8	7.5 ± 6.1
Indice de Masse Corporelle (kg.m²)	29.5 ± 3.7	29.3 ± 3.7
Présence d'un syndrome métabolique (%)	72.1	73.1
HTA (%)	68.5	70.6
Présence de complications		
Coronaropathie (%)	35.2	37.5
Néphropathie (%)	22.1	31.9
Neuropathie (%)	34.5	35.0
Rétinopathie (%)	10.9	12.5
HbA1c (%)	8.32 ± 0.83	8.32 ± 0.87
Glycémie à jeun (mmol/L)	9.87 ± 2.64	9.67 ± 2.39

Annexe 4-2

Note interne:

A noter: dose maximale de SU à l'entrée au mois égale à 50% de la dose maximale autorisée chez 86% des patients; 40% des patients prenaient un SU (glibenclamide 37%, gliclazide 19%).Plusieurs analyses en sous groupes étaient prévues dans cette étude: patients âgés de plus de 65 ans, Cl Cr < 80ml/mn, HbA&c de départ > 8%, analyse post hoc de la tolérance digestive.

Evolution de l'HbA1c (population générale, en fonction de l'âge, de l'HbA1c et de la fonction rénale.

Tableau 3 : Evolution de l'HbA1c dans la population FAS et dans les sous-groupes de patients sévères ou fragiles

		benfluorex			placebo			différence entre les groupes Δ (SE)
variable		n	HbA1c valeur initiale moyenne (DS)	différence pré-post traitement (ES)	n	HbA1c valeur initiale moyenne (DS)	différence pré-post traitement (ES)	
Population complète		151	8.54 (± 0.88)	-0.82 (0.08)	156	8.55 (± 0.97)	- 0.19 (0.11)	-1.01*** (0.13)
Sous-groupes	HbA1c> 8%	93	8.9 (± 0.53)	-1.15 (0.11)	89	8.96 (± 0.76)	-0.05 (0.15)	-1.10*** (0.18)
	Âge > 65 ans	70	8.39 (± 0.50)	-0.86 (0.10)	82	8.53 (± 0.87)	-0.05 (0.13)	-0.81*** (0.17)
	Clairance créat ≤ 80 mL/min	62	8.57 (± 0.76)	-0.78 (0.12)	78	8.63 (± 0.87)	- 0.27 (0.13)	-1.16*** (0.20)

*** p<0.001

Diminution de l'HbA1c de -0,82% par rapport à la valeur de base (ITT) après 18 semaines de traitement. Augmentation de l'HbA1c dans le groupe placebo: différence entre les 2 groupes de -1,01 (p< 0,001) en faveur de Médiator.

3. Evolution des principaux paramètres glycémiques et lipidiques

Tableau 4 : Evolution des principaux paramètres biologiques dans la population FAS

	benfluorex			placebo			différence entre les groupes
	N	valeur initiale moyenne (DS)	différence pre-post (ES)	n	valeur initiale moyenne (DS)	différence pré-post (ES)	Δ (ES)
Glycemie à jeun mmol/L	159	8.89 (± 3.57)	-1.22 (0.20)	156	9.71 (± 3.89)	0.51 (0.33)	-1.65*** (0.37)
HOMA- IR Index	157	9.62 (± 7.99)	-1.75 (0.50)	150	9.55 (± 7.95)	-0.42 (0.65)	-0.81**+
LDL cholesterol mmol/L	149	3.60 (± 0.89)	-0.27 (0.06)	152	3.52 (± 0.89)	0.04 (0.05)	-0.28*** (0.07)
Triglycerides mmol/L	151	2.56 (± 1.62)	-0.11+	152	2.73 (± 1.32)	0.05+	-0.16* (0.07)

***p< 0.001 **p<0.01 *p< 0.05 +test non paramétrique

Annexe 4-2

Evolution des autres paramètres:

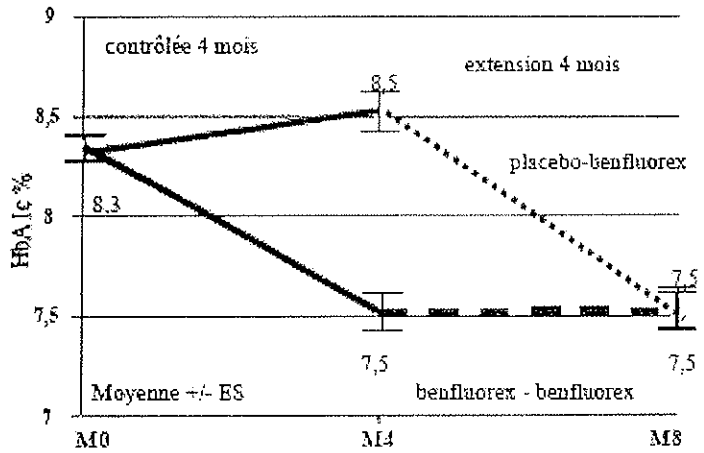
Diminution du poids observée dans les deux groupes de traitement: -1,3 kg sous Méditaor et -0,7 sous placebo (significative), amélioration de l'insulinorésistance, amélioration de la glycémie à jeun (significativement entre les 2 groupes) dès la 4ème semaine,

Paramètres lipidiques: diminution des TG de 7% (diminution modeste mais significative dans le groupe Médiator vs placebo). Diminution modeste du LDL, de -5,1ù sous Médiator versus +2,3% sous placebo. Variations du HDL-c non significatives.

Absence de modification de la Pression artérielle :

Analyses des résultats dans les sous groupes pré- définis: Baisse de l'HbA1c plus importante dans le groupe avec une HbA1c > 8% versus la population générale. Chez les patients avec une HbA1c < 8% à « baseline », diminution de -0,6% dans le groupe traité par Médiator versus +0,53% sous placebo. D'après la firme, la baisse de l'HbA1c est du même ordre de grandeur chez les patients âgés de plus de 65ans versus la population générale de l'essai. Idem résultats identiques chez les patients présentant une insuffisance rénale versus la population générale.

Figure 2 : Evolution de l'HbA1c pendant la période en double aveugle suivie de la période d'extension de l'étude



- Glycémie à jeun (mmol/L), moyenne (DS)

Groupe	Effectif	M0	M8–M0	M8–M4
BB	135	9.94 (2.4)	- 1.36 (2.6)	- 0.02 (2.1)
PB	145	9.61 (2.3)	- 1.10 (2.8)	-1.66 (2.7)

- HOMA-IR (index), moyenne (DS)

Groupe	Effectif	M0	M8–M0	M8–M4
BB	140	6.90 (8.5)	- 1.98 (6.6)	- 0.04 (3.5)
PB	142	6.34 (8.1)	- 1.55 (9.0)	-1.06 (7.1)

- LDL-cholestérol (mmol/L), moyenne (DS)

Groupe	Effectif	M0	M8–M0	M8–M4
BB	134	3.60 (0.8)	- 0.23 (0.7)	0.02 (0.6)
PB	146	3.53 (0.9)	- 0.14 (0.7)	- 0.14 (0.6)

- Triglycéridémie (mmol/L), moyenne (DS)

Groupe	Effectif	M0	M8–M0	M8–M4
BB	136	2.33 (2.0)	- 0.37 (1.5)	- 0.28 (2.1)
PB	146	2.13 (1.3)	- 0.24 (1.1)	- 0.25 (1.1)

Note d'évaluation :

1. Faisant suite à la réunion d'Octobre 2006, un avis a été demandé au Groupe Pré-Clinique de l'Afssaps sur la pertinence des modèles animaux proposées afin d'étudier les éventuels effets du benfluorex sur l'hypertension artérielle pulmonaire. Leurs conclusions feront l'objet d'un relevé d'avis spécifique.

2. Analyse des données d'efficacité soumises pour chacune des deux indications :

2.1. Indication en tant qu'« ***Adjuvant au régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours nécessaire*** ».

=> Le mécanisme d'action du benfluorex sur les lipides reste difficile à préciser malgré les études soumises :

- les effets in vitro les plus fréquemment retrouvés sont une inhibition de la synthèse des acides gras, entraînant une baisse des triglycérides dans certains modèles animaux. Néanmoins, de nombreuses autres substances donnent des résultats similaires dans les modèles animaux.

- dans les modèles animaux in vivo (Etude de Brindley), il est difficile de différencier les résultats sur le lipides de la diminution de la prise alimentaire dans le groupe des animaux traités.

Une inhibition de l'ACAT in vitro a été montrée mais son retentissement clinique n'est pas démontré ; les études utilisant des inhibiteurs de l'ACAT n'ont pas toutes rapporté une réduction du LDLc et une étude récente parue dans le NEJM en 2006 (ACTIVATE) a montré l'absence d'effet sur la progression de l'athérome évaluée par écho-endoscopie coronaire chez 408 patients avec CAD angiographiquement documentée.

- Les études cliniques des effets sur les paramètres lipidiques peuvent être scindées en deux groupes : celles antérieures à 1992 et celles postérieures à 1992. En effet, après cette date, les effets hypotriglycéridémiants du produit sont devenus plus discrets et plusieurs études ne montrent pas de différence par rapport au placebo.

A noter que les études anciennes comportaient un nombre de sujets faible (n <40), avec une dyslipidémie plus prononcée que dans l'étude Moulin (TG environ 4 mmol/l), avec des valeurs initiales des paramètres lipidiques pas toujours identiques entre les groupes des traitement (étude versus clofibrate de Graisely), les valeurs du LDL-cholestérol n'étaient pas toujours disponibles.

Une méta-analyse de l'efficacité sur les TG dans les études les plus récentes montre que l'action du produit sur les TG est inconstante et ne correspondant pas à ce qui est attendu pour une molécule avec cette indication. Sur 6 études (avec des effectifs variés, de 10 à 242 patients), mais comportant un placebo et un tirage au sort, 5 études ne montrent pas de diminution significative des TG par rapport au groupe placebo (Louvet, Tomasi, Moulin, Velusi, Del Prato, Biancchi).

Dans l'indication de traitement adjuvant des hypertriglycéridémies, l'étude Moulin montre une réduction de seulement 7% des triglycérides sous benfuorex (p = 0,027) et de 6% du LDLc (p = 0,001). La différence entre le groupe benfluorex et le groupe placebo à la 18ème semaine était de -0,28 mmol/l (0,10 g/l) pour le LDL et de – 0,16 mmol/l pour les triglycérides. La répercussion clinique de cette différence est très faible et inférieure à celles observée avec les autres hypolipidémiants (statines, ézétrol pour le LDL, fibrates pour les TG). De plus, aucune donnée de protection cardiovasculaire n'est disponible. A noter par ailleurs que la publication de l'étude Moulin dans la revue Diabetes Care (en 2006) ne fait pas mention de l'effet du benfluorex sur les TG, ni dans l'abstract ni dans la discussion.

Au total, les données d'efficacité soumises montrent une efficacité très modeste voire inexistante sur les triglycérides y compris dans l'étude Moulin récente, l'efficacité sur les autres paramètres lipidiques n'étant pas démontrée. A noter que dans les étude soumises, les paramètres lipidiques sont uniquement étudiées comme critères secondaires. Compte tenu de ces éléments il semble difficile de maintenir l'indication actuelle en comme « Traitement adjuvant des hypertriglycéridémies ». Des études complémentaires d'efficacité sur l'efficacité du benfluorex sur les paramètres lipidiques en tant que critère primaire seraient nécessaires afin de mieux étayer cette efficacité. De plus, compte tenu des alternatives thérapeutiques actuelles, le maintien de cette indication pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et en particulier sur les triglycérides et ayant démontré par ailleurs un efficacité en termes de prévention cardiovasculaire. Des études complémentaires versus placebo et comparatives seraient nécessaires chez des patients dyslipidémiques et/ou diabétiques.

2.2. Indication en tant qu '« ***Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale ».***

Pour rappel, dans cette indication, il avait été demandé à la firme de soumettre d'autres études pour valider cette indication. A cet effet, la firme a soumis en Septembre 2000 l'étude Del Prato pour laquelle seul le bras placebo a été considéré comme recevable, les résultats du bras versus metformine n'étant pas recevables compte tenu d'insuffisances méthodologiques relevées par les experts.

En 2002, il avait été demandé à la firme de réaliser une nouvelle étude évaluant l'effet du benfluorex en monothérapie et en association avec d'autres antidiabétiques oraux, en particulier chez des patients pour lesquels la metformine est contre-indiquée ou mal

tolérée.

L'étude Moulin (publiée dans Diabetes Care en 2006) est une étude multicentrique, internationale, randomisée en double aveugle, d'une durée de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par SU et intolérants ou ayant une contre indication à la metformine. Le critère principal était l'HbA1c ; les critères secondaires : insulinémie, glycémie à jeun, paramètres lipidiques, index d'insulino-résistance HOMA. Trois sous-groupes ont été analysés : HbA1c > 8%, âge > 65 ans et clairance de la créatininémie < 80ml/mn. Etude de supériorité avec une différence de 0.6% entre les groupes sur l'HbA1c.

Résultats :

Après 18 semaines de traitement, les résultats d'efficacité sur les paramètres glucidiques de cette étude montrent que :

- l'HbA1c est diminuée de -0.82% dans le groupe benfluorex (versus baseline) et de -1% versus le groupe placebo. 34.2% et 19% arrivent à une HbA1c ≤ 7% et > 6.5% contre 11% et 5% respectivement sous placebo. Baisse de l'HbA1c significative dès la 4ème semaine ; d'après la firme, l'effet est du même ordre entre les trois sous groupes pré définis ;
- l'insulinorésistance s'améliore significativement sous benfluorex ; la glycémie à jeun baisse significativement dès la 4ème semaine sous benfluorex.
- la perte de poids était de 1.3 kg sous benfluorex et de 0.7kg sous placebo ;
- noter, dans cette étude, la dose de SU utilisée n'était pas maximale puisqu'elle correspondant à la dose maximale tolérée soit ≥ 50% de la dose maximale de l'AMM chez 86% des patients.
- concernant les analyses en sous-groupes : la baisse de l'HbA1c est très faible chez les patients avec une HbA1c < 8% :-0.36% (-0.57 ;-0.15) sous benfluorex versus +0.53 % (0.25 ;0.80) sous placebo ;

En termes de sécurité d'emploi, dans cette étude, 53% des patients ont présenté un EI sous benfluorex et 51% sous placebo :

- les troubles neurologiques ont été plus fréquents sous benfluorex (9% versus 6.3%) ;
- les troubles digestifs sont rapportés chez 15.1% des patients sous benfluorex et 10% sous placebo : il s'agit d'une diarrhée la plupart du temps (trois fois plus fréquente sous traitement). Chez les patients intolérants à la metformine (n=184), 15.2% sous benfluorex versus 15.3% sous placebo ont présenté une EI de type gastro-intestinal. Chez les patients sans intolérance digestive à la metformine (n=142), 13.4% sous benfluorex et 4% sous placebo ont présenté des désordres gastro-intestinaux. Globalement la tolérance digestive est du même ordre que les patients soient intolérants ou non à le metformine ; une intolérance à la metformine en prédispose donc pas à une intolérance au benfluorex ;
- Aucune modification significative de la pression artérielle, de la fréquence cardiaque, des paramètres biologiques ou à l'ECG n'a été observée ;
- Hypoglycémies : 20 patients rapportent 37 épisodes (sans confirmation biologique). Elles ont tendance à être plus fréquents sous benfluorex que sous placebo ce qui est attendu compte tenu de la baisse plus importante de l'HbA1c sous benfluorex. Aucun épisode n'a été considéré comme sévère. Elles seraient cependant légèrement plus fréquentes chez les patients > 65 ans et chez les patients ayant une clairance de la créatinine < 8 ml/min.

Annexe 4-2

Commentaires :

- les données de compliance au traitement ne sont que partiellement fournies ;
- d'un point de vue méthodologique, la validité du modèle utilisé pour l'analyse de la variation de l'HbA1c est douteuse dans la mesure où des tests viennent rejeter l'hypothèse de normalité des résidus. L'impact de ces résultats aurait dû être discuté et des modèles ne requérant pas la normalité des résidus auraient dû être utilisés. Cette remarque vaut non seulement pour l'analyse du critère principal mais également pour l'analyse du glucose, de l'insuline et du HDL-cholestérol.
- Concernant la prise en compte de covariables, on peut noter que l'analyse de la variation de l'HbA1c a été ajustée sur la valeur de l'HbA1c à la baseline, toutefois il semblerait que l'ajustement soit réalisé avec la variable utilisée pour stratifier la randomisation (≤ ou > 8%). Les résultats devraient également être ajustés sur la variable continue (et pas seulement qualitative).
- On peut ajouter que si les résultats de la variation de l'HbA1c sont présentés avec ajustement sur la variation de poids, on ne sait pas s'ils sont également ajustés sur la valeur de l'HbA1c à la baseline et le centre (ou la zone géographique).
- A noter, la définition des hypoglycémies dans l'étude Moulin serait à préciser ;

A noter, d'autres études sont soumises dans le dossier par la firme mais ne sont pas considérées comme recevables compte tenu du faible nombre de patients inclus.

En conclusion :

Les experts sont unanimes pour affirmer que les données d'efficacité du benfluorex sur les paramètres lipidiques ne sont pas suffisantes pour maintenir cette indication.

En ce qui concerne l'indication relative au métabolisme glucidique, les données soumises et en particulier les résultats de l'étude Moulin récente (en seconde intention, en association à un SU) semblent montrer une efficacité sur les paramètres glucidiques, en particulier l'HbA1c et ceci indépendamment de la perte de poids. Néanmoins, aucune conclusion définitive ne peut être portée sur cette efficacité compte tenu des réserves méthodologiques soulevées par les experts (voir ci-dessus). D'un commun accord, les experts sont cependant d'avis que bien qu'obsolète, l'indication telle que libellée peut être maintenue dans l'attente d'un dépôt complet de données d'efficacité et de sécurité d'emploi sur les paramètres glucidiques (études en cours, dépôt de dossier prévu en 2007 d'après la firme). A noter enfin, aucune demande de modification de cette indication n'a été demandée par la firme dans le cadre de cette réévaluation du bénéfice/risque.

AVIS DU GT AD HOC SUR LES MEDICAMENTS UTILISES EN DIABETOLOGIE, ENDOCRINOLOGIE, UROLOGIE ET GYNECOLOGIE N° 6 DU 21 DECEMBRE 2006 :

- **AVIS DEFAVORABLE** au maintien de l'indication : *« Adjuvant au régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours nécessaire. Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée».*

En effet, les données soumises montrent une efficacité très modeste voire inexistante sur les triglycérides y compris dans l'étude Moulin récente ; l'efficacité sur les autres paramètres lipidiques n'étant pas démontrée. A noter que dans les études soumises, les paramètres lipidiques sont uniquement étudiées comme critères secondaires et non comme critères primaires comme cela est requis pour des études cliniques visant à l'obtention d'une telle indication. Compte tenu de ces éléments il semble difficile de maintenir l'indication actuelle en comme « Traitement adjuvant des hypertriglycéridémies ». Des études complémentaires d'efficacité sur l'efficacité du

Annexe 4-2

benfluorex sur les paramètres lipidiques en tant que critère primaire seraient nécessaires afin de mieux étayer cette efficacité. De plus, compte tenu des alternatives thérapeutiques actuelles, le maintien de cette indication pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et en particulier sur les triglycérides et ayant démontré par ailleurs un efficacité en termes de prévention cardiovasculaire.

- **AVIS FAVORABLE** au maintien de l'indication suivante : « *Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale* ». En effet, les données soumises et en particulier celles de l'étude Moulin semblent montrer une efficacité sur les paramètres glucidiques, en particulier l'HbA1c et ceci indépendamment de la perte de poids.

Néanmoins, aucune conclusion définitive ne peut être portée sur cette efficacité compte tenu des réserves méthodologiques soulevées concernant la validité du modèle utilisé pour l'analyse du critère principal, la manière de prendre en compte la valeur de l'HbA1c à la baseline, et la prise en compte simultanée de la variation de poids, de la zone géographique et de la valeur de l'HbA1c à la baseline.

D'un commun accord, les experts sont cependant d'avis que bien qu'obsolète, l'indication telle que libellée peut être maintenue en l'état dans l'attente d'un dépôt complet de données d'efficacité et de sécurité d'emploi plus solides du benfluorex permettant de revoir le libellé de cette indication.

Les rubriques concernées du RCP et de la Notice sont modifiées en conséquence comme suit :

ANNEXE I

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé de 700 mg

Pour les excipients, voir rubrique 6.1..

3. FORME PHARMACEUTIQUE

Comprimé enrobé

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

~~- Adjuvant du régime adapté dans les hypertriglycéridémies;~~
- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque : L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

4.2 Posologie et mode d'administration

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:

- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.

En association à un régime adapté, Médiator constitue un traitement *adjuvant* : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

4.3. Contre-indications

- Hypersensibilité au chlorhydrate de benfluorex ou à l'un des constituants ;
- Pancréatites chroniques avérées.

4.4. Mises en garde et précautions particulières d'emploi

Les troubles métaboliques relevant d'un traitement par Médiator sont essentiellement observés chez l'adulte. La prescription de Médiator n'est donc pas justifiée chez l'enfant.

Si, après une période d'administration de quelques mois (3 à 6 mois), une diminution satisfaisante de concentrations sériques de lipides ou de glucose n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

4.6. Grossesse et allaitement

Grossesse:
Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.
En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un

éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.
En conséquence, par mesure de prudence, il est préférable de ne pas utiliser ce médicament pendant la grossesse. En cas d'exposition fortuite, il conviendra d'interrompre ce traitement.

Allaitement
En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

L'attention des conducteurs est attirée sur la somnolence pouvant survenir lors de l'utilisation de ce médicament.

4.8. Effets indésirables

Les effets secondaires suivants ont été observés :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, confusion, somnolence ou états vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles;

- très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, oedème de Quincke;

- élévation des enzymes hépatiques, hépatite (très rare).

4.9. Surdosage

En cas d'absorption massive, le traitement sera uniquement symptomatique: lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience ainsi que des fonctions respiratoire et cardiaque.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

HYPOCHOLESTEROLEMIANT ET HYPOTRIGLYCERIDEMIANT
Code ATC : C10AX04

~~Actions de Médiator sur le métabolisme lipidique:~~
~~Chez l'animal (rat), Médiator diminue l'absorption intestinale des triglycérides.~~
~~Cet effet a été également observé chez l'homme en pharmacologie clinique et serait dû à une diminution de l'activité de la lipase pancréatique.~~

~~Les effets suivants ont été également observés chez l'animal:~~
~~- diminution de la synthèse hépatique des triglycérides et du cholestérol, *in vitro* et *in vivo* (rat);~~
~~- diminution de la stéatose hépatique induite par des régimes riches en lipides, riches en glucides (rat obèse) ainsi qu'au cours du diabète expérimental (rat);~~
~~- limitation de l'incorporation du cholestérol dans la paroi artérielle (lapin).~~
~~Ces différents mécanismes pourraient expliquer en partie la diminution du cholestérol et des triglycérides observée chez l'homme.~~

Annexe 4-2

Actions de MEDIATOR sur le métabolisme glucidique:

Chez l'animal, les effets suivants ont été observés:

- facilitation de la pénétration et de l'utilisation cellulaire du glucose (rat);

- diminution de l'hyperglycémie chez le rat diabétique (insulinoprive ou non), diminution de l'hyperglycémie (mesurée par l'aire d'HPO) chez le lapin.

MEDIATOR n'a pas d'action sur l'insulino-sécrétion; la survenue d'hypoglycémie est peu probable.

Effet complémentaire de MEDIATOR:

Une baisse de l'uricémie d'environ 14 % a été observée chez des patients obèses hyperuricémiques traités par Médiator en association à un régime adapté.

5.2 Propriétés pharmacocinétiques

L'absorption gastro-intestinale est rapide et totale.

Après administration orale, le pic de concentration plasmatique est maximal entre 1 et 2 heures.

L'élimination est rapide et totale par voie urinaire. Huit heures après l'absorption, 74 % de la dose administrée est éliminée dans les urines.

L'élimination se fait en 2 phases :

- une première phase rapide (60 % en 3 ou 4 heures);
- une seconde phase lente, de 36 heures environ.

5.3 Données de sécurité précliniques

Sans objet.

Annexe 4-2

ANNEXE III B

NOTICE

.....

1. QU'EST-CE QUE MEDIATOR 150 mg, comprimé enrobé ET DANS QUEL CAS EST-IL UTILISÉ ?

MEDIATOR 150 mg, comprimé enrobé contient du chlorhydrate de benfluorex.

MEDIATOR 150 mg se présente sous la forme de comprimés enrobés.

Boîtes de 10, 20, 24, 30, 60 et 100 comprimés.

Ce traitement est en préconisé comme adjuvant à un régime adapté :

~~- dans les hypertriglycéridémies *(taux de lipides élevés dans le sang)* ;~~

- chez les diabétiques avec surcharge pondérale *(taux de sucre élevé dans le sang)*.

2. INFORMATIONS NÉCESSAIRES AVANT D'UTILISER MEDIATOR 150 mg, comprimé enrobé

MEDIATOR 150 mg, comprimé enrobé NE DOIT JAMAIS ETRE UTILISE dans les cas suivants :

- allergie au chlorhydrate de benfluorex ou à l'un des composants du produit;

- en cas de pancréatite chronique *(insuffisance de fonctionnement chronique du pancréas)*.

MISES en GARDE et PRECAUTIONS PARTICULIERES D'EMPLOI avec MEDIATOR 150 mg, comprimé enrobé :

Un régime alimentaire adapté doit être poursuivi pendant toute la durée du traitement.

Si après une période de plusieurs mois (3 à 6 mois), une diminution des concentrations ~~de lipides ou~~ de glucose (sucre) dans le sang n'est pas obtenue, votre médecin pourra envisager d'autres moyens thérapeutiques adaptés à votre cas.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase *(maladies métaboliques rares)*.

Grossesse/Allaitement:

Il est préférable de ne pas utiliser ce médicament pendant la grossesse ou au cours de l'allaitement.

Si vous découvrez que vous êtes enceinte pendant le traitement, consultez votre médecin car lui seul peut juger de la nécessité de le poursuivre.

Conduite de véhicules et utilisation de machines:

L'attention est attirée sur le risque de somnolence pouvant survenir avec ce médicament.

Sportifs:

Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

Liste des excipients à effet notoire:

Saccharose.

Prise ou utilisation d'autres médicaments:

Sans objet.

3. COMMENT PRENDRE MEDIATOR 150 mg, comprimé enrobé ?

Posologie:

RESERVE A L'ADULTE

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:

- 1ère semaine: 1 comprimé par jour, au cours du dîner;

- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;

- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

La posologie peut-être ramenée à 2 comprimés par jour, voire 1 comprimé par jour, en fonction des résultats biologiques.

DANS TOUS LES CAS, SE CONFORMER STRICTEMENT A L'ORDONNANCE DE VOTRE MEDECIN.

Si vous avez pris plus de MEDIATOR 150 mg, comprimé enrobé que vous n'auriez d :

Les signes de surdosage peuvent être des troubles digestifs (nausées, vomissements, diarrhée), une sensation vertigineuse voire une somnolence. En cas d'apparition de ces troubles, consultez votre médecin ou votre pharmacien.

Si vous oubliez de prendre MEDIATOR 150 mg, comprimé enrobé:

Ne prenez pas de double dose pour compenser la dose simple que vous avez oubliée de prendre.

Effets pouvant apparaître lorsque le traitement par MEDIATOR 150 mg, comprimé enrobé est arrêté :

Sans objet.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS avec MEDIATOR 150 mg, comprimé enrobé ?

Comme tous les médicaments, MEDIATOR 150 mg, comprimé enrobé est susceptible d'avoir des effets indésirables :

- troubles digestifs: nausées, vomissements, diarrhée, maux d'estomac ;

- sensation de fatigue, voire somnolence ;

- confusion ;

- sensations vertigineuses.

Ces effets ont été observés à des posologies supérieures à 3 comprimés par jour et varient en fonction de la susceptibilité individuelle des patients.

- très rares cas de manifestations allergiques : éruptions cutanées soudaines, urticaire, malaise brutal avec hypotension (diminution de la pression artérielle), œdème de Quincke (brusque gonflement du

visage et du cou). Dans ce cas, le traitement devra immédiatement être interrompu.

- élévation des enzymes hépatiques (anomalies biologiques au niveau du foie). Très rares cas d'hépatite.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

Annexe 4-2

MEDIATOR 150, comprimé

(Benfluorex)

Revue des données d'efficacité

Conclusions du Groupe DEUG

Agence française de sécurité sanitaire des produits de santé

afssaps

C. REY-QUINIO

COM d'AMM du 5 Avril 2007

MEDIATOR :

Indications actuelles

afssaps

AMM octroyée en 1976, 1ère tranche de validation en 1987 (hypertriglycéridémies), 2nde tranche en 1990 (indication « diabète »:

- Adjuvant au régime adapté dans les hypertriglycéridémies.

- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Annexe 4-2

MEDIATOR et activité hypolipémiante

afssaps

Le mécanisme d'action sur les lipides reste difficile à préciser malgré les données soumises :

- Effets *in vitro* : inhibition de la synthèse des acides gras entraînant une baisse des TG (modèles animaux)

- Etudes *in vivo* chez l'animal (Brindley): inhibition de l'ACAT mais retentissement clinique non démontré (pas de diminution du LDL-c) et effet indépendant de la prise alimentaire non démontré

MEDIATOR et lipides Données d'efficacité clinique (1)

afssaps

10 études cliniques soumises :

- Etudes versus placebo (entre 1978 et 2006) anciennes à l'exception de l'étude MOULIN
=> au total : 394 patients traités
Remarques : faible nombre de patients, dyslipidémie variable selon les études, LDL-c non toujours disponible
Etude MOULIN : diminution de -7% des TG et de -6% du LDL-c

- 4 études versus produits de référence (fibrates)
=> 163 patients traités présentant une hyperlipidémie (IIa, IIb, IV)

Annexe 4-2

MEDIATOR et lipides
Données d'efficacité clinique (2)

afssaps

Méta-analyse de l'efficacité de MEDIATOR sur les triglycérides :
- 6 études (Louvet, Tomasi, Moulin, Velusi, Del Prato et Biancchi)
- effectifs variés de 10 à 242 patients
- études comportant un placebo, et TAS

=> 5 études sans effet sur les TG versus placebo
=> diminution inconstante des TG, ne correspondant pas à l'effet attendu pour une molécule dans cette indication
=> efficacité sur les autres paramères lipidiques non démontrée

Au total, **efficacité très modeste sur les TG** et **non démontrée sur les autres paramètres lipidiques** (paramètres uniquement étudiés comme critères secondaires)

MEDIATOR
et activité hypoglycémiante

afssaps

Plusieurs mécanismes d'action évoqués :
- Action sur le **métabolisme du glycogène** (rat): augmentation de la synthèse du glycogène, **diminution de la glycogénolyse** stimulée par le glucagon (Melin)
- Diminution de la **production hépatique de glucose** et **effets sur la néoglocogenèse** (Tielens, Zorzano)
- Amélioration de la **sensibilité à l'insuline** (4 études: Brindley, Portha, Serrasas et Storlien)
- **Amélioration de l'insulino-résistance musculaire** avec **effet de majoration du transporteur GLUT-4** (Sevilla, Storlien, Zorzano er l'oxydation du glucose(Bailey)
- **Pas d'effet sur la sécrétion basale d'insuline** (rat normal ou diabétique)

=> **Effet insulino- sensibilisateurs chez l'Homme** avec **effet sur les transporteurs de glucose, effet direct sur le foie** et enfin **réduction du contenu musculaire en TG.**

Annexe 4-2

MEDIATOR et glucides
Données d'efficacité clinique (1)

afssaps

Etudes anciennes analysées lors de la validation de l'indication en 1990 dans différentes populations :

3 études versus placebo retenues par la firme (Velussi, Tomassi et Louvet).
HbA1c : diminution de – 0.8 (Tomassi) sous régime seul , sous régime seul + SU de -0.9% (Velussi) et de -1.7% (Louvet)

Etude Del Prato versus placebo et versus metformine (1998):
- 0.86% entre le groupe placebo et le groupe benfluorex mais qualité de l'essai médiocre (défauts méthodologiques)

Etude MOULIN
Méthodologie (1)

afssaps

Méthodologie: étude multicentrique, randomisée en DA de 18 semaines de l'efficacité et la sécurité d'emploi de 450 mg/jour de benflurex vs placebo chez 325 patients diabétiques de type 2 mal équilibrés (HbA1c entre 7 et 10%) **par un SU, ou intolérants ou ayant une CI à la metformine.**
Deux phases :
- période en DA de 18 sem.: supériorité du benfluorex vs placebo sur l'HbA1c (différence attendue de 0.6%)
- période en ouvert de 16 sem. : données de safety à long terme en association à un SU ou à l'acarbose
Critères d'évaluation: HbA1c, GAJ, insulinémie à jeun/Critères secondaires (TG, HDL, LDL-c)
3 sous-groupes : HbA1c > 8%, âge > 65 ans et clairance de la créatini. < 80ml/ml

Annexe 4-2

Etude MOULIN
Méthodologie (2)

afssaps

METHODOLOGIE

M0 — M4 — M8

SU dose maximale tolérée

Benfluorex + SU

Placebo + SU

Benfluorex + SU

Critères d'inclusion :
diabétiques de type 2, âge > 18 ans
Surpoids : IMC de 25 à 40 kg/m2
Insuffisamment contrôlés : HbA1c de 7 à 10 %
Sous dose maximale tolérée de SU depuis 2 mois Intolérance ou contre-indication à la metformine

COM d'AMM du 05-04-2007

Etude MOULIN
Résultats (1)

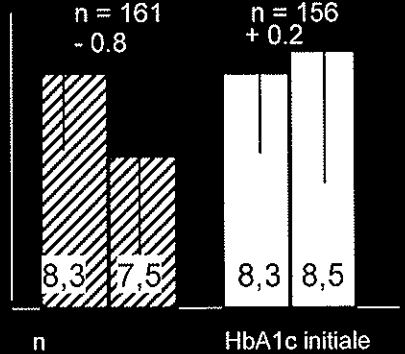
afssaps

EFFICACITE : HBA1c – ITT

benfluorex versus placebo en ITT : 97% des inclus

Δ HbA1c: - 1.0%
p < 0,001

Moyenne +/- DS



Δ vs placebo			
Per Protocol :	265	8.3	- 1.1
Age > 65 ans	152	8.3	- 0.8
HbA1c > 8%	182	8.9	- 1.1

COM d'AMM du 05-04-2007

Annexe 4-2

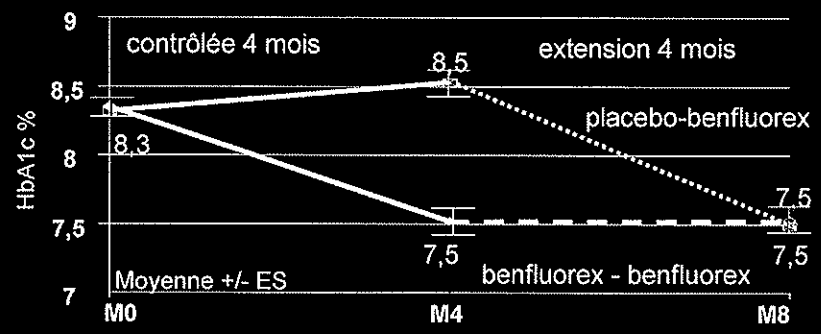
Etude MOULIN

Résultats (2)

afssaps

EVOLUTION DE L'HbA1c

Effet maintenu jusqu'à 8 mois



L'effet de benfluorex est reproductible dans le groupe initialement traité par placebo

MEDIATOR et glucides

En résumé ....

afssaps

- Diminution de l'HbA1c de - 0.82% dans le groupe benfluorex (vs baseline) et de -1% vs placebo
- Baisse signifcative dès la 4ème semaine, identique dans les 3 sous-groupes étudiés
- HbA1c ≤ 7% chez 34.2% sous benfluorex et 11% sous placebo
- HbA1c > 6.5% chez 19% sous benfluorex et 5% sous placebo
- GAJ significativement diminuée dès la 4ème semaine
- Perte de poids de 1.3 kg sous benfluorex et 0.7 kg sous placebo
- Baisse de l'HbA1c très faible pour HbA1c < 8% soit -0.36% sous benfluorex et +0.53% sous placebo
=> L'efficacité en seconde intention en association à un SU semble démontrée et ceci indépendemment de la perte de poids MAIS réserves méthodologiques soulevées par les experts

Annexe 4-2

MEDIATOR
Libellé d'indication retenu :

afssaps

- Adjuvant au régime adapté dans les hypertriglycéridémies.

- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

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COM d'AMM du 05-04-2007

Annexe 4-3

COMMISSION d'AMM N° 419 DU 5 AVRIL 2007

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoire SERVIER

Demande déposée le

Principe actif:	**Benfluorex**
Caractère d'originalité	**Réévaluation de Bénéfice Risque**
Classe ATC:	**Système cardio-vasculaire/Hypolipémiants (C10A: hypocholestérolémiants et hypotriglycéridémiants)**

TYPE DE DEMANDE:

Faisant suite à la demande de réévaluation de bénéfice Risque de la Commission Nationale de Pharmacovigilance de Juin 2006, une revue des études d'efficacité dans les deux indications actuelles de l'AMM a été déposée par la firme.

Pour rappel, MEDIATOR (chlhorydrate de benfuorex) est commercialisé depuis 1987 dans les indications suivantes:

- *« Adjuvant au régime adapté dans les hypertryglycéridémies. La poursuite du traitement est toujours nécessaire.*
- *Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.*

Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée».

HISTORIQUE DE L'EVALUATION DES DONNEES RELATIVES AU MEDIATOR

- Date d'AMM : 16-07-1976

- 1995. Inscription sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes. Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables de ces produits et étant donné les restrictions de leur délivrance, le CTPV a craint une dérive de l'utilisation du benfluorex comme anorexigène.

- 1998: 1ère enquête de Pharmacovigilance. Présentation des effets indésirables en CTPV (plusieurs séances) en 1998 ainsi qu'au groupe Européen de PV le 30-11-2000, entraînant des modifications de la rubrique 4.8. du RCP (ajout de « confusion » comme effet indésirable».

- 1987: validation de la 1ère tranche dans l'indication « hypertriglycéridémies »

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- **1990 :** dépôt du dossier de la 8ème tranche de validation dans l'indication en « diabétologie » ; nombreux échanges entre l'Afssaps et la firme entre 1990 et 1995 sur la nature des données à soumettre afin de valider cette indication (type d'étude, population cible, etc.), aboutissant finalement en 1998 au dépôt de l'étude Del Prato (étude de l'efficacité du benfluorex versus placebo et metformine sur les paramètres glucidiques (voir ci-dessous données cliniques). En attente de cette étude, l'indication telle que libellée lors de l'octroi de l'AMM a été maintenue.

- **Septembre 2000:** demande d'extension d'indication au «*Diabète de type II insulino-dépendant, en association au régime adapté, lorsque ce régime n'est pas suffisamment suffisant pour rétablir à lui seul l'équilibre glycémique* ». Une seule étude de phase III **(Etude Del Prato)**, randomisée, en double insu, benfluorex versus placebo et metformine a été soumise à l'appui de cette demande (A noter, cette étude réalisée a été réalisée à la demande de l'Afssaps; protocole revu en concertation avec l'Afssaps). Un avis défavorable a été émis par le Groupe de Travail PTC2 ainsi que par la COM d'AMM. Après recours de la firme de cette décision, cet avis a été maintenu par la COM d'AMM. En effet, compte tenu des défauts de la qualité méthodologique de cet essai (ayant l'objet par ailleurs d'une inspection), aucune conclusion n'a pu être formulée sur la taille de l'effet: i) du benfluorex versus placebo; ii) du benfluorex versus metformine (non-infériorité non démontrée : déséquilibre des taux d'HbA1c entre les groupes à l'inclusion, 68% seulement inclus dans l'analyse per protocole, 25% de patients inclus à tort). A noter également, aucune efficacité sur les paramètres lipidiques n'a été mise en évidence dans cette étude. En conclusion, la COM d'AMM (20-09-2002) a demandé qu'une étude évaluant l'efficacité du benfulorex en monothérapie et en association avec d'autres antidiabétiques oraux soit effectuée; l'association devant être également étudiée chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisants rénaux, sujets âgés)

- 2004-2005/Seconde enquête de Pharmacovigilance

Cette 2nd enquête fait suite à plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique rapportés avec le benfluorex. De ce fait, une actualisation des données relatives aux troubles neuro-psychiatriques observés avec cette spécialité a été décidée. L'enquête a ensuite été étendue aux hypertensions artérielles pulmonaires du fait de la notification d'un cas d'HTAP associé à la prise de benfluorex. Les conclusions de la CNPV sont les suivantes:

1. en ce qui concerne les troubles neuro-psychiatriques: « *cette enquête confirme la réalité du risque de survenue de « confusions » en présence de Médiator. Il est proposé que cet effet, déjà mentionné dans le RCP soit détaillé comme suit :* ***« troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) ».***
2. en ce qui concerne l'HTAP: « *compte tenu de l'incidence des HTAP idiopathiques (1 à 2 millions et par an), le nombre de cas d'HTAP idiopathique rapportés dans l'enquête ne constitue pas un signal significatif de toxicité du Mediator dans la classe organe cardio-vasculaire* ».

La discussion en CNPV (29-11-2005, adoptée le 16-06-2006) a par ailleurs porté sur les éléments suivants (extrait):

Les ventes de Médiator en Europe sont réalisées en quasi totalité en France. Les données DOREMA d'avril 2005 montrent une utilisation dans 46,3% dans les dylipidémies et dans 8,3% dans d'autres indications. L'effet anorexigène du benfluorex n'a pas été démontré. Toutefois, les membres de la CNPV craignent un mésusage, en particulier dans l'obésité. Dans ce contexte, une étude d'utilisation de prescription serait utile.

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Il est à noter que le renouvellement quinquennal du produit intervient dans 2 ans en France et que des données d'efficacité dans le diabète existent mais restent limitées et mériteraient d'être réévaluées.

Le bilan de pharmacovigilance confirme les données de sécurité d'emploi du Médiator déjà connues. Les effets neuro-psychiatriques décrits actuellement dans le RCP sous le terme « confusion » doivent être détaillés. Il n'y a pas actuellement assez de données pour affirmer l'existence de syndrome de sevrage. Le faible nombre de cas décrits d'HTAP idiopathique associés au Médiator doit être relativisé par rapport à la sous-notification habituelle en pharmacovigilance. Afin d'évaluer au mieux les risques potentiels de l'utilisation de Médiator, il conviendrait de réaliser:
i) une étude d'utilisation/prescription de Médiator;
ii) une étude expérimentale sur un modèle animal permettant d'évaluer le potentiel de Médiator à engendrer des HTAP;
iii) une étude au niveau des Centres d'évaluation et d'information sur la pharmacodépendance (CEIP) afin d'évaluer un éventuel problème de pharmacodépendance. A ce titre, une saisine de la Commission Nationale des stupéfiants et psychotropes sera effectuée.
Enfin, il a été proposé d'étudier la possibilité d'interroger les registres d'HTAP existant dans 17 centres, afin de rechercher, dans une étude rétrospective cas-témoins, le rôle éventuel du benfluorex.
Au vue des résultats présentés et des discussions, la CNPV a décidé une réévaluation de la balance Bénéfice-Risque de Médiator.

13 Octobre 2006/Réunion firme/Afssaps (PV, SURBOUM, PTC2/CRPV de Besançon)/Discussion des modalités de mise en oeuvre des études demandées par la CNPV, en particulier : i) étude sur un modèle animal d'HTAP; ii) étude d'utilisation-Prescription de Médiator.

=> Lors de cette réunion ont été présentés les types de modèle expérimentaux in vivo existants d'HTAP (modèle de stimuli patho-physiologique comme l'hypoxie aïgue ou chronique chez le rat ou la souris, stimulis chimiques comme la manocrotaline chez le rat, les modèles dits génétiques comme le rat Fawn-Hooded)

La firme retiendrait plus particulièrement un modèle d'étude de l'effet du benfluorex en conditions d'hypoxie ou de normoxie avec études des paramètres hémodynamiques, de l'index d'hypertrophie ventriculaire droit et du « remoduling » vasculaire pulmonaire (ou analyse histologique de la muscularisation des artérioles.

=> Données relatives à la commercialisation. A ce jour, le produit reste commercialisé dans 6 pays : Grèce, France, Pologne, Malte, Luxembourg et Chypre. L'Espagne et l'Italie n'ont pas demandé de renouvellement de l'AMM lors du dernier RQ dans ces deux pays.

=> Données de prescription. La firme a présenté des données de prescription issues de l'observatoire de prescriptions Thalès. 5 groupes ou populations pour lesquels Mediator est prescrit ont été identifiés (deux périodes d'observation: de 05/04 à 04/05 et de 05/05 à 04/05).
A - Patients dyslipidémiques +/- 50% des patients traités
B – Patients diabétiques de type 2 soit 1,8% (à confirmer)
C (A+B) - soit 15,2%
D – Ni A ni B (patients en **surpoids ou obèses, soit 14,3%)**
E – Ni A ni B + autre diagnostic (non précisé, HTA? Rapport Taille/Hanche élevé ?), **soit 8,1%.**
A noter, les chiffres de prescription sont stables pour les deux périodes étudiées.
Au total, +/- 20% de patients reçoivent du Médiator hors indications de l'AMM (14,3% +

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8,1%). Des précisions seraient à apporter sur cette population de patients traités (leur poids?, sont-ils obèses ou non?, Quelles sont les raisons de la prescription de Médiator (prescription saisonnière à l'automne ou non?). D'autres réunions sont envisagées avec la firme afin d'étayer les différents points discutés lors de cette réunion.

CONTENU DU DOSSIER:

En vue de la réévaluation de bénéfice Risque, le dossier déposé par la firme repose essentiellement sur des données d'études anciennes et ayant déjà l'objet d'expertise depuis la commercialisation du produit. Seule une nouvelle étude clinique : l'étude MOULIN apporte de nouvelles données dans l'indication en « diabétologie ».

Le rapport est structuré en 3 parties:

1. Un rappel du mécanisme d'action supposé de la molécule;
2. Des données d'efficacité dans chacune des 2 indications actuelles, avec une analyse plus particulière des données de l'étude MOULIN (indication « diabétologie »).
3. Une synthèse des données de sécurité d'emploi issues des études cliniques et de la pharmacovigilance.

1. MECANISME D'ACTION DE MEDIATOR

1. Activité hypoglycémiante

La firme met en avant des propriétés insulino-sensibilisatrices chez l'Homme avec un effet sur les transporteurs de glucose, un effet direct sur le foie avec augmentation de la synthèse du glycogène et inhibition de la néoglucogenèse et enfin une réduction du contenu musculaire en triglycérides. Les données suivantes sont soumises:

=> Etude in vitro sur modèles cellulaires chez le rat => action sur le métabolisme du glycogène : augmentation de la synthèse du glycogène et diminution de la glycogénolyse stimulée par le glucagon (Melin, 1991).

=> Diminution de la production hépatique de glucose et effet sur la néoglucogenèse (Tielens 1993 et Zorzano 1996 et Kohl 2002

=> 4 études sur l'amélioration de l'insulinosensibilité (Brindley 1991, Portha 1993, Serrasas 1993 et Storlien 1993).

=> 4 études sur l'amélioration de l'insulino-résistance musculaire avec effet de majoration du transporteur GLUT-4 (Sevilla 1999, Storlien 1993, Zorzano 1996) et l'oxydation du glucose (Bailey 1992)

=> Pas d'effet sur le sécrétion basale d'insuline (chez le rat normal ou diabétique (Portha 1993 et Serradas 1993). Voir Note interne ci-dessous.

Note interne:

D'après la firme, ces données permettent de conclure que le benfluorex a un effet insulino-sensibilisateur chez l'Homme démontré par les 3 études citées de clamp hypersinsulinique. Un effet direct sur le foie avec augmentation de la synthèse du glycogène et inhibition de la néoglucogenèse aurait également été mis en évidence.

Le benfluorex améliorerait l'insulino-sensibilité musculaire avec un effet sur les transporteurs de glucose. Enfin, la firme souligne que le mécanisme d'action du benfluorex diffère de celui des autres insulino-sensibilisateurs comme la metformine et les glitazones.

En effet, la mesure de l'expression des enzymes clés contrôlant le métabolisme du glucose et des acides gras libres après 48 heures d'incubation aurait montré une diminution franche de la CPT1, enzyme responsable de l'entrée des acides gras dans la mitochondrie, et de la PEPCK impliquée dans l'activation de gluconéogenèse. Cet effet serait propre à Médiator (déjà mis en exergue en 2000) puisque dans les mêmes conditions expérimentales, l'action inhibitrice de la metformine est indépendante de l'oxydation des acides gras et semble être en rapport avec une augmentation du potentiel redox de la cellule hépatique, les glitazones (étude avec la troglitazone) freine l'activation des acides gras en inhibant l'acyl-CoA synthase, réaction préalable à leur oxydation.

Il est noter qu'en 2000 (lors de la soumission de l'étude versus placebo et metformine, des données relatives à l'activité hypoglycémiante avaient déjà été soumises. D'après les experts mandatés, les données du dossier ne permettaient pas à l'époque de conclure à une augmentation de la sensibilité à l'insuline sous benfluorex Les conclusions suivantes avaient été émises:

- l'absence d'effet direct de Médiator sur la sécrétion d'insuline induite par le glucose ou l'arginine avait été confirmée in vitro à partir de cellules de pancréas isolées perfusées de rats témoins et de rats diabétiques (Serradas, Portha 1993);

- 3 études de pharmacodynamie contrôlées en double aveugle utilisant des techniques de clamp hyperinsulinique euglycémique (Biancchi 1993, Ricchio 1993) et isoglycémique (De Feo 1993 ont étudié l'utilisation périphérique de glucose. Deux de ces études ont étudié la production hépatique de glucose; une (De Feo) a montré une diminution de cette production; l'autre étude (De Ricchio) n'a pas mis en évidence de variation. Une étude complémentaire de Bianchi réalisée en 1996 n'avait pas montré d'amélioration de la consommation de glucose sous benfluorex. Sur la base de ces éléments, aucune certitude

Tableau 1 Evolution de la sensibilité à l'insuline

	Nb patients	Trait[*]	Valeurs basales	Valeurs finales	p**
Riccio Captation du glucose (µmol/kg/min) (40 dernières minutes du clamp, perfusion d'insuline qsp insulinémie=480 pmol/L au dessus de la valeur basale)	14	Med Pla p*	26.8±1.4 29.7±3.4	34.5±1.1 27.2±4.0	<0.05 NS -
Bianchi[§] Taux de perfusion de glucose (µmol/kg/min) (30dernières minutes du clamp, perfusion d'insuline 0.1 U/kg/h)	10	Med Pla	- -	5.36±0.49 3.87±0.83	- -
De Feo Taux de perfusion de glucose (µmol/kg/min) (2 dernières heures du clamp, perfusion d'insuline 3 mU/kg/min, *soit0.06U/kg/h*)	20	Med Pla p*	28.5±0.93 27.6±2.00 0.847	32.2±0.62 27.2±2.00 <0.001	0.004 0.307

*MEDIATOR® *vs placebo* ; ** valeurs finales vs valeurs basales
§ Etude croisée, clamps réalisé en fin de période, pas de valeurs basales

sur le mécanisme d'action de cette molécule n'avait pu être mis en évidence.

Dans le présent argumentaire déposé, la firme s'appuie sur ces 3 mêmes études et conclut que ces études permettent de confirmer l'action de benfluorex sur le métabolisme

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glucidique et le situe clairement dans la classe des insulino-sensibilisateurs. L'ensemble des résultats et leur cohérence ont conduit à mettre en place deux études pivot visant à confirmer l'efficacité hypoglycémiante du benfluorex chez les patients diabétiques de type 2 (Moulin 2006, Del Prato 2003). Voir données d'efficacité plus loin.

Un avis d'expert sur le mécanisme d'action de cette molécule est requis.

2. Activité hypolipémiante

Une action sur les différentes étapes enzymatiques régulant le métabolisme des acides gras, des triglycérides et du cholestérol aurait été mise en évidence in vitro. Aucune donnée dynamique ou clinique n'est fournie par la firme afin d'étayer le mécanisme d'action annoncé.

Note interne:
A noter qu'en 2000 lors de l'analyse des données de l'étude clinique versus placebo et versus metformine (Del Prato) les experts mandatés avaient tous souligné l'absence d'effet du benfluorex sur les paramètres lipidiques.

Extrait du rapport d'expertise sur le mécanisme d'action de l'activité hypolipémiante:

Benfluorex exerce une action sur différentes étapes enzymatiques régulant le métabolisme des acides gras, des triglycérides et du cholestérol.

In vitro, les données expérimentales sur hépatocytes isolés et homogénats de foie montrent que benfluorex diminue l'incorporation de C^{14} acétate dans les acides gras (Melin, 1991 ; Beynen 1992) et réduit l'activité de la phosphatidate-phosphorylase (Geelen,1977), enzyme responsable de la conversion du phosphatidate en diglycérides. Benfluorex et son principal métabolite (S 422) provoquent une inhibition dose dépendante d'une enzyme microsomiale, l'Acyl CoA cholestérol acyltransférase, augmentant le catabolisme des LDL (Low Density Lipoprotein) (Mazière,1991 ; Orsière, 1995).

Les effets inhibiteurs sur la synthèse des triglycérides sont confirmés *in vivo* sur différents modèles d'insulino-résistance chez le rongeur. L'administration de benfluorex (50 mg/kg) pendant un mois améliore l'action de l'insuline et réduit l'accumulation de triglycérides dans les muscles squelettiques (Storlien, 1993). L'administration à court terme de benfluorex diminue la triglycéridémie et la cholestérolémie chez le rat hyperphagique (Brindley, 1991). L'administration de benfluorex (10 mg/kg), à long terme (9 mois) entraîne une diminution des taux circulants de triglycérides et de cholestérol, ainsi que de l'insulinémie et de la glycémie post prandiale chez le rat obèse (Marquié, 1998).

En résumé, un effet hypolipémiant, portant sur les triglycérides et sur le cholestérol total, est observé sur de nombreux modèles animaux, après une administration courte ou prolongée de benfluorex.

2. DONNES D'EFFICACITE DE MEDIATOR

Présentation et analyse des données soumises par indication

=> Adjuvant du régime adapté dans les hypertriglycéridémies.

Dix études sont soumises par la firme pour soutenir cette indication: i) versus placebo (chez 394 patients) ;ii) 4 études versus fibrates (chez 163 patients) chez des patients présentant une hyperlipidémie associée ou non à un diabète de type 2.

Etudes versus placebo (réalisées entre 1978 et 2006). Il s'agit d'études anciennes à l'exception de l'étude MOULIN (soumise 2006).

Quand les mesures ont été effectuées sur les différentes fractions du cholestérol total, on observe une réduction significative du taux de LDL-cholestérol après traitement par benfluorex de 29.3%, ($p<0.05$) (Soltero, 1988) et de 5 % ($p < 0.05$) en comparaison au placebo (Moulin, 2006). Par ailleurs une augmentation significative du taux de HDL-cholestérol de l'ordre de 7.8 à 44.3% a été rapportée dans les études Mazzi et Di Martino.

Ces études ont inclus des patients de pathologies diverses (anomalies polymétaboliques, hyperlipidémie, diabète ou intolérance au glucose). Elles ont été menées selon un schéma croisé, parallèle ou séquentiel durant une période de 15 à 180 jours. A noter que dans l'étude Di Martino, le comparateur est le régime seul et que dans les études Del Prato et Moulin chez le diabétique de type 2, il s'agit de sous-groupes de 87 et 112 patients respectivement dont le taux de triglycérides à l'inclusion est >2.2mmol/L.
Les résultats figurent dans le tableau 8.

L'analyse de ces études a montré qu'un traitement par benfluorex diminue le taux de triglycérides (-8.3% à -56.1%) et du cholestérol total (-4.8% à -36.6%). L'importance de la diminution est dépendante de la valeur initiale ce qui explique la large fourchette des variations observées. Cet effet hypolipémiant, à la fois sur les triglycérides et le cholestérol, est démontré dans chaque catégorie de patients (hyperlipidémiques, diabétiques et polymétaboliques).

Mazzi 1985	hyperlipidémie IIb ou IV*	cross-over	7 (IV)	120	Bf : -30.0* Pl : -17.2		Bf : -56.1% Pl : -27.9*	-
Ranquin 1987	hyperlipidémie IV*	cross-over	22	40	Bf : -4.9 Pl : + 0.02		Bf : -32.7 Pl : - 11.7	-
Soltero 1988	hyperlipidémie IIa, IIb*	séquentielle	20	56	Bf : -20.7* Pl : 1.7	ND	Bf : -10.8* Pl : -0.5	
Di Martino 1989	obésité+anomalie métabolique	groupe parallèle	50	180	Bf : -6.8 * Contrôle : - 2.6	ND	Bf : -24.7* Contrôle : - 13.8*	ND
Bianchi, 1993	diabète type 2 + obésité	cross-over	10	15	Bf : -10** Pl : -8%	-	Bf : -36 Pl : -25%	
Del Prato, 2003 (Analyse complémentaire en annexe 8)	diabète type 2 + hypertriglycéridémie	groupe parallèle	72	180	ND		Bf : -24 * Pl : +24	+
Moulin, 2006	diabète type 2 + hypertriglycéridémie	groupe parallèle	112	126	Bf : -6* Pl : 0.0	-	Bf : -12* Pl : - 6	

a=classification de Fredrickson
ND=non déterminé
**=effet significatif valeur finale versus valeur initiale*
+ = différence intergroupe significative

Etudes versus produit de référence (fibrates), réalisées entre 1980 et 1986 => 5 études

La dyslipidémie des patients inclus est fréquemment associée à une intolérance au glucose et à une hyperuricémie dans le cadre d'un syndrome plurimétabolique. Dans ces études, on observe une diminution significative de l'uricémie sous benfluorex (-11.3%) (Graisely, Balestreri, Nathan) tandis que les fibrates ne la modifient pas (−1.4%), à l'exception du fénofibrate (Sommariva). Chez les patients non diabétiques, une amélioration de la tolérance au glucose est rapportée, et chez les patients diabétiques une réduction de l'hémoglobine glyquées qui ne sont pas observées sous fibrates (Graisely, di Perri, Balestreri, Sommariva).

L'ensemble des résultats démontrent qu'un traitement par benfluorex entraîne une diminution des triglycérides (-20.5% à -52.7%) et du cholestérol (-9.6% à -20.9%). L'amplitude de l'effet hypolipémiant est comparable à celui obtenu avec les fibrates (-19.0% à -49.7% et -4.9% à -22.7% respectivement).

=> Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale

Pour rappel, en réponse à la demande de l'Afssaps de validation de l'indication «en « diabétologie » en 1990, la firme avait mis en place un programme d'études de l'efficacité du benfluorex dans différentes populations. Le programme d'étude avait pour but d'explorer l'efficacité et la sécurité d'emploi du benfluorex dans différentes populations (extrait relevé d'avis GT PTC2 N°1 du 21-09-2000)

- Patients insuffisamment contrôlés par régime seul (**Velussi**, 1996) => comparaison à un placebo en monothérapie;
- Patients insuffisamment contrôlés par un SU en monothérapie
  Deux anciennes études : Stucci 1996, **Louvet** 1995) => comparaison de Médiator à un placebo en association à un traitement par SU à dose maintenue constante pendant l'étude.
- Patients insuffisamment contrôlés par une insulinothérapie (Bianchi et Pontiroli 1996);
- Patients insuffisamment contrôlés par metformine en monothérapie (Pr Roger) => comparaison de Médiator à un placebo en association à la metformine à dose maintenue constante pendant l'étude, après une période de pré-inclusion de 2 mois sous metformine seule,
- Patients insulino-requérants (Pr Leutenegger) => comparaison de Médiator au placebo en association à l'insuline, dont la dose pouvait être modifiée en cours d'étude.

Seules trois de ces études (Velussi, Tomassi et Louvet) sont reprises par la firme dans le présent rapport soumis (noms des auteurs en gras dans le texte ci-dessous).

Etude	N	Durée (mois)	Comparateur	Cholestérol total mmol/l		Triglycéride mmol/l	
				Benfluorex Δ (%) p * p**	Fibrate Δ (%) p * p**	Benfluorex Δ (%) p * p**	Fibrate Δ (%) p * p**
Graisely, 1980	24	2	Clofibrate	-9.1% <0.001	-7.7% <0.001 NS	-35.5% <0.05	-31.5% <0.05 NS
Di Perri, 1981	28	2	Clofibrate	-17.8%	-10.1% <0.05	-40.5%	-19.0% <0.05
Nathan, 1981	43	4	Clofibrate	-10.4% <0.05	-17.7% <0.001 NS	-20.5% <0.05	-28.6% <0.01 NS
Balestreri, 1982	40	2	Clofibrate	-20.9% <0.001	-22.7% <0.001 NS	-52.7% <0.001	-38.5% <0.001 S
Sonnmarva, 1986b	28	1	fénofibrate bézafibrate	-16.7% <0.001	-8.7% NS -4.9% NS	-33.1% <0.005	-49.7% <0.02 -44.3% <0.005

p : valeurs finales vs valeurs basales ; p** : différence entre groupes (benfluorex vs référence) ; NS=non significatif*

Etudes versus placebo

=> La firme fait référence à trois anciennes études versus placebo dont les résultats sont présentés dans le tableau ci-dessous

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Auteurs (réf)	Durée	Effectif	Traitement associé	HbA1c initiale (SD)	HbA1c différence versus placebo
Velussi 1996 (rapport en annexe 5)	3 mois	32	Régime seul	6.7 % (± 0.8)	-0.9 % p = 0.024
Tomasi 1996 (rapport en annexe 6)	3 mois	68	Régime + sulfamide hypoglycémiant	8.7 % (± 0.9)	-0.8 % p = 0.007
Louvet 1996	3 mois	25	Régime + sulfamide	8.5 % (± 1.7)	-1.7 % p = 0.025

l'étude Del
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ne expertise

Critères d'inclusion

Patients diabétiques de type 2, en surpoids (IMC compris entre 25 et 40Kg/m^2), insuffisamment contrôlés par régime seul (HbA1c initiale comprise entre 7.5 et 10 % ou glycémie à jeun comprise entre 7.8 et 13.9 mmol/L).

La population FAS est constituée de 259 patients et 128 patients respectivement pour le groupe benfluorex et pour le groupe placebo, soit 88 % et 89 % de la population incluse (répartition : 2:1).

Les groupes sont comparables à l'inclusion. La moyenne d'âge est de 56 ± 9 ans, le diabète connu depuis 5 ± 5.5 ans. Les valeurs basales d'HbA1c sont de 7.7 % ± 1.6 dans le groupe benfluorex et de 7.4 % ± 1.5 % dans le groupe placebo, traduisant une sévérité modérée du diabète comme attendu dans cette population.

Conclusions de la firme:

L'HbA1c est significativement améliorée sous benfluorex et s'altère sous placebo ce qui conduit à une différence entre les groupes de 0.86% (p<0.001) et de 1.01 % (p < 0.001) après ajustement sur la valeur basale d'HbA1c. L'analyse en per protocole confirme ces résultats.

Des résultats identiques sont observés pour la glycémie à jeun avec une différence entre les groupes de 1.33mmol/L (p<0.001) (tableau 6). Le nombre d'arrêts de traitement pour inefficacité thérapeutique est plus important sous placebo (10.4 %) que sous benfluorex (6.8 %) (p = 0.19).

spontanément

variables	benfluorex (DS)		placebo (DS)		différence [95 % IC]
	n	moyenne (ES)		n	
HbA1c (%)					
M0		7.7 (± 1.6)	7.4 (± 1.5)		
M6		7.1 (± 1.5)	7.9 (± 1.9)		
Différence entre les groupes	258	-0.86 (0.17)		127	[-1.20; -0.52]***
Différence entre les groupes ajustée sur la valeur basale		-1.01 (0.14)			[-1.28; -0.74]***
Glycémie à jeun (mmol/L)					
M0		10.0 (± 2.9)	9.7 (± 2.3)		
M6		8.8 (± 2.3)	10.1 (± 3.1)		
Différence entre les groupes	253	-1.33 (0.28)		123	[-1.89; -0.77]***

***p <0.001

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Pour rappel, les conclusions de la COM d'AMM du 09-12-1999 avaient été les suivantes: « ... Il est noté une efficacité du benfluorex versus placebo. Néanmoins, il n'est pas possible d'évaluer sur la taille de l'effet compte tenu des défauts de qualité des données. ... En effet, compte tenu des défauts de la qualité méthodologique de cet essai, aucune conclusion n'avait pu être formulée sur la taille de l'effet: i) du benfluorex versus placebo; ii) du benfluorex versus metformine. L'octroi d'une AMM dans le diabète de type 2 avait été rejetée. De manière plus précise, le groupe placebo de cette étude avait également soulevé de nombreuses remarques sur la qualité des analyses et résultats.

=> Etude MOULIN

An 18-week multinational, randomised double-blind study of the effect of benfluorex versus placebo in combination with SU for the treatment of type 2 diabetes, followed by a 16-week open label period with benfluorex given as combination with SU or in multiple combination.

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Méthodologie

Etudes comportant 2 périodes ii) période en ouvert de 16 semaines.

i) période en double aveugle (DA) de 18 semaines dont l'objectif principal était de démontrer la supériorité du benfluorex versus placebo, en association à un SU, sur l'évolution de l'HbA1c sur une période de 18 semaines chez des patients diabétiques de type 2 mal contrôlés par SU en monothérapie et chez qui l'utilisation de la metfomrine est contre-indiquée ou non recommandée. Etude multicentrique, en double aveugle, en groupes parallèles, comparative versus placebo.

ii) période en ouvert 16 semaines ayant pour objectif d'obtenir des données d'efficacité et de sécurité d'emploi à long terme du benfluorex en association avec un SU et, si nécessaire, à l'acarbose (3ème ADO pouvant être prescrit).

Période 1 : étude en double aveugle de 18 semaines

Population : 325 patients diabétiques de type 2 avec HbA1c entre 7 et 10% à l'inclusion insuffisamment équilibrés par SU (pendant 4 mois avant l'inclusion ou 2 mois à dose maximale tolérée, en surpoids (IMC entre 25 et 40 kg/m²).

Objectifs : principal : démontrer la supériorité du benfluorex versus placebo, en association à une SU, sur l'évolution de l'HbA1c pendant une période de 18 semaines chez des patients diabétiques de type 2 mal contrôlés par SU en monothérapie, et chez qui l'utilisation de la metformine n'est pas recommandée (problèmes de tolérance) ou est contre indiquée. L'objectif de la phase d'extension en ouvert est d'obtenir des données d'efficacité et de tolérance du benfluorex en association aux SU et si nécessaire à un 3 ème agent l'acarbose.

Méthodologie: étude multicentrique (63 centres et 7 pays), randomisée, stratifiée à « baseline » sur le taux d'HbA1c et le pays.

Critères d'efficacité. Principal : HbA1c à chaque visite. Secondaires :glycémie à jeun, insulinémie à jeun, paramètres lipidiques (TG, Hdl, LDL cholestérol). Analyse de la sécurité d'emploi : poids, tension artérielle, recueil des événements indésirables, etc.).

Résultats (phase en double aveugle seulement)

1 Caractéristiques démographiques des patients inclus

	benfluorex (n = 165)	placebo (n = 160)
Age (années)	62.9 ± 10.8	64.6 ± 10.3
Sexe (hommes/femmes)	86 79	68 92
Durée du diabète (années)	6.8 ± 5.8	7.5 ± 6.1
Indice de Masse Corporelle (kg/m²)	29.5 ± 3.7	29.3 ± 3.5
Présence d'un syndrome métabolique (%)	72.1	73.1
HTA (%)	68.5	70.6
Présence de complications		
Coronaropathie (%)	36.2	37.5
Néphropathie (%)	32.1	31.9
Neuropathie (%)	14.5	15.0
Rétinopathie (%)	10.9	12.5
HbA1c (%)	8.32 ± 0.83	8.32 ± 0.87
Glycémie à jeun (mmol/L)	9.87 ± 2.54	9.67 ± 2.39

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Note interne:

A noter: dose maximale de SU à l'entrée au mois égale à 50% de la dose maximale autorisée chez 86% des patients; 40% des patients prenaient un SU (glibenclamide 37%, gliclazide 19%).Plusieurs analyses en sous groupes étaient prévues dans cette étude: patients âgés de plus de 65 ans, Cl Cr < 80ml/mn, HbA&c de départ > 8%, analyse post hoc de la tolérance digestive.

Evolution de l'HbA1c (population générale, en fonction de l'âge, de l'HbA1c et de la fonction rénale.

Tableau 3 : Evolution de l'HbA1c dans la population FAS et dans les sous-groupes de patients sévères ou fragiles

		benfluorex			placebo			
variable		n	HbA1c valeur initiale moyenne (DS)	différence pré-post traitement (ES)	n	HbA1c valeur initiale moyenne (DS)	différence pré-post traitement (ES)	différence entre les groupes Δ (SE)
Population complète		151	*8.34 (± 0.83)*	-0.82 (0.08)	156	*8.33 (± 0.87)*	− 0.19 (0.11)	**-1.01*** ** (0.13)
Sous-groupes	HbA1c> 8%	93	*8.9 (± 0.55)*	-1.15 (0.11)	89	*8.96 (± 0.56)*	-0.05 (0.15)	**-1.10*** ** (0.18)
	Âge > 65 ans	70	*8.29 (± 0.80)*	-0.86 (0.10)	82	*8.31 (± 0.87)*	-0.03 (0.13)	**-0.81*** ** (0.17)
	Clairance créat ≤ 80 mL/min	82	*8.37 (± 0.76)*	-0.78 (0.12)	78	*8.32 (± 0.87)*	− 0.27 (0.15)	**-1.16*** ** (0.20)

*** p<0.001

Diminution de l'HbA1c de -0,82% par rapport à la valeur de base (ITT) après 18 semaines de traitement. Augmentation de l'HbA1c dans le groupe placebo: différence entre les 2 groupes de -1,01 (p< 0,001) en faveur de Médiator.

3. Evolution des principaux paramètres glycémiques et lipidiques Evolution des autres

Tableau 4 : Evolution des principaux paramètres biologiques dans la population FAS

	benfluorex			placebo			différence entre les groupes
	N	valeur initiale moyenne (DS)	différence pré-post (ES)	n	valeur initiale moyenne (DS)	différence pré-post (ES)	Δ (ES)
Glycemie a jeun mmol/L	159	*9.89 (± 2.57)*	-1.22 (0.10)	156	*9.73 (± 2.59)*	0.51 (0.13)	**-1.65*** ** (0.27)
HOMA- IR Index	157	*6.62 (± 7.99)*	-1.75 (0.50)	150	*9.35 (± 7.95)*	-0.42 (0.65)	**-0.81**+**
LDL cholesterol mmol/L	149	*3.60 (± 0.86)*	-0.27 (0.06)	152	*3.53 (± 0.89)*	0.04 (0.05)	**-0.28*** ** (0.07)
Triglycerides mmol/L	151	*2.36 (± 1.62)*	-0.11+	152	*2.11 (± 1.32)*	0.05+	**-0.16*** (0.07)

***p<0.001 **p<0.01 *p< 005 + test non parametrique

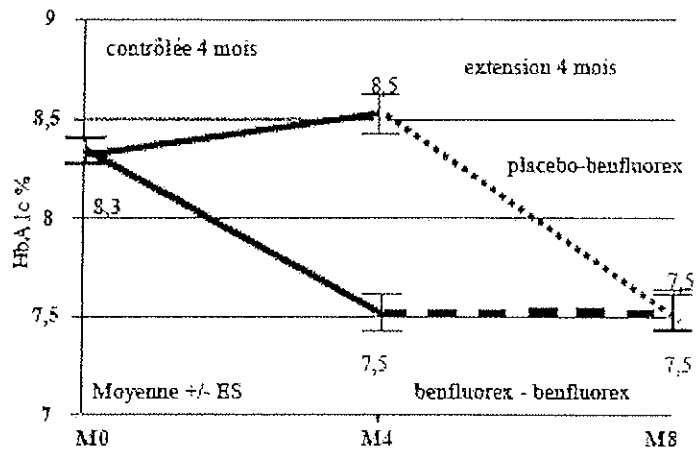
Diminution du poids observée dans les deux groupes de traitement: -1,5 kg sous Méditaor et -0,7 sous placebo (significative), amélioration de l'insulinorésistance, amélioration de la glycémie à jeun (significativement entre les 2 groupes) dès la 4ème semaine,

Paramètres lipidiques: diminution des TG de 7% (diminution modeste mais significative dans le groupe Médiator vs placebo). Diminution modeste du LDL, de -5,1ù sous Médiator versus +2,3% sous placebo. Variations du HDL-c non significatives.

Absence de modification de la Pression artérielle :

Analyses des résultats dans les sous groupes pré- définis: Baisse de l'HbA1c plus importante dans le groupe avec une HbA1c > 8% versus la population générale. Chez les patients avec une HbA1c < 8% à « baseline », diminution de -0,6% dans le groupe traité par Médiator versus +0,53% sous placebo. D'après la firme, la baisse de l'HbA1c est du même ordre de grandeur chez les patients âgés de plus de 65ans versus la population générale de l'essai. Idem résultats identiques chez les patients présentant une insuffisance rénale versus la population générale.

Figure 2 : Evolution de l'HbA1c pendant la période en double aveugle suivie de la période d'extension de l'étude



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- Les études cliniques des effets sur les paramètres lipidiques peuvent être scindées en deux groupes : celles antérieures à 1992 et celles postérieures à 1992. En effet, après cette date, les effets hypotriglycéridémiants du produit sont devenus plus discrets et plusieurs études ne montrent pas de différence par rapport au placebo.

A noter que les études anciennes comportaient un nombre de sujets faible (n <40), avec une dyslipidémie plus prononcée que dans l'étude Moulin (TG environ 4 mmol/l), avec des valeurs initiales des paramètres lipidiques pas toujours identiques entre les groupes des traitement (étude versus clofibrate de Graisely), les valeurs du LDL-cholestérol n'étaient pas toujours disponibles.

Une méta-analyse de l'efficacité sur les TG dans les études les plus récentes montre que l'action du produit sur les TG est inconstante et ne correspondant pas à ce qui est attendu pour une molécule avec cette indication. Sur 6 études (avec des effectifs variés, de 10 à 242 patients), mais comportant un placebo et un tirage au sort, 5 études ne montrent pas de diminution significative des TG par rapport au groupe placebo (Louvet, Tomasi, Moulin, Velusi, Del Prato, Biancchi).

Dans l'indication de traitement adjuvant des hypertriglycéridémies, l'étude Moulin montre une réduction de seulement 7% des triglycérides sous benfuorex (p = 0,027) et de 6% du LDLc (p = 0,001). La différence entre le groupe benfluorex et le groupe placebo à la 18ème semaine était de -0,28 mmol/l (0,10 g/l) pour le LDL et de – 0,16 mmol/l pour les triglycérides. La répercussion clinique de cette différence est très faible et inférieure à celles observée avec les autres hypolipidémiants (statines, ézétrol pour le LDL, fibrates pour les TG). De plus, aucune donnée de protection cardiovasculaire n'est disponible. A noter par ailleurs que la publication de l'étude Moulin dans la revue Diabetes Care (en 2006) ne fait pas mention de l'effet du benfluorex sur les TG, ni dans l'abstract ni dans la discussion.

Au total, les données d'efficacité soumises montrent une efficacité très modeste voire inexistante sur les triglycérides y compris dans l'étude Moulin récente, l'efficacité sur les autres paramètres lipidiques n'étant pas démontrée. A noter que dans les étude soumises, les paramètres lipidiques sont uniquement étudiées comme critères secondaires. Compte tenu de ces éléments il semble difficile de maintenir l'indication actuelle en comme « Traitement adjuvant des hypertriglycéridémies ». Des études complémentaires d'efficacité sur l'efficacité du benfluorex sur les paramètres lipidiques en tant que critère primaire seraient nécessaires afin de mieux étayer cette efficacité. De plus, compte tenu des alternatives thérapeutiques actuelles, le maintien de cette indication pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et en particulier sur les triglycérides et ayant démontré par ailleurs un efficacité en termes de prévention cardiovasculaire. Des études complémentaires versus placebo et comparatives seraient nécessaires chez des patients dyslipidémiques et/ou diabétiques.

2.2. Indication en tant qu'« ***Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale*** ».

Pour rappel, dans cette indication, il avait été demandé à la firme de soumettre d'autres études pour valider cette indication. A cet effet, la firme a soumis en Septembre 2000 l'étude Del Prato pour laquelle seul le bras placebo a été considéré comme recevable, les résultats du bras versus metformine n'étant pas recevables compte tenu d'insuffisances méthodologiques relevées par les experts.

En 2002, il avait été demandé à la firme de réaliser une nouvelle étude évaluant l'effet du

benfluorex en monothérapie et en association avec d'autres antidiabétiques oraux, en particulier chez des patients pour lesquels la metformine est contre-indiquée ou mal tolérée.

L'étude Moulin (publiée dans Diabetes Care en 2006) est une étude multicentrique, internationale, randomisée en double aveugle, d'une durée de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par SU et intolérants ou ayant une contre indication à la metformine. Le critère principal était l'HbA1c ; les critères secondaires : insulinémie, glycémie à jeun, paramètres lipidiques, index d'insulino résistance HOMA. Trois sous-groupes ont été analysés : HbA1c > 8%, âge > 65 ans et clairance de la créatininémie < 80ml/mn. Etude de supériorité avec un différence de 06% entre les groupes sur l'HbA1c.

Résultats :

Après 18 semaines de traitement, les résultats d'efficacité sur les paramètres glucidiques de cette étude montrent que :

- l'HbA1c est diminuée de -0.82% dans le groupe benfluorex (versus baseline) et de 1% versus le groupe placebo. 34.2% et 19% arrivent à une HbA1c ≤ 7% et > 6.5% contre 11% et 5% respectivement sous placebo. Baisse de l'HbA1c significative dès la 4ème semaine ; d'après la firme, l'effet est du même ordre entre les trois sous groupes pré définis ;
- l'insulinorésistance s'améliore significativement sous benfluorex ; la glycémie à jeun baisse significativement dès la 4ème semaine sous benfluorex.
- la perte de poids était de 1.3 kg sous benfluorex et de 0.7kg sous placebo ;
- noter, dans cette étude, la dose de SU utilisée n'était pas maximale puisqu'elle correspondant à la dose maximale tolérée soit ≥ 50% de la dose maximale de l'AMM chez 86% des patients.
- concernant les analyses en sous-groupes : la baisse de l'HbA1c est très faible chez les patients avec une HbA1c < 8% :-0.36% (-0.57 ;-0.15) sous benfluorex versus +0.53 % (0.25 ;0.80) sous placebo ;

En termes de sécurité d'emploi, dans cette étude, 53% des patients ont présenté un EI sous benfluorex et 51% sous placebo :

- les troubles neurologiques ont été plus fréquents sous benfluorex (9% versus 6.3%) ;
- les troubles digestifs sont rapportés chez 15.1% des patients sous benfluorex et 10% sous placebo : il s'agit d'une diarrhée la plupart du temps (trois fois plus fréquente sous traitement). Chez les patients intolérants à la metformine (n=184), 15.2% sous benfluorex versus 15.3% sous placebo ont présenté une EI de type gastro-intestinal. Chez les patients sans intolérance digestive à la metformine (n=142), 13.4% sous benfluorex et 4% sous placebo ont présenté des désordres gastro-intestinaux. Globalement la tolérance digestive est du même ordre que les patients soient intolérants ou non à le metformine ; une intolérance à la metformine en prédispose donc pas à une intolérance au benfluorex ;
- Aucune modification significative de la pression artérielle, de la fréquence cardiaque, des paramètres biologiques ou à l'ECG n'a été observée ;
- Hypoglycémies : 20 patients rapportent 37 épisodes (sans confirmation biologique). Elles ont tendance à être plus fréquents sous benfluorex que sous placebo ce qui est attendu compte tenu de la baisse plus importante de l'HbA1c sous benfluorex. Aucun épisode n'a été considéré comme sévère. Elles seraient cependant légèrement plus

fréquentes chez les patients > 65 ans et chez les patients ayant une clairance de la créatinine < 80 ml/min.

Commentaires :

- les données de compliance au traitement ne sont que partiellement fournies ;
- d'un point de vue méthodologique, l'analyse des résultats sur l'HbA1c a été ajustée en fonction du poids. Or, la méthode d'ajustement utilisée montre qu'une fois l'ajustement effectué, les « résidus » de l'effet n'ont pas une distribution normale. Ces résultats devraient à nouveau être analysés en utilisant une méthode d'ajustement permettant d'obtenir une distribution normale (voir la méthode utilisée pour l'ajustement de l'effet sur les paramètres lipidiques en fonction du poids).
- A noter que la randomisation a été stratifiée en fonction de l'HBA1c (≤ ou > 8%) ; les résultats sur l'HbA1c devraient être ajustés selon le taux de base ce qui n'est pas le cas dans les résultats soumis. De même, les résultats sur les paramètres devraient être ajustés en fonction des valeurs à l'inclusion ce qui n'est pas le cas.
- A noter, la définition des hypoglycémies dans l'étude Moulin serait à préciser ;

A noter, d'autres études sont soumises dans le dossier par la firme mais ne sont pas considérées comme recevables compte tenu du faible nombre de patients inclus.

En conclusion :

Les experts sont unanimes pour affirmer que les données d'efficacité du benfluorex sur les paramètres lipidiques ne sont pas suffisantes pour maintenir cette indication.

En ce qui concerne l'indication relative au métabolisme glucidique, les données soumises et en particulier les résultats de l'étude Moulin récente (en seconde intention, en association à un SU) semblent montrer une efficacité sur les paramètres glucidiques, en particulier l'HbA1c et ceci indépendamment de la perte de poids. Néanmoins, aucune conclusion définitive ne peut être portée sur cette efficacité compte tenu des réserves méthodologiques soulevées par les experts (voir ci-dessus). D'un commun accord, les experts sont cependant d'avis que bien qu'obsolète, l'indication telle que libellée peut être maintenue dans l'attente d'un dépôt complet de données d'efficacité et de sécurité d'emploi sur les paramètres glucidiques (études en cours, dépôt de dossier prévu en 2007 d'après la firme). A noter enfin, aucune demande de modification de cette indication n'a été demandée par la firme dans le cadre de cette réévaluation du bénéfice/risque.

AVIS DU GT AD HOC SUR LES MEDICAMENTS UTILISES EN DIABETOLOGIE, ENDOCRINOLOGIE, UROLOGIE ET GYNECOLOGIE N° 6 DU 21 DECEMBRE 2006 :

- **AVIS DEFAVORABLE** au maintien de l'indication : *« Adjuvant au régime adapté dans les hypertriglycéridémies. Remarque: l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée».*

En effet, les données soumises montrent une efficacité très modeste voire inexistante sur les triglycérides y compris dans l'étude Moulin récente ; l'efficacité sur les autres paramètres lipidiques n'étant pas démontrée. A noter que dans les études soumises, les paramètres lipidiques sont uniquement étudiées comme critères secondaires et non comme critères primaires comme cela est requis pour des études cliniques visant à l'obtention d'une telle indication. Compte tenu de ces éléments il semble difficile de maintenir l'indication actuelle en comme « Traitement adjuvant des hypertriglycéridémies ». Des études complémentaires d'efficacité sur l'efficacité du benfluorex sur les paramètres lipidiques en tant que critère primaire seraient nécessaires afin de mieux étayer cette efficacité. De plus, compte tenu des alternatives thérapeutiques actuelles, le maintien de cette indication pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et

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en particulier sur les triglycérides et ayant démontré par ailleurs une efficacité en termes de prévention cardiovasculaire.

- **AVIS FAVORABLE** au maintien de l'indication suivante : « *Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* ». En effet, les données soumises et en particulier celles de l'étude Moulin semblent montrer une efficacité sur les paramètres glucidiques, en particulier l'HbA1c et ceci indépendamment de la perte de poids.

Néanmoins, aucune conclusion définitive ne peut être portée sur cette efficacité compte tenu des réserves méthodologiques soulevées : i) l'analyse des résultats sur l'HbA1c a été ajustée en fonction du poids. Or, la méthode d'ajustement utilisée montre qu'une fois l'ajustement effectué, les « résidus » de l'effet n'ont pas une distribution normale ce qui devrait être le cas. Ces résultats devraient à nouveau être analysés en utilisant une méthode d'ajustement permettant d'obtenir une distribution normale (voir la méthode utilisée pour l'ajustement de l'effet sur les paramètres lipidiques en fonction du poids).

De plus, la randomisation ayant été stratifiée en fonction de l'HBA1c (≤ ou > 8%), les résultats sur l'HbA1c devraient être également ajustés en fonction du taux de base de l'HbA1c ce qui n'est pas le cas dans les résultats soumis.

D'un commun accord, les experts sont cependant d'avis que bien qu'obsolète, l'indication telle que libellée peut être maintenue en l'état dans l'attente d'un dépôt complet de données d'efficacité et de sécurité d'emploi plus solides du benfluorex permettant de revoir le libellé de cette indication.

PRESENTATION DU DOSSIER EN COMMISSION D'AMM DU 5 AVRIL 2007:

Les conclusions du Groupe DEUG de l'évaluation des données d'efficacité dans les indications actuelles ainsi que les conclusions sur la sécurité d'emploi du benfluorex sont présentées à la Commission d'AMM pour discussion et décision finale sur le rapport Bénéfice/Risque de cette spécialité. Pour rappel, cette revue du Bénéfice/Risque a été initiée à la demande de la CNPV.

Résumé de la dernière étape de l'évaluation des données relatives au MEDIATOR :

1. Les conclusions du Groupe DEUG de l'évaluation des données d'efficacité ont été présentées à la Commission Nationale de Pharmacovigilance le 27 Mars 2007.

2. La firme a également été auditionnée lors de cette Commission. Une Mise à jour des données d'utilisation du benfluorex chez les médecins généralistes en fonction des indications, à partir de l'observatoire THALES, a été présentée par la firme. Ont été étudiées deux périodes : de mai 2004 à avril 2005 et de mai 2005 à avril 2006. Cinq groupes de patients ont été identifiés : A, B, C, D et E. En résumé, d'après ces données, la firme conclut (voir tableau ci-dessous) :

- qu'environ 80% des prescriptions de MEDIATOR sont réalisées chez des patients dyslipidémiques et / ou diabétiques (80,3% en 2004-2005 / 80,5 % en 2005-2006) ;
- qu'environ 11% des prescriptions MEDIATOR sont réalisées chez des patients « obèses » (11,5% en 2004-2005 / 10,7% en 2005-2006) ;
- que ces taux restent stables au cours du temps ;
- que concernant la saisonnalité des prescriptions de MEDIATOR, l'analyse n'a pas montré de différences entre le groupe « obésité » et le total de patients sous MEDIATOR ;
- le profil des patients traités par MEDIATOR (âge/sexe/IMC) reste stable sur les deux périodes.

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Répartition du nombre de prescriptions et de patients traités en fonction du diagnostic (Valeurs extrapolées à partir des données brutes). Document de la firme.

		de mai 2004 à fin avril 2005		de mai 2005 à fin avril 2006	
		Nombre de patients MEDIATOR	Nombre de prescriptions MEDIATOR générées	Nombre de patients MEDIATOR	Nombre de prescriptions MEDIATOR générées
A	Patients dyslipidémiques	270 307	669 998	266 869	668 490
		50,6%	44,8%	51,0%	45,5%
B	Patients diabétiques	63 161	223 395	58 969	213 551
		11,8%	14,9%	11,3%	14,5%
C	Patients dyslipidémiques et diabétiques	81 389	308 222	80 682	301 770
		15,2%	20,6%	15,4%	20,5%
D	Patients avec diagnostic obésité / surcharge pondérale associé à la prescription	76 443	172 527	73 193	157 879
		14,3%	11,5%	14,0%	10,7%
E	Patients avec d'autres diagnostics associés à la prescription de MEDIATOR	43 049	121 235	43 615	127 264
		8,1%	8,1%	8,3%	8,7%
Total MEDIATOR		534 350	1 495 378	523 328	1 468 955
		100,0%	100,0%	100,0%	100,0%

3. Une actualisation du rapport national de pharmacovigilance sur le benfluorex (mise à jour du rapport du 29 novembre 2005) a également été présentée par le CRPV chargé de l'enquête Nationale de Pharmacovigilance. Une revue des troubles neuropsychiatriques ainsi que des cas d'HTAP a été présentée (extrait) :
- au total : 39 notifications dont 4 cas nouveaux de troubles psychiatriques depuis novembre 2005 à type de dépression, agitation, délire de persécution et délire (2 cas nouveaux).

- HTAP : Fréquence : 13/20 cas d'HTAP (2 post embolique et 5 post capillaires) ont été observés. Nombre de boîtes vendues : 125 524 279 soit 51 613 601 mois de traitement. Ce qui représente 1 cas pour 9 655 713 boites vendues et 3 970 277 mois de traitement.
3 cas d'HTAP idiopathique ont été également observés soit 1 cas pour 41 0841 426 boites ou 17 204 533 mois de traitement. Au total, l'incidence de l'HTAP idiopathique est de 1 à 2 cas /million et par an.

AVIS DE LA COM d'AMM 419 DU 5 AVRIL 2007 :

Après présentation et discussion des conclusions du Groupe de Travail DEUG sur les données d'efficacité et des conclusions de la CNPV sur les données de sécurité d'emploi, les conclusions suivantes ont été émises :

1. La COM d'AMM suit l'avis DEFAVORABLE émis par le Groupe DEUG au maintien de l'indication : « *Adjuvant au régime adapté dans les hypertriglycéridémies. L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée*», les données soumises ne montrant en effet qu'une efficacité très modeste et inconstante dans les études soumises sur les triglycérides et une absence d'efficacité sur les autres paramètres lipidiques tels que le LDL-cholestérol.

2. La COM d'AMM suit également l'avis du Groupe DEUG pour le maintien de l'indication : « *Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* » dans son libellé actuel. En l'attente de données plus complètes sur l'efficacité du benfluorex en

association aux autres antidiabétiques oraux, la COM d'AMM n'a pas souhaité modifier le libellé actuel. A ce jour, seule l'étude MOULIN a permis de montrer une efficacité du benfluorex sur l'HbA1c en association à un sulfamide hypoglycémiant. D'autres études sont en cours dont une étude multicentrique, randomisée visant à comparer l'efficacité du benfluorex (150 mg bid ou 150 mg tid) à la pioglitazone (30 mg od ou 45 mg bid) en association à un sulfamide hypoglycémiant.

3. La COM d'AMM souhaite que les modifications d'ajout d'effets indésirables suivants tels que décidés par la CNPV soient mentionnées au sein de la rubrique 4.8. du RCP : *« troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) »* et de la rubrique correspondante de la Notice.

4. Une inspection de l'étude MOULIN, seule étude à ce jour ayant montré une efficacité sur les paramètres glucidiques a été proposée et acceptée par les membres de la COM d'AMM. Une saisine sera adressée en ce sens à la DIE (Direction de l'Inspection des Etablissements).

5. Enfin, les membres de la COM d'AMM souhaitent qu'une communication soit faite sur l'usage hors AMM de cette spécialité ainsi que sur la seule indication retenue après réévaluation des bénéfice/risque de cette spécialité.

Au total, le libellé de l'indication retenu est le suivant : «Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ».

Le RCP modifié ainsi que la Notice dans leur intégralité figurent ci-après.

ANNEXE I

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorhydrate de benfluorex ..... 150,00 mg
pour un comprimé enrobé de 700 mg

Pour les excipients, voir rubrique 6.1..

3. FORME PHARMACEUTIQUE

Comprimé enrobé

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Annexe 4-3

4.2 Posologie et mode d'administration

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:

- 1ère semaine: 1 comprimé par jour, au cours du dîner;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.

En association à un régime adapté, MEDIATOR constitue un traitement *adjuvant* : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

4.3. Contre-indications

- Hypersensibilité au chlorhydrate de benfluorex ou à l'un des constituants ;
- Pancréatites chroniques avérées.

4.4. Mises en garde et précautions particulières d'emploi

Les troubles métaboliques relevant d'un traitement par MEDIATOR sont essentiellement observés chez l'adulte. La prescription de Médiator n'est donc pas justifiée chez l'enfant.

Si, après une période d'administration de quelques mois (3 à 6 mois), une diminution satisfaisante de concentrations sériques de glucose n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

4.6. Grossesse et allaitement

Grossesse:
Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.
En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.

En conséquence, par mesure de prudence, il est préférable de ne pas utiliser ce médicament pendant la grossesse. En cas d'exposition fortuite, il conviendra d'interrompre ce traitement.

Allaitement
En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

L'attention des conducteurs est attirée sur la somnolence pouvant survenir lors de l'utilisation de ce médicament.

4.8. Effets indésirables

Les effets secondaires suivants ont été observés :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou états vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles;

- **troubles de fonetions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations).**

- très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quincke;

- très rares cas d'élévation des enzymes hépatiques, hépatite.

4.9. Surdosage

En cas d'absorption massive, le traitement sera uniquement symptomatique: lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience ainsi que des fonctions respiratoire et cardiaque.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

~~HYPOCHOLESTEROLEMIANT ET HYPOTRIGLYCERIDEMIANT~~
~~Code ATC : C10AX04~~

Actions de MEDIATOR sur le métabolisme glucidique:

Chez l'animal, les effets suivants ont été observés:

- facilitation de la pénétration et de l'utilisation cellulaire du glucose (rat);

- diminution de l'hyperglycémie chez le rat diabétique (insulinoprive ou non), diminution de l'hyperglycémie (mesurée par l'aire d'HPO) chez le lapin.

MEDIATOR n'a pas d'action sur l'insulino-sécrétion; la survenue d'hypoglycémie est peu probable.

Annexe 4-3

5. 2 Propriétés pharmacocinétiques

L'absorption gastro-intestinale est rapide et totale.

Après administration orale, le pic de concentration plasmatique est maximal entre 1 et 2 heures.

L'élimination est rapide et totale par voie urinaire. Huit heures après l'absorption, 74 % de la dose administrée est éliminée dans les urines.

L'élimination se fait en 2 phases :

- une première phase rapide (60 % en 3 ou 4 heures);
- une seconde phase lente, de 36 heures environ.

5. 3 Données de sécurité précliniques

Sans objet.

ANNEXE III B

NOTICE

.....

1 - QU'EST-CE QUE MEDIATOR 150 mg, comprimé enrobé ET DANS QUEL CAS EST-IL UTILISÉ ?

MEDIATOR 150 mg, comprimé enrobé contient du chlorhydrate de benfluorex.

MEDIATOR 150 mg se présente sous la forme de comprimés enrobés.

Boîtes de 10, 20, 24, 30, 60 et 100 comprimés.

Ce traitement est en préconisé comme adjuvant à un régime adapté :

- chez les diabétiques avec surcharge pondérale *(taux de sucre élevé dans le sang)*.

2. INFORMATIONS NÉCESSAIRES AVANT D'UTILISER MEDIATOR 150 mg, comprimé enrobé

MEDIATOR 150 mg, comprimé enrobé NE DOIT JAMAIS ETRE UTILISE dans les cas suivants :

- allergie au chlorhydrate de benfluorex ou à l'un des composants du produit;
- en cas de pancréatite chronique *(insuffisance de fonctionnement chronique du pancréas)*.

MISES en GARDE et PRECAUTIONS PARTICULIERES D'EMPLOI avec MEDIATOR 150 mg, comprimé enrobé :

Un régime alimentaire adapté doit être poursuivi pendant toute la durée du traitement.

Si après une période de plusieurs mois (3 à 6 mois), une diminution des concentrations de glucose (sucre) dans le sang n'est pas obtenue, votre médecin pourra envisager d'autres moyens thérapeutiques adaptés à votre cas.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase *(maladies métaboliques rares)*.

Grossesse/Allaitement:

Il est préférable de ne pas utiliser ce médicament pendant la grossesse ou au cours de l'allaitement.

Si vous découvrez que vous êtes enceinte pendant le traitement, consultez votre médecin car lui seul peut juger de la nécessité de le poursuivre.

Conduite de véhicules et utilisation de machines:

L'attention est attirée sur le risque de somnolence pouvant survenir avec ce médicament.

Sportifs:

Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

Liste des excipients à effet notoire:

Saccharose.

Prise ou utilisation d'autres médicaments:

Sans objet.

3. COMMENT PRENDRE MEDIATOR 150 mg, comprimé enrobé ?

Posologie:

RESERVE A L'ADULTE

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante:

- 1ère semaine: 1 comprimé par jour, au cours du dîner;

- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner;

- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

La posologie peut-être ramenée à 2 comprimés par jour, voire 1 comprimé par jour, en fonction des résultats biologiques.

DANS TOUS LES CAS, SE CONFORMER STRICTEMENT A L'ORDONNANCE DE VOTRE MEDECIN.

Si vous avez pris plus de MEDIATOR 150 mg, comprimé enrobé que vous n'auriez d :

Les signes de surdosage peuvent être des troubles digestifs (nausées, vomissements, diarrhée), une sensation vertigineuse voire une somnolence. En cas d'apparition de ces troubles, consultez votre médecin ou votre pharmacien.

Si vous oubliez de prendre MEDIATOR 150 mg, comprimé enrobé:

Ne prenez pas de double dose pour compenser la dose simple que vous avez oubliée de prendre.

Annexe 4-3

Effets pouvant apparaître lorsque le traitement par MEDIATOR 150 mg, comprimé enrobé est arrêté :

Sans objet.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS avec MEDIATOR 150 mg, comprimé enrobé ?

Comme tous les médicaments, MEDIATOR 150 mg, comprimé enrobé est susceptible d'avoir des effets indésirables :

- troubles digestifs: nausées, vomissements, diarrhée, maux d'estomac ;

- sensation de fatigue, voire somnolence ;

- sensations vertigineuses.

Ces effets ont été observés à des posologies supérieures à 3 comprimés par jour et varient en fonction de la susceptibilité individuelle des patients.

- très rares cas de manifestations allergiques : éruptions cutanées soudaines, urticaire, malaise brutal avec hypotension (diminution de la pression artérielle), œdème de Quincke (brusque gonflement du visage et du cou). Dans ce cas, le traitement devra immédiatement être interrompu.

- **troubles de fonctions cognitives (désorientation temporo-spatiale), troubles du comportement : agitation, délire, troubles de la perception (hallucinations).**

- élévation des enzymes hépatiques (anomalies biologiques au niveau du foie). Très rares cas d'hépatite.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

Annexe 4-3

RÉPUBLIQUE FRANÇAISE

afssaps

Agence française de sécurité sanitaire des produits de santé

COMMISSION D'AUTORISATION DE MISE SUR LE MARCHE DES MEDICAMENTS

Réunion n° 419 du 5 avril 2007

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Annexe 4-3

RÉPUBLIQUE FRANÇAISE

COMMISSION D'AUTORISATION DE MISE SUR LE MARCHE DES MEDICAMENTS

Réunion n° 419 du 5 avril 2007

Abréviations utilisées dans les tableaux :	
AMM ; autorisation de mise sur le marché*	**P.Nat** : Procédure Nationale
P.R.M : Procédure de reconnaissance mutuelle	**P.C** : Procédure Centralisée
P.D.C. Procédure décentralise	**RQ** : Renouvèlement Quinquennal
DMI : Demande de modification de l'information scientifique de l'AMM	

Après vérification du quorum, le Président de la Commission d'AMM ouvre la séance.

Un conflit d'intérêt important a été identifié concernant un membre de la commission au titre des dossiers du produit Mediator. (cf:IV point d'information et de suivi : Médiator)

I. Procès verbal de la Commission d'AMM n°418

Le procès verbal de la commission n° 418 du 22/03/07 a été présenté par le président de la commission d'AMM et approuvé à l'unanimité.

II. Présentation et discussion des dossiers[1] examinés par les groupes de travail thérapeutiques

Les dossiers suivants, ont été présentés à commission d'AMM et approuvés à l'unanimité :

1. Nutrition hépato gastroentérologie

CREON 40 000 U, granulés gastro-résistants en gélule	SOLVAY PHARMA	DMI	P.Nat
MOVIPREP, poudre pour solution buvable en sachet	NORGINE PHARMA	DMI	PRM

2. Anti-infectieux (V.I.H. et hépatites virales)

MAXEPA 1g, capsule molle	PIERRE FABRE	DMI	P.Nat

3. Cardio- thrombose

INTERCYTON 200 mg, gélule	UCB PHARMA	DMI	P.Nat
PRAVASTATINE MERCK 10 mg, 20 mg, 40 mg, comprimé pelliculé sécable	MERCK GENERIQUES	DMI	PRM
FOSINOPRIL/HYDROCHLOROTHIAZIDE TEVA 20mg/12.5 mg, comprimés sécables	TEVA	DMI	PRM

[1] Seuls les avis favorables, susceptibles de fonder une décision d'autorisation de mise sur le marché, sont retranscrits.

EZETROL 10 mg, comprimé **EZETIMIBE MSD 10 mg**, comprimé	MSD	DMI	PRM
FOSINOPRIL/HYDROCHLOROTHIAZIDE TEVA 20mg/12.5 mg, comprimés sécables	TEVA	Demande d'AMM	PRM

4. Onco-Hématologie

OXALIPLATIN MEDAC 5 mg/ml, poudre pour solution pour perfusion	Medac	Demande d'AMM	PRM
OXALIPLATIN RATIOPHARM, poudre pour solution pour perfusion	Ratiopharm	Demande d'AMM	PRM

5. Spécialités de prescription médicale facultative

ACTIFED ALLERGIE CETIRIZINE 10 mg, comprimé pelliculé sécable	PFIZER Santé Grand Public	DMI	P.Nat
HEXAMEDINE AGI PHARMA A 1 POUR MILLE, solution pour application locale	AGI Pharma	Demande d'AMM	P.Nat
HEXAMEDINE PHARMADEVELOPPEMENT A 1 POUR MILLE, solution pour application locale	Pharma Développement	Demande d'AMM	P.Nat

III. Présentation et discussion des dossiers examinés par les groupes de travail Pharmaceutique et les groupes de travail transversaux

1. Dossiers présentés par le Président de la Commission :

Les dossiers suivants, ont été présentés à la Commission d'AMM et approuvés à l'unanimité.

VAXIGRIP, suspension injectable vaccin grippal inactivé à virion fragmenté	SANOFI PASTEUR	DMI	P.Nat
VAXIGRIP, suspension injectable en ampoule vaccin grippal inactivé à virion fragmenté	SANOFI PASTEUR	DMI	P.Nat
TETAGRIP, suspension injectable en seringue préremplie vaccin tétanique et grippalinactivé à virion fragmenté	SANOFI PASTEUR	DMI	P.Nat
MUTAGRIP, suspension injectable seringue préremplie vaccin grippal inactivé à virion fragmenté	SANOFI PASTEUR MSD	DMI	PRM
VAXIGRIP, suspension injectable seringue préremplie vaccin grippa l inactivé à virion	SANOFI PASTEUR	DMI	PRM

fragmenté			
VAXIGRIP ENFANTS, suspension injectable seringue préremplie vaccin grippal inactivé à virion fragmenté	SANOFI PASTEUR	DMI	PRM
SPECIALITES RISPERDAL ET RISPERDALCONSTA L.P	JANSSEN-CILAG	DMI	P.Nat
ALCOOL MODIFIE 70%, solution pour application locale	API	Demande d'AMM	P.Nat
CELANCE 1 mg, **0,25 mg**, **0,05 mg**, comprimé sécable	LILLY France	DMI	P. Nat
DOGMATIL 200 mg, comprimé sécable	Sanofi Aventis France	DMI	P.Nat
DOGMATIL 50 mg, gélule			
DOGMATIL 100 mg/2ml, solution injectable (IM)			
DOGMATIL 0,5 g/100ml SANS SUCRE, solution buvable édulcorée au cyclamate			
DOGMATIL 0,5 g/100ml SANS SUCRE, solution buvable édulcorée à la saccharine			
JOSIR LP 0,4 mg, microgranules à libération prolongée en gélule	BOEHRINGER INGELHEIM France	DMI	P.Nat
MECIR LP 0,4 mg, comprimé pelliculé à libération prolongée	BOEHRINGER INGELHEIM FRANCE	DMI	P.Nat
OMEXEL LP 0, 4 mg comprimé pelliculé à libération prolongée	ASTELLAS PHARMA	DMI	P.Nat
OMIX LP 0,4 mg, microgranules à libération prolongée en gélule	YAMANOUCHI PHARMA	DMI	P.Nat
TAMSULOSINE BIOGARAN LP 0,4 mg, gélule à libération prolongée	BIOGARAN	DMI	P.Nat
TAMSULOSINE BIOORGANICS LP 0,4 mg, gélule à libération prolongée	BIOORGANICS BV	DMI	P.Nat
TAMSULOSINE EG LP 0,4 mg, gélule à libération prolongée	EG LABO	DMI	P.Nat
TAMSULOSINE MERCK LP 0,4 mg, gélule à libération prolongée	MERCK Géériques	DMI	P.Nat
TAMSULOSINE QUALIMED LP 0,4 mg, gélule à libération prolongée	QUALIMED	DMI	P.Nat

PROCUTA 5 mg, 10 mg, 20 mg, 40 mg, capsule molle	EXPANSCIENCE	DMI	PNat
RINGER LACTATE MACOPHARMA, solution pour perfusion	MACOPHARMA	DMI	PRM
RITALINE 10 mg, comprimé	NOVARTIS PHARMA	DMI	P. Nat
RITALINE LP, 20 mg, **30 mg**, **40 mg**, gélule à libération modifiée			
TAMSULOSINE KIRON LP 0,4 mg, gélule à libération prolongée	KIRON PHARMACEUTICA	DMI	PRM
TAMSULOSINE QUALIMED LP 0,4 mg, gélule à libération prolongée	QUALIMED	DMI	PRM
TAMSULOSINE MERCK GENERIQUES LP 0,4 mg, gélule à libération prolongée	MERCK GENERIQUES	DMI	PRM
TAMSULOSINE WINTHROP LP 0,4 mg, gélule à libération prolongée	WINTHROP MEDICAMENTS	DMI	PRM
TAMSULOSINE SANDOZ LP 0,4 mg, gélule à libération prolongée	SANDOZ	DMI	PRM
TAMSULOSINE DCI PHARMA LP 0,4 mg, gélule à libération prolongée	DCI PHARMA	DMI	PRM
TAMSULOSINE G CAM LP 0,4 mg, gélule à libération prolongée	GGAM	DMI	PRM
TAMSULIJN LP 0,4 mg, gélule à libération prolongée	KIRON PHARMACEUTICA	DMI	PRM
TAMSULOSIN RATIOPHARM LP 0,4 mg, gélule à libération prolongée	RATIOPHARM	DMI	PRM

Les dossier suivants, ont été présentés à la Commission d'AMM et approuvés à l'unanimité :

2. Dossiers étudiés par le groupe reproduction, grossesse & allaitement

3. Dossiers étudiés par le groupe pharmaceutique

4. Dossiers étudiés par le groupe pharmaceutique génériques

5. Dossiers étudiés par le groupe de travail Pharmaceutique des Produits Biologiques et des Produits issus des Biotechnologies

Annexe 4-3
REPUBLIQUE FRANÇAISE

IV Point d'information et de suivi

1. MEDIATOR

Avant d'ouvrir le débat sur cette spécialité, le Président demande au membre de la Commission identifié comme ayant un conflit d'intérêt avec le laboratoire de quitter la salle.

Mediator, comprimé pelliculé à 150 mg	Servier	bénéfice/risque	Proc.Nat

Après présentation et discussion des conclusions du Groupe de Travail sur les médicaments de diabétologie, endocrinologie, urologie et gynécologie sur les données d'efficacité et des conclusions de la Commission nationale de Pharmacovigilance sur les données de sécurité d'emploi, les conclusions suivantes ont été émises [1] :

1. Avis favorable à la mention des effets indésirables neuropsychiatriques tels que proposés par la Commission nationale de pharmacovigilance au niveau de la rubrique 4.8. "Effets indésirables" du RCP et de la notice : «troubles de fonctions cognitives : désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) ».

2. Avis DEFAVORABLE au maintien de l'indication : « Adjuvant au régime adapté dans les hypertriglycéridémies ». L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée, les données soumises ne montrant en effet qu'une efficacité très modeste et inconstante sur les triglycérides et une absence d'efficacité sur les autres paramètres lipidiques tels que le LDL-cholestérol. Le maintien de cette indication pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et en particulier les triglycérides, ces hypolipémiants ayant démontré par ailleurs une efficacité en termes de prévention cardiovasculaire.

3. Avis FAVORABLE au maintien de l'indication : « Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » dans son libellé actuel. Néanmoins, aucune conclusion définitive ne peut être portée sur cette efficacité compte tenu de certaines réserves émises sur la méthodologie de l'étude MOULIN, étude pivot dans cette indication. De plus, dans l'attente des résultats d'une autre étude en cours sur les paramètres glucidiques (en association avec d'autres antidiabétiques oraux), aucun motif de protection de la santé publique ne s'oppose à ce que l'indication telle que libellée soit maintenue.

4. Compte tenu des éléments versés dans le dossier de réévaluation, proposition d'inspection de l'essai clinique MOULIN.

5. Les membres de la Commission d'AMM souhaitent qu'une communication soit faite sur l'usage hors AMM de ce médicament.

[1] Cette modification de l'AMM du médicament médiator à été notifiée à la firme le 25 juillet 2007

2. Avis sur le seuil d'éthanol dans les solutions buvables administrées à l'enfant

Ce rapport fait à la demande de l'Afssaps par le groupe de travail « médicaments » de la cellule opérationnelle de toxicovigilance, a été approuvé à l'unanimité par les membres de la Commission.
Ce document propose des valeurs de seuil d'éthanol dans les solutions buvables administrées à l'enfant.

3. Projets de fiches patients

Le projet de fiche patient " **le rhume de l'adulte** " a été présenté aux membres de la Commission d'AMM et approuvé à l'unanimité.

Ces fiches patients élaborées pas l'Afssaps, dans le cadre de la promotion du bon usage des produits de santé seront rassemblées pour constituer un guide sur le bon usage des médicaments à « prescription médicale facultative ».
Ces fiches seront publiées sur le site Internet de l'Afssaps.

4. Mise au point sur l'utilisation de la spécialité TYSABRI® 300 mg

La spécialité TYSABRI®(NATALIZUMAB) a fait l'objet d'une Autorisation de Mise sur le Marché européenne le 27 juin 2006. Elle est indiquée dans le traitement de fond des formes très actives de sclérose en plaques rémittente-récurrente (SEP RR) chez les patients adultes uniquement.

Le natalizumab est un anticorps monoclonal anti- α4-intégrine humanisé.

Le projet du plan de gestion des risques (PGR) a été présenté, pour avis aux membres de la Commission ainsi que la constitution du groupe référent qui aura pour mission d'établir de façon prospective des recommandations en cas de besoin afin de mieux encadrer les risques liés à ce médicament. Ce PGR est disponible sur le site Internet de l'Afssaps (afssaps.sante.fr dans la rubrique Sécurité sanitaire & vigilances/plan de gestion des risques)

5. Rapports publics d'évaluation & Fiches de synthèse

SEROPLEX, SIPRALEX, toutes formes

Une extension d'indication a été octroyée à Seroplex® et Sipralex® (escitalopram) dans le traitement des Troubles Obsessionnels Compulsifs de l'adulte. Cette extension d'indication fait l'objet d'un rapport public d'évaluation (RapPE) qui a été présenté pour Avis, aux membres de la Commission d'AMM.

Ce RapPE est disponible sur le site Internet de L'Afssaps. (afssaps.sante.fr dans la rubrique Documentation & publications/rapports publics d'évaluation)

V. Procédures décentralisées

Demandes d'AMM ou de modifications d'AMM étudiées par la commission et concernant des médicaments en procédure décentralisée.

- OXCARBAZEPINE MERCK 150 mg, comprimé pelliculé (Lab. MERCK GENERIQUES)
- OXCARBAZEPINE MERCK 300 mg, comprimé pelliculé (Lab. MERCK GENERIQUES)
- OXCARBAZEPINE MERCK 12 mg, comprimé pelliculé (Lab. MERCK GENERIQUES)
- OXCARBAZEPINE QUALIMED 150 mg, comprimé pelliculé (Lab. GENERICS UK LTD)
- OXCARBAZEPINE QUALIMED 300 mg, comprimé pelliculé (Lab. GENERICS UK LTD)
- OXCARBAZEPINE QUALIMED 600 mg, comprimé pelliculé (Lab. GENERICS UK LTD)

Les dossiers ont été approuvés par les membres de la Commission sans modification.

VI. Procédures de reconnaissance mutuelle

Demandes d'AMM ou de modifications d'AMM étudiées par la commission et concernant des médicaments en procédure de reconnaissance mutuelle.

- NAROPEINE 2 mg/ml, solution injectable en ampoule
- NAROPEINE 2 mg/ml, solution injectable en poche (Lab. ASTRAZENECA)
- LANZOR 15 mg, microgranules gastrorésistants en gélule
- LANZOR 30 mg, microgranules gastrorésistants en gélule (Lab. Sanofi-Aventis France)
- OGAST 15 mg, microgranules gastrorésistants en gélule
- OGAST 30 mg, microgranules gastrorésistants en gélule
- OGASTORO 15 mg, comprimé orodispersible
- OGASTORO 30 mg, comprimé orodispersible (Lab. Takeda)
- SUMATRIPTAN TEVA 50 mg, comprimé pelliculé sécable
- SUMATRIPTAN TEVA 100 mg, comprimé pelliculé (Lab. TEVA CLASSICS)

Les dossiers ont été approuvés par les membres de la Commission sans modification.

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Agence française de sécurité sanitaire des produits de santé

COMMISSION D'AUTORISATION DE MISE SUR LE MARCHE DES MEDICAMENTS

Réunion n°419 du 5 avril 2007

Feuille d'émargement

Président

M. Daniel VITTECOQ

Vice-présidents

M. Jean-François BERGMANN

Mme Anne GAYOT

Membres

Titulaires

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M. Jacques BELEGAUD
Mme Marie-Claude BONGRAND
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M. Jean DOUCET
Mme Isabelle FOURASTE
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M. Jean-Yves LE HEUZEY
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M. Philippe LECHAT
M. Jean-Noël TALBOT
M. Claude THERY
M. Pierre VEYSSIER
M. Jean-Michel WARNET

Représentants des académies

Titulaires
M. Jean Paul GIROUD
M. Jean-Roger CLAUDE

Suppléant
M. Joël GUILLEMAIN

Présidents de Commissions

Commission Nationale de la Pharmacovigilance
Commission des Stupéfiants et des Psychotropes

Directeur général de l'Afssaps ou son représentant

Mme Sophie FORNAIRON

Directeur général de la santé ou son représentant

Mme Nadine DAVID
M. Nicolas PRISSE

Invités

LEEM

Mme Chrystel JOUAN-FLAHAULT
Mme Anne CARPENTIER

Annexe 4-4

RÉPUBLIQUE FRANÇAISE

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Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

Saint-Denis, le

25 JUIL. 2007

M. le Pharmacien responsable
Laboratoires SERVIER
22 rue Garnier
92578 NEUILLY SUR SEINE cedex

LETTRE RECOMMANDEE AVEC AVIS DE RECEPTION

Dossier suivi par : Mme Catherine REY QUINIO
Mme Anne-Marie CHAMPART
Mme Beatrice POROKHOV
Mme Emilie ALLIEZ
Mme Carole FOSSET MARTINETTI

Réf à rappeler : VNL10008 / CIS 6 242 648 7
COM 419

Monsieur,

Je vous prie de bien vouloir trouver ci-joint, l'ampliation de la décision portant modification de l'autorisation de mise sur le marché de la spécialité :

MEDIATOR 150mg, comprimé enrobé,

suite à la réévaluation du rapport bénéfice / risque du benfluorex.

La présente décision peut faire l'objet d'un recours contentieux devant le Conseil d'Etat dans un délai de deux mois à compter de la date de réception.

Je vous rappelle qu'il vous appartient de prendre toutes dispositions nécessaires à la mise en œuvre de ces modifications, dans les plus brefs délais.

Je vous prie d'agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation
Le Directeur de
l'Evaluation Thérapeutique et de
la Gestion des Procédures d'AMM

Monsieur le Docteur Eric ABADIE

Annexe 4-4

RÉPUBLIQUE FRANÇAISE

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Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation des Médicaments et des Produits Biologiques

Saint-Denis, le

Réf. à rappeler : VNL10008 / CIS 6 242 648 7
COM 419

25 JUIL. 2007

DECISION

DU :

portant modification de l'autorisation de mise sur le marché de la spécialité :

MEDIATOR 150mg, comprimé enrobé

LE DIRECTEUR GENERAL DE L'AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Vu le code de la santé publique, cinquième partie, notamment les articles L. 5121-8, L. 5121-20, R.5121-21 et suivants et R.5121-47 ;

Vu l'autorisation de mise sur le marché (AMM) validée octroyée le 22 avril 1987, modifiée ;

Vu la lettre du 16 mars 2006 demandant aux laboratoires SERVIER de soumettre toute donnée d'efficacité et de sécurité en vue de la réévaluation du rapport bénéfice/risque de la spécialité MEDIATOR 150mg, comprimé enrobé ;

Vu la réponse des laboratoires SERVIER en date du 16 juin 2006 ;

Vu l'avis de la Commission d'AMM prévu à l'article R. 5121-50 du code de la santé publique en date du 5 avril 2007 ;

Vu la lettre du 29 mai 2007 informant les laboratoires SERVIER de l'intention de l'Agence française de sécurité sanitaire des produits de santé de procéder à des modifications de l'AMM de la spécialité MEDIATOR 150mg, comprimé enrobé, concernant les rubriques « Indications thérapeutiques », « Mises en garde spéciales et précautions particulières d'emploi », « Propriétés pharmacodynamiques » et « Effets indésirables » du résumé des caractéristiques du produit (RCP), de la notice et de l'étiquetage et l'invitant à presenter ses observations ;

Vu les réponses des laboratoires SERVIER en date du 15 juin 2007 et 29 juin 2007 ;

Considérant le principe général de prééminence de la protection de la santé publique énoncé par le second considérant de la directive 2001/83/CE du Parlement européen et du Conseil du 6 novembre 2001 instituant un code communautaire ;

Considérant que les notions de nocivité et d'effet thérapeutique ne peuvent être examinées qu'en relation réciproque et n'ont de signification relative qu'appréciées en fonction de l'état d'avancement de la science et compte tenu de la destination du médicament ;

Considérant que l'exigence d'une évaluation du rapport bénéfice/risque présenté par un médicament ne vise pas exclusivement l'octroi de l'AMM, mais implique une évaluation continue ;

Considérant, en l'espèce, que l'analyse des données actuellement disponibles relatives à la sécurité d'emploi et à l'efficacité du médicament MEDIATOR 150mg, comprimé enrobé, met en exergue les éléments suivants :

Annexe 4-4

Données d'efficacité :

Dans l'indication du traitement adjuvant du régime adapté dans les hypertriglycéridémies, les données d'efficacité soumises montrent une efficacité très modeste voire inexistante sur les triglycérides, y compris dans l'étude Moulin où l'efficacité sur les autres paramètres lipidiques tels que le LDL cholestérol n'est pas démontrée.
En l'absence d'étude complémentaire d'efficacité du benfluorex sur les paramètres lipidiques en tant que critère primaire et compte tenu de l'existence d'alternatives thérapeutiques, il n'est pas justifié de maintenir cette indication, qui pourrait conduire à une perte de chance pour les patients puisqu'il existe des hypolipémiants plus efficaces sur les paramètres lipidiques et en particulier les triglycérides, ces hypolipémiants ayant démontré par ailleurs une efficacité en termes de prévention cardiovasculaire. Cette indication doit donc être supprimée.

Dans l'indication du traitement adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale, les résultats de l'étude Moulin semblent montrer une efficacité sur les paramètres glucidiques, en particulier l'HbA1c et ceci indépendamment de la perte de poids.
Néanmoins, à ce jour, aucune conclusion définitive ne peut être portée sur cette efficacité.
Toutefois, dans l'attente de l'analyse des réponses complémentaires apportées sur les aspects méthodologiques de cette etude, ainsi que des résultats de l'inspection qui va être diligentée, aucun motif de protection de la santé publique ne s'oppose à ce que l'indication telle que libellée soit maintenue.

Données de sécurité :

Le bilan de pharmacovigilance réalisé en 2005 et complété en 2007 confirme les données de sécurité d'emploi du benfluorex déjà connues.
S'agissant des troubles neuropsychiatriques, les données disponibles confirment la réalité du risque de survenue de confusions. Cet effet indésirable, déjà mentionné dans le RCP, doit donc être détaillé comme suit : « Troubles des fonctions cognitives : désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception : hallucinations. ».
En revanche, il n'existe pas suffisamment de données permettant d'affirmer l'existence d'un syndrome de sevrage.
Enfin, le faible nombre de cas d'hypertension artérielle pulmonaire idiopathique associées au benfluorex (1 cas pour 17 204 533 mois de traitement) ne constitue pas un signal significatif de toxicité du benfluorex mais doit cependant être interprété par rapport à la sous-notification habituelle en pharmacovigilance.

Considérant que dans ces conditions, il apparaît nécessaire de modifier l'AMM de la spécialité MEDIATOR 150mg, comprimé enrobé, afin de supprimer l'indication du traitement adjuvant du régime adapté dans les hypertriglycéridémies et de détailler les effets indésirables neuropsychiatriques.
Les modifications liées aux indications concernent les rubriques « Indications thérapeutiques », « Mises en garde spéciales et précautions particulières d'emploi » et « Propriétés pharmacodynamiques » du RCP.
Les modifications liées aux troubles neuropsychiatriques, concernent la rubrique « Effets indésirables » du RCP.
Les autres annexes de l'AMM sont modifiées en conséquence.
En outre, compte tenu de la modification des indications de la spécialité MEDIATOR 150mg, le code ATC (Anatomical Therapeutic Chemical classification system) est remplacé par le code « A16AX / Divers médicaments des voies digestives et du métabolisme », dans l'attente du reclassement du benfluorex selon la classification ATC par l'Organisation Mondiale de la Santé (OMS), sur proposition des laboratoires SERVIER auprès de l'OMS ;

DECIDE :

ARTICLE 1er
L'autorisation de mise sur le marché validée octroyée le 22 avril 1987 à la spécialité pharmaceutique dénommée :

MEDIATOR 150mg, comprimé enrobé,

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dont le titulaire est :

Laboratoires SERVIER
22 rue Garnier
92578 NEUILLY SUR SEINE cedex

est modifiée.

ARTICLE 2
Les informations jointes à la présente décision remplacent les informations correspondantes des annexes de l'autorisation de mise sur le marché en vigueur.

ARTICLE 3
Le directeur de l'Evaluation des Médicaments et des Produits Biologiques est chargé de l'exécution de la présente décision.

FAIT A ST DENIS, le 25 JUIL. 2007

LE DIRECTEUR GENERAL

Pour le Directeur Général
et par délégation
Le Directeur de
l'Evaluation Thérapeutique et de
la Gestion des Procédures d'AMM

Monsieur le Docteur Eric ABADIE

P.J. : 4 annexes

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ANNEXE I

RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Chlorhydrate de benfluorex ..... 150,00 mg

pour un comprimé enrobé

Pour les excipients, voir rubrique 6.1

3. FORME PHARMACEUTIQUE

Comprimé enrobé.

4. DONNÉES CLINIQUES

4.1 Indications thérapeutiques

Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

4.2 Posologie et mode d'administration

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante :

- 1ère semaine: 1 comprimé par jour, au cours du dîner ;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner ;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.

En association à un régime adapté, Médiator constitue un traitement adjuvant : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

4.3 Contre-indications

- Hypersensibilité au chlorhydrate de benfluorex ou à l'un des constituants.
- Pancréatites chroniques avérées.

4.4 Mises en garde spéciales et précautions particulières d'emploi

Les troubles métaboliques relevant d'un traitement par Médiator sont essentiellement observés chez l'adulte. La prescription de Médiator n'est donc pas justifiée chez l'enfant.

Si, après une période d'administration de quelques mois (3 à 6 mois), une diminution satisfaisante des concentrations sériques de glucose n'est pas obtenue, des moyens thérapeutiques complémentaires ou différents doivent être envisagés.

L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase.

4.5 Interactions avec d'autres médicaments et autres formes d'interactions

Sans objet.

4.6 Grossesse et allaitement

Grossesse

Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.

En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique du benfluorex lorsqu'il est administré pendant la grossesse.

En conséquence, par mesure de prudence, il est préférable de ne pas utiliser ce médicament pendant la grossesse. En cas d'exposition fortuite, il conviendra d'interrompre ce traitement.

Allaitement

En l'absence de données sur le passage du benfluorex dans le lait maternel, ce médicament est déconseillé au cours de l'allaitement

4.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

L'attention des conducteurs est attirée sur la somnolence pouvant survenir lors de l'utilisation de ce médicament.

4.8 Effets indésirables

Les effets secondaires suivants ont été observés :

- troubles digestifs (nausées, vomissements, gastralgies, diarrhée), asthénie, somnolence ou états vertigineux. Toutefois, ils s'observent plus particulièrement aux posologies supérieures à 3 comprimés par jour et varient en fonction des susceptibilités individuelles ;
- très rares cas de réactions anaphylactiques, hypotension, choc, rash cutané, urticaire, œdème de Quicke ;
- élévation des enzymes hépatiques, hépatite (très rares).
- Confusion, troubles des fonctions cognitives : désorientation tempo-spatiale, troubles du comportement : agitation, délire, troubles de la perception hallucinations (très rare).

4.9 Surdosage

En cas d'absorption massive, le traitement sera uniquement symptomatique: lavage d'estomac, diurèse osmotique, correction des troubles électrolytiques éventuels, surveillance de la pression artérielle, de l'état de conscience ainsi que des fonctions respiratoire et cardiaque.

5. PROPRIÉTÉS PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

Classe pharmacothérapeutique : DIVERS MEDICAMENTS DES VOIES DIGESTIVES ET DU METABOLISME

Code ATC : A16AX

Actions de Médiator sur le métabolisme glucidique:

Chez l'animal, les effets suivants ont été observés :

- facilitation de la pénétration et de l'utilisation cellulaire du glucose (rat) ;
- diminution de l'hyperglycémie chez le rat diabétique (insulinoprive ou non), diminution de l'hyperglycémie (mesurée par l'aire d'HPO) chez le lapin.

Médiator n'a pas d'action sur l'insulino-sécrétion ; la survenue d'hypoglycémie est peu probable.

Effet complémentaire de Médiator :

Une baisse de l'uricémie d'environ 14 % a été observée chez des patients obèses hyperuricémiques traités par Médiator en association à un régime adapté

5.2 Propriétés pharmacocinétiques

L'absorption gastro-intestinale est rapide et totale.

Après administration orale, le pic de concentration plasmatique est maximal entre 1 et 2 heures.

L'élimination est rapide et totale par voie urinaire. Huit heures après l'absorption, 74 % de la dose administrée est éliminée dans les urines.

L'élimination se fait en 2 phases :

- une première phase rapide (60 % en 3 ou 4 heures) ;
- une seconde phase lente, de 36 heures environ.

5.3 Données de sécurité précliniques

Sans objet.

6. DONNÉES PHARMACEUTIQUES

6.1 Liste des excipients

Amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane (E171), éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

6.2 Incompatibilités

Sans objet.

6.3 Durée de conservation

3 ans.

6.4 Précautions particulières de conservation

Pas de précautions particulières de conservation.

6.5 Nature et contenu de l'emballage extérieur

10, 20, 24, 30, 60, 100 ou 270 comprimés sous plaquettes thermoformées (PVC-Aluminium)

6.6 Instructions pour l'utilisation, la manipulation et l'élimination

(Voir rubrique 4.2).

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

LABORATOIRES SERVIER
22, RUE GARNIER
92200 NEUILLY-SUR-SEINE CEDEX

8. PRÉSENTATIONS ET NUMÉROS D'IDENTIFICATION ADMINISTRATIVE

- 317 553-3 :10 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
- 317 555-6 : 20 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
- 317 556-2 : 24 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
- 317 557-9 : 30 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
- 317 558-5 : 60 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
- 317 559-1 : 100 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)
- 371 971-4 : 270 comprimés enrobés sous plaquettes thermoformées (PVC-Aluminium)

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9. DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

10. DATE DE MISE À JOUR DU TEXTE

CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I.

Annexe 4-4

ANNEXE II

A- TITULAIRE DE L'AUTORISATION DE FABRICATION RESPONSABLE DE LA LIBÉRATION DES LOTS ET NOM ET ADRESSE DU PRODUCTEUR DE SUBSTANCE ACTIVE BIOLOGIQUE

LABORATOIRES SERVIER INDUSTRIE
905, ROUTE DE SARAN
45520 GIDY

B- CONDITIONS LIÉES A L'AUTORISATION DE MISE SUR LE MARCHÉ

B.1. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I.

B.2. AUTRES CONDITIONS

Nom du laboratoire de contrôle officiel des médicaments responsable de la libération de lots : sans objet.

C- ENGAGEMENTS DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

Sans objet.

D- COMPOSITION QUALITATIVE ET QUANTITATIVE EN EXCIPIENTS

Sans objet.

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ANNEXE IIIA

ETIQUETAGE

MENTIONS DEVANT FIGURER SUR L'EMBALLAGE EXTÉRIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTÉRIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. COMPOSITION EN SUBSTANCES ACTIVES

Chlorhydrate de benfluorex ..... 150,00 mg

pour un comprimé enrobé

3. LISTE DES EXCIPIENTS

Excipient à effet notoire : saccharose.

4. FORME PHARMACEUTIQUE ET CONTENU

Comprimé enrobé.

Boîte de 10, 20, 24, 30, 60, 100 ou 270 comprimés.

5. MODE ET VOIE(S) D'ADMINISTRATION

Voie orale.

6. MISE EN GARDE SPÉCIALE INDIQUANT QUE LE MÉDICAMENT DOIT ÊTRE CONSERVÉ HORS DE LA PORTÉE ET DE LA VUE DES ENFANTS

Tenir hors de la portée et de la vue des enfants.

7. AUTRE(S) MISE(S) EN GARDE SPÉCIALE(S), SI NÉCESSAIRE

Lire attentivement la notice avant utilisation.

8. DATE DE PÉREMPTION

EXP {MM/AAAA}

9. PRÉCAUTIONS PARTICULIÈRES DE CONSERVATION

Pas de précautions particulières de conservation.

10. PRÉCAUTIONS PARTICULIÈRES D'ÉLIMINATION DES MÉDICAMENTS NON UTILISÉS OU DES DÉCHETS PROVENANT DE CES MÉDICAMENTS S'IL Y A LIEU

Sans objet.

Annexe 4-4

11. NOM ET ADRESSE DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

Titulaire :

LABORATOIRES SERVIER
22, RUE GARNIER
92200 NEUILLY-SUR-SEINE CEDEX

Exploitant :

LABORATOIRES SERVIER
22, RUE GARNIER
92200 NEUILLY-SUR-SEINE CEDEX

Fabricant :

LABORATOIRES SERVIER INDUSTRIE
905, ROUTE DE SARAN
45520 GIDY

12. PRÉSENTATIONS ET NUMÉROS D'IDENTIFICATION ADMINISTRATIVE

Médicament autorisé N° :

13. NUMÉRO DU LOT DE FABRICATION

Lot {numéro}

14. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

Liste I.

15. INDICATIONS D'UTILISATION

Sans objet.

PICTOGRAMME DEVANT FIGURER SUR L'EMBALLAGE EXTERIEUR OU, EN L'ABSENCE D'EMBALLAGE EXTERIEUR, SUR LE CONDITIONNEMENT PRIMAIRE

Le pictogramme doit être conforme à l'arrêté du 18 juillet 2005 pris pour l'application de l'article R.5121-139 du code de la santé publique et relatif à l'apposition d'un pictogramme sur le conditionnement extérieur de certains médicaments et produits.

Annexe 4-4

MENTIONS MINIMALES DEVANT FIGURER SUR LES PLAQUETTES THERMOFORMÉES OU LES FILMS THERMOSOUDÉS

1. DÉNOMINATION DU MÉDICAMENT

MEDIATOR 150 mg, comprimé enrobé

2. NOM DU TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ

TITULAIRE/EXPLOITANT : LABORATOIRES SERVIER

3. DATE DE PÉREMPTION

EXP {MM/AAAA}

4. NUMÉRO DE LOT

Lot {numéro}

Annexe 4-4

MENTIONS MINIMALES DEVANT FIGURER SUR LES PETITS CONDITIONNEMENTS PRIMAIRES

1. DÉNOMINATION DU MÉDICAMENT ET VOIE(S) D'ADMINISTRATION

Sans objet.

2. MODE D'ADMINISTRATION

Sans objet.

3. DATE DE PÉREMPTION

Sans objet.

4. NUMÉRO DE LOT

Sans objet.

5. CONTENU EN POIDS, VOLUME OU UNITÉ

Sans objet.

Annexe 4-4

ANNEXE IIIB

NOTICE

Concerne les médicaments pouvant être obtenus uniquement sur ordonnance :

Veuillez lire attentivement l'intégralité de cette notice avant de prendre ce médicament.

- Gardez cette notice, vous pourriez avoir besoin de la relire.
- Si vous avez d'autres questions, si vous avez un doute, demandez plus d'informations à votre médecin ou à votre pharmacien.

Ce médicament vous a été personnellement prescrit. Ne le donnez jamais à quelqu'un d'autre, même en cas de symptômes identiques, cela pourrait lui être nocif.

Dénomination du médicament

MEDIATOR 150 mg, comprimé enrobé

Liste complète des substances actives et des excipients

La substance active est :

Chlorhydrate de benfluorex ..... 150,00 mg

pour un comprimé enrobé

Les autres composants sont :

Amidon de maïs, bicarbonate de sodium, carmellose sodique, cire d'abeille blanche, dioxyde de titane (E171), éthylcellulose, monooléate de glycérol, polysorbate 80, povidone, saccharose, silice colloïdale anhydre, stéarate de magnésium, talc.

Nom et adresse du titulaire de l'autorisation de mise sur le marché et du titulaire de l'autorisation de fabrication responsable de la libération des lots, si différent

Titulaire :

LABORATOIRES SERVIER
22, RUE GARNIER
92200 NEUILLY-SUR-SEINE CEDEX

Exploitant :

LABORATOIRES SERVIER
22, RUE GARNIER
92200 NEUILLY-SUR-SEINE CEDEX

Fabricant :

LABORATOIRES SERVIER INDUSTRIE
905, ROUTE DE SARAN
45520 GIDY

1. QU'EST-CE QUE MEDIATOR 150 mg, comprimé enrobé ET DANS QUEL CAS EST-IL UTILISÉ ?

Forme pharmaceutique et contenu ; classe pharmacothérapeutique

Médiator 150 mg, comprimé enrobé contient du chlorhydrate de benfluorex.

Médiator 150 mg se présente sous la forme de comprimés enrobés.

Boîtes de 10, 20, 24, 30, 60, 100 et 270 comprimés.

Annexe 4-4

Indications thérapeutiques

Ce traitement est préconisé comme adjuvant à un régime adapté chez les diabétiques avec surcharge pondérale (taux de sucre élevé dans le sang).

2. QUELLES SONT LES INFORMATIONS NÉCESSAIRES AVANT DE PRENDRE MEDIATOR 150 mg, comprimé enrobé?

Liste des informations nécessaires avant la prise du médicament

Sans objet.

Contre-indications

Ne prenez jamais MEDIATOR 150 mg, comprimé enrobé dans les cas suivants :

- allergie au chlorhydrate de benfluorex ou à l'un des composants du produit ;
- en cas de pancréatite chronique (insuffisance de fonctionnement chronique du pancréas).

Précautions d'emploi ; mises en garde spéciales

Faites attention avec MEDIATOR 150 mg, comprimé enrobé dans les cas suivants :

Un régime alimentaire adapté doit être poursuivi pendant toute la durée du traitement.

Si après une période de plusieurs mois (3 à 6 mois), une diminution des concentrations de glucose (sucre) dans le sang n'est pas obtenue, votre médecin pourra envisager d'autres moyens thérapeutiques adaptés à votre cas.

En raison de la présence de saccharose, ce médicament ne doit pas être utilisé en cas d'intolérance au fructose, de syndrome de malabsorption du glucose et du galactose ou de déficit en sucrase-isomaltase (maladies métaboliques rares).

Interactions avec les aliments et les boissons

Sans objet.

Utilisation pendant la grossesse et l'allaitement

Grossesse et Allaitement

Il est préférable de ne pas utiliser ce médicament pendant la grossesse ou au cours de l'allaitement.

Si vous découvrez que vous êtes enceinte pendant le traitement, consultez votre médecin car lui seul peut juger de la nécessité de le poursuivre.

Sportifs

Attention, cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopage.

Effets sur l'aptitude à conduire des véhicules ou à utiliser des machines

Conduite de véhicules et utilisation de machines :

L'attention est attirée sur le risque de somnolence pouvant survenir avec ce médicament.

Liste des excipients à effet notoire

Liste des excipients à effet notoire : saccharose.

Interaction avec d'autres médicaments

Sans objet.

Annexe 4-4

3. COMMENT PRENDRE MEDIATOR 150 mg, comprimé enrobé ?

Instructions pour un bon usage

Sans objet.

Posologie, Mode et/ou voie(s) d'administration, Fréquence d'administration et Durée du traitement

Posologie

RESERVE A L'ADULTE.

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante :

- 1ère semaine: 1 comprimé par jour, au cours du dîner ;
- 2ème semaine: 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner ;
- à partir de la 3ème semaine: 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

La posologie peut-être ramenée à 2 comprimés par jour, voire 1 comprimé par jour, en fonction des résultats biologiques.

Dans tous les cas, se conformer strictement à l'ordonnance de votre médecin.

Symptômes et instructions en cas de surdosage

Si vous avez pris plus de MEDIATOR 150 mg, comprimé enrobé que vous n'auriez dû :

Les signes de surdosage peuvent être des troubles digestifs (nausées, vomissements, diarrhée), une sensation vertigineuse voire une somnolence. En cas d'apparition de ces troubles, consultez votre médecin ou votre pharmacien.

Instructions en cas d'omission d'une ou de plusieurs doses

Si vous oubliez de prendre MEDIATOR 150 mg, comprimé enrobé :

Ne prenez pas de dose double pour compenser la dose simple que vous avez oublié de prendre.

Risque de syndrome de sevrage

Sans objet.

4. QUELS SONT LES EFFETS INDÉSIRABLES ÉVENTUELS ?

Description des effets indésirables

Comme tous les médicaments, MEDIATOR 150 mg, comprimé enrobé est susceptible d'avoir des effets indésirables.

- troubles digestifs : nausées, vomissements, maux d'estomac ;
- sensation de fatigue, voire somnolence ;
- sensations vertigineuses.

Ces effets ont été observés à des posologies supérieures à 3 comprimés par jour et varient en fonction de la susceptibilité individuelle des patients.

- très rares cas de manifestations allergiques : éruptions cutanées soudaines, urticaire, malaise brutal avec hypotension (diminution de la pression artérielle) œdème de Quicke (brusque gonflement du visage et du cou). Dans ce cas, le traitement devra immédiatement être interrompu.
- élévation des enzymes hépatiques (anomalies biologiques au niveau du foie). Très rares cas d'hépatite.
- Très rares cas de confusion, troubles des fonctions cognitives : désorientation tempo-spatiale, troubles du comportement : agitation, délire, troubles de la perception hallucinations.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

Annexe 4-4

5. COMMENT CONSERVER MEDIATOR 150 mg, comprimé enrobé ?

Conditions de conservation et date de péremption

Pas de précautions particulières de conservation.

Tenir hors de la portée et de la vue des enfants.

Ne pas utiliser après la date de péremption figurant sur la boîte.

Si nécessaire, mises en garde contre certains signes visibles de détérioration

Sans objet.

La dernière date à laquelle cette notice a été approuvée est le {date}

Annexe 4-5

DIRECTION DE L=EVALUATION
DES MÉDICAMENTS ET DES
PRODUITS BIOLOGIQUES

Dossier suivi par : Dr C. Rey-Quinio
Tel : 01.55.87.34.45/Fax : 01.55.87.34.42
Catherine.rey-quinio@afssaps.sante.fr

Saint-Denis, le 21 Mai 2007

Note à l'attention de M. BERTOYE
DIE/Inspection des Essais Cliniques

Objet : Médiator/Demande d'Inspection Etude Moulin

En date du 5 Avril dernier, les conclusions de la réévaluation du Bénéfice/Risque de la spécialité Médiator effectuées par le Groupe de Travail DEUG ont été présentées et validées par la Commission d'Autorisation de Mise sur le Marché, à savoir un avis défavorable au maintien de l'indication « adjuvant au régime adapté dans les hypertriglycéridémies », et un avis favorable au maintien de l'indication : « Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ».

La Commission a par ailleurs souhaité devant les questions méthodologiques soulevées par les résultats de l'étude Moulin qu'une inspection de cette étude soit effectuée (voir relevé d'avis). **L'étude Moulin** (publiée dans Diabetes Care en 2006) est une étude multicentrique, internationale, randomisée en double aveugle, d'une durée de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par SU et intolérants ou ayant une contre indication à la metformine. Le critère principal était l'HbA1c; les critères secondaires: insulinémie, glycémie à jeun, paramètres lipidiques, index d'insulino-résistance HOMA. Trois sous-groupes ont été analysés: HbA1c > 8%, âge > 65 ans et clairance de la créatininémie < 80ml/mn. Il s'agit d'une étude de supériorité avec une différence attendue de 0.6% entre les groupes sur l'HbA1c. Les résultats de cette étude (utilisation en seconde intention, en association à un sulfamide hypoglycémiant) semblent montrer une efficacité du benfluorex sur les paramètres glucidiques, en particulier l'HbA1c et ceci indépendamment de la perte de poids. Néanmoins, aucune conclusion définitive n'a été portée sur l'efficacité du benfluorex compte-tenu des réserves méthodologiques soulevées par les experts mandatés. A noter, cette étude est la seule étude à ce jour ayant montré une efficacité sur les paramètres glucidiques en seconde intention, en association à un autre antidiabétique oral.

Je vous remercie de me faire savoir dans quels délais l'inspection de cette étude pourra être menée par votre Département. A noter, en l'attente des résultats de cette inspection, ainsi que des résultats d'études complémentaires sur le métabolisme glucidique actuellement en cours, la Commission d'AMM a décidé, sur proposition du Groupe DEUG, qu'aucune modification du libellé de l'indication restante ne serait effectuée.

Vous souhaitant bonne réception de ces éléments, nous restons à votre entière disposition pour de plus amples renseignements sur ce dossier si besoin est.

Cordialement,

Copies
S. Fornairon
J.H. Trouvin
O. Leblaye

PJ Relevé d'Avis

Annexe 4-6

Expéditeur:	Olivier LEBLAYE
Destinataire:	Catherine REY-QUINIO
CC:	Anny FETTER; Pierre BERTOYE
Date:	vendredi 30 novembre 2007 18:31
Objet:	Retour d'info inspections Médiator

Catherine,

Quelques mots pour te tenir informée de l'avancement du dossier Médiator. Informations préliminaires, la procédure contradictoire avec les différents sites inspectés est nécessaire pour que l'on puisse considérer ces observations comme définitives et en tirer des conclusions. Donc infos internes pour le moment.

4 inspections ont été menées :

- le promoteur, Servier. Quelques observations de forme, mais globalement on peut dire qu'ils ont correctement suivi leur essai, au moins en terme de fréquence de monitoring, et ce dans tous les pays impliqués (y compris Malaisie et Afrique du Sud).

- le labo centralisé en charge des dosages d'HbA1c, MDS Pharma Services à Hambourg. Quelques points à vérifier à partir de documents reçus après l'inspection, mais a priori pas de problème.

- centre n°201 (Dr Alawi, investigateur coordonnateur DE, 16 patients sélectionnés, 13 randomisés) : ça commence à se dégrader un peu. Nous avons revu les données de 12 patients. Pas mal de petites incohérences entre le rapport de l'essai et les dossiers médicaux, chacune sans impact sur les résultats (erreurs de dates, de début ou de fin de traitements ou d'événements indésirables, de comptabilité de médicaments...) mais montrant une qualité de monitoring un peu légère malgré sa fréquence. Une déviation au protocole non rapportée par l'investigateur et non vue par le moniteur est à noter : l'augmentation de dose du traitement d'un patient par glimépiride en cours d'essai., ce qui peut avoir un impact sur le critère d'évaluation principal.

- centre n°207 (Dr Müller, également en Allemagne, 40 patients sélectionnés, 27 inclus). Là, ça se gâte carrément. Nous avons revu les dossiers de 10 patients et les ECGs de tous les patients. Très peu d'information dans les dossiers médicaux. En particulier la dose du traitement de fond par sulfonylurée n'était que rarement enregistrée avant l'essai, ce qui ne permet pas de vérifier qu'elle était stable (c'était noté pour la période de l'essai lui-même). "Trous" dans les prescriptions de sulfonylurée, il nous a dit qu'il donnait des échantillons gratuits à ses patients (il en avait effectivement 2 pleins tiroirs). Généralement pas d'info dans les dossiers médicaux concernant l'intolérance à la metformine (critère d'inclusion). Et surtout, nous avons un gros problème sur les ECGs : pour un patient, l'ECG semaine 0 et l'ECG semaine 18 sont identiques, c'est juste une réimpression en mettant une date différente dessus. Et pour 2 patients, les ECGs de l'essai sont très différents de ceux

que nous avons dans le dossier médical du patient et ne proviennent manifestement pas de même bonhomme. S'il n'y avait qu'un ECG dans le dossier ou un ECG dans l'essai, on pourrait se dire que c'est une bête erreur, mais c'est un peu plus compliqué. Nous avons un patient pour lequel les 3 ECGs de l'essai proviennent bien d'une même personne et sont anormaux, avec des signes d'ischémie sur toutes les dérivations standard et en V5-V6 plus un rabotage de r en V1-V2-V3. Aucun de ces signes sur un ECG d'avant l'essai et 2 ECGs d'après l'essai trouvés dans le dossier médical (et les 3 ECGs du dossier ont un tracé tout à fait similaire). Pour un autre, le dossier médical mentionne une anomalie d'Ebstein, avec une insuffisance aortique et mitrale et une hypertrophie ventriculaire, mais il n'y en a aucun signe sur les 3 ECGs de l'essai, qui sont différents de ceux du dossier médical. L'investigateur nous dit que les ECGs ont été faits par son infirmière et que lui a fait tout le reste, mais que peut on croire dans ce cas... Mes collègues allemands doivent voir avec leur service juridique s'ils pourraient contacter les patients pour vérifier qu'ils ont bien participé à l'essai, comme nous le faisons dans ce genre de cas chez des investigateurs français.

Je te tiendrai au courant de l'avancement du dossier et des résultats de la procédure contradictoire.

Olivier

Annexe 4-7

RÉPUBLIQUE FRANÇAISE

afssaps

Agence française de sécurité sanitaire des produits de santé

Direction de l'évaluation des médicaments et des produits biologiques
Département de l'évaluation de la qualité pharmaceutique
Dossier suivi par Anne Dunand / Antoine Sawaya
Tél. +33 (0)1 55 87 33 57 / 33 60
Fax. +33 (0)1 55 87 41 02/33 52
E-mail anne.dunand@afssaps.sante.fr / antoine.sawaya@afssaps.sante.fr

Saint-Denis, le 23 DEC. 2010

Note

à l'attention de la mission de l'Inspection Générale des Affaires Sociales sur le retrait du benfluorex

Objet : Eléments relatifs à l'octroi, suspension, retrait de l'AMM des spécialités génériques de MEDIATOR, ainsi qu'à l'instruction de la demande d'AMM.
Réf. : Demande des membres de la mission IGAS du 22 décembre 2010 dans le cadre de l'enquête relative au retrait du benfluorex

Lors de l'entretien mené avec Madame Rey-Quinio le 22 décembre 2010, dans le cadre de l'enquête de l'IGAS relative au retrait des spécialités à base de benfluorex, Monsieur Marie, Inspecteur de la Mission, a posé deux questions relatives aux spécialités génériques de MEDIATOR.

1. **Génériques de Médiator : type de procédure (positionnement réglementaire) ; type de données soumises (relevés d'avis), date de décision.**

Deux demandes d'Autorisation de Mise sur le Marché (AMM) ont été déposées à l'AFSSaPS le 8 décembre 2005 par les Laboratoires MERCK GENERIQUES (aujourd'hui nommés MYLAN) et QUALIMED. L'AMM des spécialités BENFLUOREX MERCK GENERIQUES et QUALIMED a été demandée dans le cadre de la procédure nationale, par référence à l'article 10 (1) de la Directive 2001/83/CE modifiée, qui définit les conditions d'autorisation d'un médicament générique, et en référence à la spécialité de référence MEDIATOR 150 mg, comprimé enrobé.

Le dossier versé à l'appui des demandes d'AMM comprenait, conformément aux dispositions de l'article R. 5121-28 du Code de la santé publique (CSP), outre les données chimiques et pharmaceutiques, une étude de biodisponibilité comparée démontrant la bioéquivalence avec la spécialité de référence (cf annexes I et II : relevés d'avis du groupe de travail sur les médicaments génériques (GTMG) n°126 du 5 octobre 2006).

En outre, la spécialité BENFLUOREX MYLAN 150 mg, comprimé enrobé (anciennement appelée BENFLUOREX MERCK 150 mg, comprimé enrobé) a été autorisée par décision du 10/03/2008, et la spécialité BENFLUOREX QUALIMED 150 mg, comprimé enrobé, par décision du 26/03/2008.

Par la suite, l'AMM des deux spécialités a été suspendue par décision du 24/11/2009, puis retirée le 20/07/2010.

2. **N'était il pas possible de suspendre l'évaluation de ces dossiers de génériques compte tenu de la révision du bénéfice risque en cours pour Médiator ? Ou était-on obligé d'octroyer les AMM pour ces deux génériques ? Sur quelle base réglementaire s'appuie-t-on ?**

Entre décembre 2005 et octobre 2006 (date du groupe de travail), ni même en mars 2008 (date d'octroi des AMM), aucun élément ne permettait de suspendre l'évaluation des demandes d'AMM pour des spécialités génériques de MEDIATOR. En effet, les motifs de refus d'AMM sont clairement définis par l'article L. 5121-9 du CSP qui dispose notamment que :

> *"L'autorisation prévue à l'article L. 5121-8 est refusée lorsqu'il apparaît que l'évaluation des effets thérapeutiques positifs du médicament ou produit au regard des risques pour la santé du patient ou la santé publique liés à sa qualité, à sa sécurité ou à son efficacité n'est pas considérée comme favorable, ou qu'il n'a pas la composition qualitative et quantitative déclarée, ou que l'effet thérapeutique annoncé fait défaut ou est insuffisamment démontré par le demandeur.*
>
> *Elle est également refusée lorsque la documentation et les renseignements fournis ne sont pas conformes au dossier qui doit être présenté à l'appui de la demande.*
>
> *Toutefois, dans des circonstances exceptionnelles et sous réserve du respect d'obligations spécifiques définies par voie réglementaire, concernant notamment la sécurité du médicament, la notification à l'Agence française de sécurité sanitaire des produits de santé de tout incident lié à son utilisation et les mesures à prendre dans ce cas, l'autorisation de mise sur le marché peut être délivrée à un demandeur qui démontre qu'il n'est pas en mesure de fournir des renseignements complets sur l'efficacité et la sécurité du médicament dans des conditions normales d'emploi. Le maintien de cette autorisation est décidé par l'agence sur la base d'une réévaluation annuelle de ces obligations et de leur respect par le titulaire.*
>
> *L'autorisation prévue à l'article L. 5121-8 est suspendue ou retirée dans des conditions déterminées par voie réglementaire et en particulier lorsqu'il apparaît que l'évaluation des effets thérapeutiques positifs du médicament ou produit au regard des risques tels que définis au premier alinéa n'est pas considérée comme favorable dans les conditions normales d'emploi, que l'effet thérapeutique annoncé fait défaut ou que la spécialité n'a pas la composition qualitative et quantitative déclarée."*

Or, au moment du dépôt du dossier (en décembre 2005) et à la date d'octroi des AMM génériques de MEDIATOR (en mars 2008), les résultats des études pour la réévaluation du rapport bénéfice/risque de la spécialité de référence étaient encore attendus.
En conséquence, l'AFSSPS ne disposait d'aucune base réglementaire pour suspendre l'évaluation et/ou refuser de délivrer les AMM génériques.
Néanmoins, tout élément nouveau issu du réexamen du MEDIATOR entraînait *de facto* un réexamen des spécialités génériques.

De plus, le groupe de travail (GTMG n°126) a prononcé un avis favorable à l'AMM en octobre 2006, confirmé par la Commission d'AMM n°410 du 09/11/2006.
Toutefois, les AMM n'ont été délivrées qu'en mars 2008, car leur octroi était conditionné à l'engagement des firmes sur un plan pour la minimisation du risque et le temps nécessaire à sa mise en place.
Il convient de noter que d'une manière générale, un délai est fréquemment observé entre le dépôt de la demande d'AMM, son octroi et la commercialisation du médicament. En effet, lorsque le dossier est jugé insuffisant, conformément à l'article R. 5121-34 du CSP, le Directeur général de l'AFSSaPS peut exiger du demandeur qu'il complète son dossier. En l'espèce, plus de deux ans séparent la demande et la décision d'AMM. Ce délai s'explique par le temps nécessaire, à l'obtention d'un plan de minimisation du risque et au recueil des informations complémentaires requises pour compléter le dossier de demande d'AMM initial.

Compte tenu de l'ensemble de ce qui précède, aucun élément ne permettait de fonder le refus des AMM demandées pour les spécialités génériques de la spécialité de référence Médiator. Et, dans ces conditions, refuser l'AMM aux spécialités génériques, alors que l'AMM de la spécialité de référence était toujours en vigueur, aurait entraîné un risque de rupture d'égalité entre les opérateurs concernés.

Mes services se tiennent à votre disposition pour tout complément d'information.

Le Directeur Général

N.B. Sont joints à cette note des courriers antérieurs échangés entre l'Afssaps et la Commission et relatifs aux génériques.

Jean MARIMBERT

ANNEXE I

REUNION GTMG N° 126 DU 05 OCTOBRE 2006

- **BENFLUOREX QUALIMED 150 mg**, comprimé enrobé

dossier n° NL 32453

CIS : 6 558 026 6

CEP R0-CEP 2002-092-Rev 02 (Chlorhydrate de benfluorex – SYNTECO SPA – Italie)

Laboratoires **QUALIMED**

Demande déposée le : **08/12/2005**
Date de dépôt de la réponse : 03/07/2006

Procédure nationale

Principe actif : **CHLORHYDRATE DE BENFLUOREX**

Caractère d'originalité : 2.1.2 Essentiellement similaire de + 10 ans
MEDIATOR 150 mg, comprimé enrobé – VNL 10008
(AMM : 16/07/1974) - Lab. SERVIER

Classe ATC : **C : SYSTEME CARDIOVASCULAIRE**

Réf. LIBRA : Pharmaco : Inhibiteurs de la synthèse du cholestérol et des triglycérides (196)
Hypolipidémiants (13)
Autres hypocholestérolemiants (195)

AVIS DU GROUPE DE TRAVAIL SUR LES MEDICAMENTS GENERIQUES N° 117 DU 02 FEVRIER 2006 : SURSIS A STATUER dans l'attente de l'avis de la toxicologie sur le risque génotoxique potentiel de l'impureté E.

Au plan biopharmaceutique

Un essai de bioéquivalence réalisé avec le comprimé 150 mg est fourni à l'appui de la présente demande.

Bref descriptif de l'étude fournie :

- L'essai fourni a été réalisé en Mars-Avril 2005 par la société PAREXEL-FARMOVS en Afrique du Sud.
- Le schéma expérimental suivi est classique ; *cross-over* 2 bras randomisé.
- Dose unique de 150 mg administrée 5 min après un petit-déjeuner standard (soit un comprimé dosé à 150 mg).
- Monitoring des concentrations plasmatiques pendant 96 heures et une période de wash-out de 19 jours entre les deux séquences de traitement.
- 46 observations analysables sont prévues par le protocole. 48 volontaires sains ont été inclus, ont fini l'étude et ont été analysés.

Les produits comparés :

Produit test :
Comprimés Benfluorex 150 mg fabriqués par ROTTENDORF à Valenciennes, FRANCE. Ces comprimés sont issus du lot n° 4004 dont la taille théorique est de 200 000 unités.

Produit de référence :
MEDIATOR 150 mg comprimés commercialisés en France par SERVIER et issus du lot 3M5203.

Analytique :

Le dosage plasmatique des deux métabolites Norfenfluramine (NFF) et de la THEP a été réalisé par FARMOVS en Afrique du Sud au moyen d'une technique LC-MS-MS, dont la LOQ s'établit à 0.2 et 0.4 ng/ml pour respectivement chacun de ces deux analytes. Cette technique est clairement décrite et validée.
Le dosage plasmatique du Benfluorex a été tenté au moyen de la même technique LC-MS-MS avec une LOQ de 0.4 ng/ml. Cette technique n'a pas permis l'exploration du Benfluorex en raison des faibles concentrations circulantes.

Commentaires :
Le demandeur doit discuter si une amélioration des performances de la techniques analytique n'était pas possible, permettant ainsi l'exploration de la molécule mère.

Les résultats :

Les résultats obtenus pour les deux métabolites Norfenfluramine et THEP sont récapitulés dans le tableau ci-dessous.

Norfenfluramine:

	Test	Référence		ICS 90 %
AUC 0-t (ng.h/ml)	416 ± 114	403 ± 108	NS	[94 ; 101] %
AUC 0-∞ (ng.h/ml)	443 ± 144	433 ± 147	NS	[95 ; 101] %
Cmax (ng/ml)	16.0 ± 3.52	15 ± 2.29	P < 0.05	[91 ; 99] %
Tmax (h)	5.5	6	NS	----------

THEP:

	Test	Référence		ICS 90 %
AUC 0-t (ng.h/ml)	80.4 ± 39	80.6 ± 40.8	NS	[92 ; 110] %
AUC 0-∞ (ng.h/ml)	86.5 ± 38.6	86.3 ± 40.3	NS	[93 ; 107] %
Cmax (ng/ml)	16.3 ± 8.25	15.6 ± 8.17	NS	[86 ; 109] %
Tmax (h)	5.5	5.5	NS	----------

Conclusion :

Basés sur les données des deux métabolites, les résultats obtenus montrent la bioéquivalence entre les deux comprimés comparés.

Au plan biopharmaceutique

QUESTIONS

Il devra être discuté si une amélioration des performances de la techniques analytique n'était pas possible, permettant ainsi l'exploration de la molécule mère inchangée.

Au plan pharmaceutique

QUESTIONS

Module 3.2 S.3

- La démonstration de la structure pourrait être complétée par un spectre RMN 13C.

Module 3.2 P.1 et 3.2 P.5

- La viscosité de la carmellose sodique devra être précisée.

Module 3.2 P.1 et 3.2 P.3

- Il devra être précisé quelle quantité de suspension d'éthylcellulose est utilisée puisqu'en 3.2.P3 et 3.2.P1 seule la quantité d'éthylcellulose est mentionnée.
- Le laurilsulfate de sodium et l'alcool cétylique contenus dans la suspension aqueuse devront figurer dans la formule.

Module 3.2 P.3

- La taille du lot industriel devra être précisée.

Module 3.2 P.5

- Les spécifications en impuretés à libération sont supérieures à celles retenues pour la matière première. Celles-ci devront être resserrées.
- Dans la formule de calcul de l'essai de dissolution, il manque un facteur 100 au dénominateur. Ceci devra être corrigé.

Module 3.2 P.8

- L'augmentation de la limite en impuretés totales n'est pas acceptable. La limite en impureté E devra être revue conformément aux résultats expérimentaux obtenus.

La durée de conservation qui pourrait être accordée est de 12 mois à une température ne dépassant pas 25°C.

Note au groupe toxicologique

- Un module 4 a été déposé par la firme et transmis au groupe toxicologique pour évaluation. Il comprend 2 études mise en oeuvre pour qualifier **l'impureté E**. Ces 2 études documentent le **risque potentiel génotoxique** de cette impureté.

Note interne

- Le stéarate de magnésium est d'origine végétale, l'attestation de UNION DERIVAN est fournie.
- Le polysorbate 80 est d'origine végétale, l'attestation de SEPPIC est fournie.
- Les monooléates de glycérol sont d'origine végétale, l'attestation de GATTEFOSSE est fournie.

AVIS DU GROUPE DE TRAVAIL SUR LES MEDICAMENTS GENERIQUES N° 121 DU 18 MAI 2006 : MESURE D'INSTRUCTION

Au plan biopharmaceutique

QUESTIONS

Il devra être discuté si une amélioration des performances de la techniques analytique n'était pas possible, permettant ainsi l'exploration de la molécule mère inchangée.

Au plan pharmaceutique

QUESTIONS

Module 3.2 S.3

- La démonstration de la structure pourrait être complétée par un spectre RMN 13C.

Module 3.2 P.1 et 3.2 P.5

- La viscosité de la carmellose sodique devra être précisée.

Module 3.2 P.1 et 3.2 P.3

- Il devra être précisé quelle quantité de suspension d'éthylcellulose est utilisée puisqu'en 3.2.P3 et 3.2.P1 seule la quantité d'éthylcellulose est mentionnée.
- Le laurilsulfate de sodium et l'alcool cétylique contenus dans la suspension aqueuse devront figurer dans la formule.

Module 3.2 P.3

- La taille du lot industriel devra être précisée.

Module 3.2 P.5

- Les spécifications en impuretés à libération sont supérieures à celles retenues pour la matière première. Celles-ci devront être resserrées.
- Dans la formule de calcul de l'essai de dissolution, il manque un facteur 100 au dénominateur. Ceci devra être corrigé.

Module 3.2 P.8

- L'augmentation de la limite en impuretés totales n'est pas acceptable. La limite en impureté E devra être revue conformément aux résultats expérimentaux obtenus.

La durée de conservation qui pourrait être accordée est de 12 mois à une température ne dépassant pas 25°C.

Avis du groupe toxicologique

Le groupe préclinique GTPC 126 du 15/03/2006 (com 401 du 11/05/2006) a émis un avis favorable. En effet :
- les données toxicologiques fournies par la firme relatives à l'impureté E sont satisfaisantes.

Note interne

- Le stéarate de magnésium est d'origine végétale, l'attestation de UNION DERIVAN est fournie.
- Le polysorbate 80 est d'origine végétale, l'attestation de SEPPIC est fournie.
- Les monooléates de glycérol sont d'origine végétale, l'attestation de GATTEFOSSE est fournie.

AVIS DU GROUPE DE TRAVAIL SUR LES MEDICAMENTS GENERIQUES N° 126 DU 05 OCTOBRE 2006 : AVIS FAVORABLE avec une durée de conservation de 12 mois à une température ne dépassant pas + 25°C

Cette spécialité est générique de MEDIATOR 150 mg, comprimé enrobé.

Au plan biopharmaceutique

Il n'était pas possible de diminuer la LOQ du benfluorex qui avait déjà été optimisée.

Au plan pharmaceutique

CLARIFICATIONS

Module 3.2.P.5

- Les nouvelles spécifications en impuretés dans le produit fini tant à libération qu'en stabilité doivent être confortées au vu des résultats sur les lots de taille industrielle.

Avis du groupe toxicologique

Le groupe préclinique GTPC 126 du 15/03/2006 (com 401 du 11/05/2006) a émis un avis favorable. En effet :
- les données toxicologiques fournies par la firme relatives à l'impureté E sont satisfaisantes.

Note Interne

- Le stéarate de magnésium est d'origine végétale, l'attestation de UNION DERIVAN est fournie.
- Le polysorbate 80 est d'origine végétale, l'attestation de SEPPIC est fournie.
- Les monooléates de glycérol sont d'origine végétale, l'attestation de GATTEFOSSE est fournie.

ANNEXE II

REUNION GTMG N° 126 DU 05 OCTOBRE 2006

- **BENFLUOREX MERCK 150 mg**, comprimé enrobé

dossier n° NL 32454

CIS : 6 114 062 9

CEP R0-CEP 2002-092-Rev 02 (Chlorhydrate de benfluorex – SYNTECO SPA – Italie)

Laboratoires **MERCK GENERIQUES**

Demande déposée le : **08/12/2005**
Date de dépôt de la réponse : 03/07/2006

Procédure nationale

Principe actif : **CHLORHYDRATE DE BENFLUOREX**

Caractère d'originalité : 2.1.2 Essentiellement similaire de + 10 ans
MEDIATOR 150 mg, comprimé enrobé – VNL 10008
(AMM : 16/07/1974) - Lab. SERVIER

Classe ATC : **C : SYSTEME CARDIOVASCULAIRE**

Réf. LIBRA : Pharmaco : Inhibiteurs de la synthèse du cholestérol et des triglycérides (196)
Hypolipidémiants (13)
Autres hypocholestérolemiants (195)

AVIS DU GROUPE DE TRAVAIL SUR LES MEDICAMENTS GENERIQUES N° 117 DU 02 FEVRIER 2006 : SURSIS A STATUER dans l'attente de l'avis de la toxicologie sur le risque génotoxique potentiel de l'impureté E.

Au plan biopharmaceutique

Un essai de bioéquivalence réalisé avec le comprimé 150 mg est fourni à l'appui de la présente demande.

Bref descriptif de l'étude fournie :

- L'essai fourni a été réalisé en Mars-Avril 2005 par la société PAREXEL-FARMOVS en Afrique du Sud.
- Le schéma expérimental suivi est classique : *cross-over* 2 bras randomisé.
- Dose unique de 150 mg administrée 5 min après un petit-déjeuner standard (soit un comprimé dosé à 150 mg).
- Monitoring des concentrations plasmatiques pendant 96 heures et une période de wash-out de 19 jours entre les deux séquences de traitement.
- 46 observations analysables sont prévues par le protocole. 48 volontaires sains ont été inclus, ont fini l'étude et ont été analysés.

Les produits comparés :

Produit test :
Comprimés Benfluorex 150 mg fabriqués par ROTTENDORF à Valenciennes, FRANCE. Ces comprimés sont issus du lot n° 4004 dont la taille théorique est de 200 000 unités.

Produit de référence :
MEDIATOR 150 mg comprimés commercialisés en France par SERVIER et issus du lot 3M5203.

Analytique :

Le dosage plasmatique des deux métabolites Norfenfluramine (NFF) et de la THEP a été réalisé par FARMOVS en Afrique du Sud au moyen d'une technique LC-MS-MS, dont la LOQ s'établit à 0.2 et 0.4 ng/ml pour respectivement chacun de ces deux analytes. Cette technique est clairement décrite et validée.
Le dosage plasmatique du Benfluorex a été tenté au moyen de la même technique LC-MS-MS avec une LOQ de 0.4 ng/ml. Cette technique n'a pas permis l'exploration du Benfluorex en raison des faibles concentrations circulantes.

Commentaires :
Le demandeur doit discuter si une amélioration des performances de la techniques analytique n'était pas possible, permettant ainsi l'exploration de la molécule mère.

Les résultats :

Les résultats obtenus pour les deux métabolites Norfenfluramine et THEP sont récapitulés dans le tableau ci-dessous.

Norfenfluramine:

	Test	Référence		ICS 90 %
AUC 0-t (ng.h/ml)	416 ± 114	403 ± 108	NS	[94 ; 101] %
AUC 0-∞ (ng.h/ml)	443 ± 144	433 ± 147	NS	[95 ; 101] %
Cmax (ng/ml)	16.0 ± 3.52	15 ± 2.29	P < 0.05	[91 ; 99] %
Tmax (h)	5.5	6	NS	----------

THEP:

	Test	Référence		ICS 90 %
AUC 0-t (ng.h/ml)	80.4 ± 39	80.6 ± 40.6	NS	[92 ; 110] %
AUC 0-∞ (ng.h/ml)	86.5 ± 38.6	86.3 ± 40.3	NS	[93 ; 107] %
Cmax (ng/ml)	16.3 ± 8.25	15.6 ± 8.17	NS	[86 ; 109] %
Tmax (h)	5.5	5.5	NS	----------

Conclusion :

Basés sur les données des deux métabolites, les résultats obtenus montrent la bioéquivalence entre les deux comprimés comparés.

Au plan biopharmaceutique

QUESTIONS

Il devra être discuté si une amélioration des performances de la techniques analytique n'était pas possible, permettant ainsi l'exploration de la molécule mère inchangée.

Au plan pharmaceutique

QUESTIONS

Module 3.2 S.3

- La démonstration de la structure pourrait être complétée par un spectre RMN 13C.

Module 3.2 P.1 et 3.2 P.5

- La viscosité de la carmellose sodique devra être précisée.

Module 3.2 P.1 et 3.2 P.3

- Il devra être précisé quelle quantité de suspension d'éthylcellulose est utilisée puisqu'en 3.2.P3 et 3.2.P1 seule la quantité d'éthylcellulose est mentionnée.
- Le laurilsulfate de sodium et l'alcool cétylique contenus dans la suspension aqueuse devront figurer dans la formule.

Module 3.2 P.3

- La taille du lot industriel devra être précisée.

Module 3.2 P.5

- Les spécifications en impuretés à libération sont supérieures à celles retenues pour la matière première. Celles-ci devront être resserrées.
- Dans la formule de calcul de l'essai de dissolution, il manque un facteur 100 au dénominateur. Ceci devra être corrigé.

Module 3.2 P.8

- L'augmentation de la limite en impuretés totales n'est pas acceptable. La limite en impureté E devra être revue conformément aux résultats expérimentaux obtenus.

La durée de conservation qui pourrait être accordée est de 12 mois à une température ne dépassant pas 25°C.

Note au groupe toxicologique

- Un module 4 a été déposé par la firme et transmis au groupe toxicologique pour évaluation. Il comprend 2 études mise en oeuvre pour qualifier l'impureté E. Ces 2 études documentent le risque potentiel génotoxique de cette impureté.

Note interne

- Le stéarate de magnésium est d'origine végétale, l'attestation de UNION DERIVAN est fournie.
- Le polysorbate 80 est d'origine végétale, l'attestation de SEPPIC est fournie.
- Les monooléates de glycérol sont d'origine végétale, l'attestation de GATTEFOSSE est fournie.

AVIS DU GROUPE DE TRAVAIL SUR LES MEDICAMENTS GENERIQUES N° 121 DU 18 MAI 2006 : MESURE D'INSTRUCTION

Au plan biopharmaceutique

QUESTIONS

Il devra être discuté si une amélioration des performances de la techniques analytique n'était pas possible, permettant ainsi l'exploration de la molécule mère inchangée.

Au plan pharmaceutique

QUESTIONS

Module 3.2 S.3

- La démonstration de la structure pourrait être complétée par un spectre RMN 13C.

Module 3.2 P.1 et 3.2 P.5

- La viscosité de la carmellose sodique devra être précisée.

Module 3.2 P.1 et 3.2 P.3

- Il devra être précisé quelle quantité de suspension d'éthylcellulose est utilisée puisqu'en 3.2.P3 et 3.2.P1 seule la quantité d'éthylcellulose est mentionnée.
- Le laurilsulfate de sodium et l'alcool cétylique contenus dans la suspension aqueuse devront figurer dans la formule.

Module 3.2 P.3

- La taille du lot industriel devra être précisée.

Module 3.2 P.5

- Les spécifications en impuretés à libération sont supérieures à celles retenues pour la matière première. Celles-ci devront être resserrées.
- Dans la formule de calcul de l'essai de dissolution, il manque un facteur 100 au dénominateur. Ceci devra être corrigé.

Module 3.2 P.8

- L'augmentation de la limite en impuretés totales n'est pas acceptable. La limite en impureté E devra être revue conformément aux résultats expérimentaux obtenus.

La durée de conservation qui pourrait être accordée est de 12 mois à une température ne dépassant pas 25°C.

Avis du groupe toxicologique

Le groupe préclinique GTPC 126 du 15/03/2006 (com 401 du 11/05/2006) a émis un avis favorable. En effet :
- les données toxicologiques fournies par la firme relatives à l'impureté E sont satisfaisantes.

Note interne

- Le stéarate de magnésium est d'origine végétale, l'attestation de UNION DERIVAN est fournie.
- Le polysorbate 80 est d'origine végétale, l'attestation de SEPPIC est fournie.
- Les monooléates de glycérol sont d'origine végétale, l'attestation de GATTEFOSSE est fournie.

AVIS DU GROUPE DE TRAVAIL SUR LES MEDICAMENTS GENERIQUES N° 126 DU 05 OCTOBRE 2006 : AVIS FAVORABLE avec une durée de conservation de 12 mois à une température ne dépassant pas + 25°C

Cette spécialité est générique de MEDIATOR 150 mg, comprimé enrobé.

Au plan biopharmaceutique

Il n'était pas possible de diminuer la LOQ du benfluorex qui avait déjà été optimisée.

Au plan pharmaceutique

CLARIFICATIONS

Module 3.2.P.5

- Les nouvelles spécifications en impuretés dans le produit fini tant à libération qu'en stabilité doivent être confortées au vu des résultats sur les lots de taille industrielle.

Avis du groupe toxicologique

Le groupe préclinique GTPC 126 du 15/03/2006 (com 401 du 11/05/2006) a émis un avis favorable. En effet :
- les données toxicologiques fournies par la firme relatives à l'impureté E sont satisfaisantes.

Note interne

- Le stéarate de magnésium est d'origine végétale, l'attestation de UNION DERIVAN est fournie.
- Le polysorbate 80 est d'origine végétale, l'attestation de SEPPIC est fournie.
- Les monooléates de glycérol sont d'origine végétale, l'attestation de GATTEFOSSE est fournie.

Annexe 4-8

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
Ministère de la santé et des solidarités

Le Ministre

Paris, le 12 MAR. 2007

Cab/MJ/DBS

Monsieur le Directeur général,

Le collège de la Haute Autorité de Santé a rendu un avis global suite à la réévaluation du service médical rendu des médicaments appartenant à la classe des vasodilatateurs.

J'ai pris la décision de maintenir la prise en charge de certains de ces médicaments aux conditions antérieures lorsqu'il n'existe pas d'alternatives thérapeutiques. J'ai aussi souhaité que des négociations de baisse de prix aient lieu entre le Comité Economique des Produits de Santé et les laboratoires concernés. Je suis convaincu qu'elles aboutiront prochainement et que l'Assurance Maladie y trouvera des satisfactions tout comme les patients prenant ces traitements.

Nous sommes associés dans la procédure d'inscription au remboursement d'un médicament, notamment au travers de la décision que vous prenez concernant le taux de participation de l'assuré. Vous avez récemment été sollicités par mes services pour attribuer un taux de remboursement à un médicament essentiellement similaire au Tanakan® dont le taux de remboursement a été maintenu à 35% en octobre dernier. Il s'agit du Vitalogink®.

Il me semble évident que tous les génériques ou médicaments essentiellement similaires à des médicaments qui n'ont pas été déremboursés ont vocation à être inscrits. En effet, cette inscription est dans tous les cas source d'économie et un refus pourrait être contesté pour rupture d'égalité.

Je vous confirme donc mon intention d'inscrire ce médicament.

Je souhaiterais qu'à l'avenir nous puissions réagir ensemble le plus rapidement possible et que ces demandes soient instruites selon la procédure normale.

Je vous prie de croire, Monsieur le Directeur général, à l'assurance de ma considération distinguée.

Xavier BERTRAND

Monsieur Frédéric VAN ROCKEGHEM
Directeur général de la CNAMTS
25-60 avenue du Pr André LEMIERRE
75986 PARIS Cedex 20

Annexe 4-8

UNION NATIONALE DES CAISSES D'ASSURANCE MALADIE

Décision fixant le taux de participation de l'assuré applicable à une spécialité pharmaceutique remboursable aux assurés sociaux

Le directeur général de l'UNCAM,

Vu le code de la sécurité sociale, notamment les articles L 322-2, R 163-10-1 et R 322-1 ;

DECIDE :

Article 1er : La participation de l'assuré pour les spécialités pharmaceutiques visées en annexe de la présente décision est fixée à 35 %.

Article 2 : La présente décision sera transmise au ministre chargé de la sécurité sociale et de la santé qui en assurera la publication au Journal officiel de la République française.

Fait à Paris, le 19 décembre 2008

Le directeur général de l'Union
Nationale des caisses d'assurance maladie

Frédéric van ROEKEGHEM

ANNEXE

Code CIP	Libellé	Taux de participation
3790267	BENFLUOREX MERCK 150 mg, comprimés enrobés, B/30 (laboratoires MYLAN SAS)	35%
3828277	BENFLUOREX QUALIMED 150 mg, comprimés enrobés, B/30 (laboratoires QUALIMED)	35%

Annexe 4-9

Rédactions successives de l'article R.163-3 du code de la sécurité sociale

Article R163-3 Version en vigueur du 21 décembre 1985 au 22 novembre 1990
Créé par Décret 85-1353 1985-12-17 art. 1 JORF 21 décembre 1985

Ne peuvent être inscrits sur la liste prévue à l'article R. 163-2, après avis de la commission prévue à l'article R. 163-9, que les médicaments qui sont présumés apporter une amélioration du service médical rendu ou une économie dans le coût de la santé.

A efficacité ou économie comparable préférence est donnée aux médicaments qui résultent d'un effort de recherche du fabricant.

Article R163-3 Version en vigueur du 22 novembre 1990 au 4 juillet 1999
Modifié par Décret n°90-1034 du 21 novembre 1990 - art. 2 JORF 22 novembre 1990

Ne peuvent être inscrits sur la liste prévue à l'article R. 163-2, après avis de la commission prévue à l'article R. 163-9, que les médicaments pour lesquels il est démontré qu'ils apportent :

- soit une amélioration du service médical rendu en termes d'efficacité thérapeutique ou, le cas échéant, d'effet secondaire ;

- soit une économie dans le coût du traitement médicamenteux.

A efficacité ou économie comparable préférence est donnée aux médicaments qui résultent d'un effort de recherche du fabricant.

Article R163-3 Version en vigueur du 4 juillet 1999 au 30 octobre 1999
Modifié par Décret n°99-554 du 2 juillet 1999 - art. 2 JORF 4 juillet 1999

Ne peuvent être inscrits sur la liste prévue à l'article R. 163-2, après avis de la commission prévue à l'article R. 163-9, que les médicaments pour lesquels il est démontré qu'ils apportent :

- soit une amélioration du service médical rendu en termes d'efficacité thérapeutique ou, le cas échéant, d'effet secondaire ;

- soit une économie dans le coût du traitement médicamenteux.

A efficacité ou économie comparable préférence est donnée aux médicaments qui résultent d'un effort de recherche du fabricant.

Article R163-3 Version en vigueur du 30 octobre 1999 au 1 janvier 2005
Modifié par Décret n°99-915 du 27 octobre 1999 - art. 1 JORF 30 octobre 1999

I. - Les médicaments sont inscrits sur la liste prévue à l'article L. 162-17 au vu de l'appréciation du service médical rendu qu'ils apportent indication par indication. Cette appréciation prend en compte l'efficacité et les effets indésirables du médicament, sa place dans la stratégie thérapeutique, notamment au regard des autres thérapies disponibles, la gravité de l'affection à laquelle il est destiné, le caractère préventif, curatif ou symptomatique

du traitement médicamenteux et son intérêt pour la santé publique. Les médicaments dont le service médical rendu est insuffisant au regard des autres médicaments ou thérapies disponibles ne sont pas inscrits sur la liste.

II. - Les spécialités génériques définies au premier alinéa de l'article L. 601-6 du code de la santé publique appartenant aux mêmes groupes génériques que des spécialités de référence inscrites sur la liste prévue à l'article L. 162-17 sont présumées remplir la condition mentionnée au I du présent article.

Article R163-3 Version en vigueur au 1 janvier 2005
Modifié par Décret n°2004-1398 du 23 décembre 2004 - art. 1 JORF 26 décembre 2004 en vigueur le 1er janvier 2005
Modifié par Décret n°2004-1398 du 23 décembre 2004 - art. 2 JORF 26 décembre 2004 en vigueur le 1er janvier 2005

I. - Les médicaments sont inscrits sur la liste prévue au premier alinéa de l'article L. 162-17 au vu de l'appréciation du service médical rendu qu'ils apportent indication par indication. Cette appréciation prend en compte l'efficacité et les effets indésirables du médicament, sa place dans la stratégie thérapeutique, notamment au regard des autres thérapies disponibles, la gravité de l'affection à laquelle il est destiné, le caractère préventif, curatif ou symptomatique du traitement médicamenteux et son intérêt pour la santé publique. Les médicaments dont le service médical rendu est insuffisant au regard des autres médicaments ou thérapies disponibles ne sont pas inscrits sur la liste.

II. - Les spécialités génériques définies au 5° de l'article L. 5121-1 du code de la santé publique appartenant aux mêmes groupes génériques que des spécialités de référence inscrites sur la liste prévue au premier alinéa de l'article L. 162-17 sont présumées remplir la condition mentionnée au I du présent article.

III. - Les spécialités bénéficiant d'une autorisation d'importation parallèle sont considérées comme remplissant la même condition de service médical rendu que la spécialité correspondante disposant d'une autorisation de mise sur le marché en France.

Mme Le Vaillant (Dominique), attachée principale d'administration centrale, adjointe au chef du bureau de l'administration des personnels et des relations sociales à la direction des services administratifs et financiers du Premier ministre ;

Mme Madelaigue (Florence), attachée principale d'administration centrale, adjointe au chef du bureau de la gestion des ressources humaines et de la formation à la direction des services administratifs et financiers du Premier ministre.

Représentants des services au sein desquels les agents non titulaires exercent leurs fonctions :

M. Louis (Jean-Robert), administrateur civil, chef du bureau de l'informatique et des télécommunications à la direction des services administratifs et financiers du Premier ministre ;

M. Brunaux (Didier), attaché principal d'administration centrale, chef du bureau du personnel et des affaires générales à la direction de la Documentation française.

Art. 3. – Le directeur des services administratifs et financiers du Premier ministre est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 26 octobre 1999.

Le Premier ministre,
Pour le Premier ministre et par délégation :
Le directeur des services administratifs et financiers,
P. PIERRARD

Le ministre de la fonction publique, de la réforme de l'Etat et de la décentralisation,
Pour le ministre et par délégation :
Par empêchement du directeur général de l'administration et de la fonction publique :
Le sous-directeur,
D. LACAMBRE

Arrêté du 29 septembre 1999 portant répartition des emplois offerts aux élèves de l'Ecole nationale d'administration achevant leur scolarité en avril 2000 (rectificatif)

NOR : *PRMG9970561Z*

Rectificatif au *Journal officiel* du 30 septembre 1999, page 14487, première colonne, 12e ligne, au lieu de : « Attaché commercial... », lire : « Conseiller commercial... ».

MINISTÈRE DE L'EMPLOI ET DE LA SOLIDARITÉ

Décret n° 99-915 du 27 octobre 1999 relatif aux médicaments remboursables et modifiant le code de la sécurité sociale (deuxième partie : Décrets en Conseil d'Etat)

NOR : *MESS9923357D*

Le Premier ministre,

Sur le rapport de la ministre de l'emploi et de la solidarité,

Vu le code de la sécurité sociale ;

Vu le code de la santé publique ;

Vu la loi n° 92-1477 du 31 décembre 1992 relative aux produits soumis à certaines restrictions de circulation et à la complémentarité entre les services de police, de gendarmerie et de douane, et notamment son article 17 ;

Vu l'avis du conseil d'administration de la Caisse nationale de l'assurance maladie des travailleurs salariés en date du 7 septembre 1999 ;

Le Conseil d'Etat (section sociale) entendu,

Décrète :

Art. 1er. – La section 1 du chapitre 3 du titre VI du livre Ier du code de la sécurité sociale est modifiée comme suit :

I. – Les articles R. 163-6 à R. 163-12 deviennent les articles R. 163-8 à R. 163-14.

II. – L'article R. 163-2 est ainsi modifié :

A. – Au premier alinéa :

1° Après les mots : « l'article L. 601 du code de la santé publique » sont ajoutés les mots : « , ainsi que ceux visés au premier alinéa de l'article 17 de la loi n° 92-1477 du 31 décembre 1992, » ;

2° La phrase : « L'arrêté mentionne les indications thérapeutiques retenues lors de l'inscription par la commission mentionnée à l'article R. 163-9 » est remplacée par la phrase suivante : « L'arrêté mentionne les seules indications thérapeutiques ouvrant droit à la prise en charge ou au remboursement des médicaments. »

B. – Au troisième alinéa :

1° Les mots : « l'article R. 163-9 » sont remplacés par les mots : « l'article R. 163-15 » ;

2° Le mot : « conditions » est remplacé par le mot : « modalités » ;

3° Après les mots : « durée de traitement », sont ajoutés les mots : « dans les indications ouvrant droit à la prise en charge ou au remboursement ».

C. – Le dernier alinéa est ainsi rédigé :

« Sous réserve des dispositions prévues au III de l'article R. 163-6, l'inscription sur la liste prévue à l'article L. 162-17 est prononcée pour une durée de cinq ans. »

III. – Les articles R. 163-3 à R. 163-5 sont ainsi rédigés :

« *Art. R. 163-3.* – I. – Les médicaments sont inscrits sur la liste prévue à l'article L. 162-17 au vu de l'appréciation du service médical rendu qu'ils apportent indication par indication. Cette appréciation prend en compte l'efficacité et les effets indésirables du médicament, sa place dans la stratégie thérapeutique, notamment au regard des autres thérapies disponibles, la gravité de l'affection à laquelle il est destiné, le caractère préventif, curatif ou symptomatique du traitement médicamenteux et son intérêt pour la santé publique. Les médicaments dont le service médical rendu est insuffisant au regard des autres médicaments ou thérapies disponibles ne sont pas inscrits sur la liste.

« II. – Les spécialités génériques définies au premier alinéa de l'article L. 601-6 du code de la santé publique appartenant aux mêmes groupes génériques que des spécialités de référence inscrites sur la liste prévue à l'article L. 162-17 sont présumées remplir la condition mentionnée au I du présent article.

« *Art. R. 163-4.* – L'inscription et le renouvellement de l'inscription des médicaments sur la liste prévue à l'article L. 162-17, ainsi que la modification des conditions d'inscription, sont prononcés après avis de la commission mentionnée à l'article R. 163-15, à l'exception des spécialités génériques définies au premier alinéa de l'article L. 601-6 du code de la santé publique, lorsque les spécialités de référence appartenant aux mêmes groupes génériques figurent sur ladite liste.

« *Art. R. 163-5.* – I. – Ne peuvent être inscrits sur la liste prévue à l'article L. 162-17 :

« 1° Les médicaments dont les éléments de conditionnement, l'étiquetage ou la notice, définis à l'article R. 5000 du code de la santé publique, ou la publicité auprès des professionnels de santé font mention d'une utilisation non thérapeutique ;

« 2° Les médicaments qui n'apportent ni amélioration du service médical rendu appréciée par la commission mentionnée à l'article R. 163-15 ni économie dans le coût du traitement médicamenteux ;

« 3° Les médicaments susceptibles d'entraîner des hausses de consommation ou des dépenses injustifiées ;

« 4° Les médicaments dont le prix proposé par l'entreprise ne serait pas justifié eu égard aux critères prévus au premier alinéa de l'article L. 162-16-1 ;

« 5° Les médicaments dont les forme, dosage ou présentation ne sont pas justifiés par l'utilisation thérapeutique. »

Les dispositions du 2° ci-dessus ne sont pas applicables aux spécialités génériques définies au premier alinéa de l'article L. 601-6 du code de la santé publique, lorsque les spécialités de référence appartenant aux mêmes groupes génériques figurent sur la liste prévue à l'article L. 162-17.

« II. – L'inscription des médicaments qui ont fait l'objet d'une publicité auprès du public au sens de l'article L. 551-3 du code de la santé publique peut être refusée. »

IV. – Sont insérés les articles R. 163-6 et R. 163-7 ainsi rédigés :

« *Art. R. 163-6.* – I. – L'inscription sur la liste prévue à l'article L. 162-17 ne peut être renouvelée, après avis de la commission mentionnée à l'article R. 163-15, que si le médicament continue de remplir la condition relative au service médical rendu prévue au I de l'article R. 163-3 dans les indications thérapeutiques pour lesquelles le renouvellement de l'inscription est demandé. Dans l'appréciation du service médical rendu, constaté dans les conditions habituelles d'utilisation du médicament, il est tenu compte des nouvelles données disponibles sur le médicament et l'affection traitée ainsi que des autres médicaments inscrits sur la liste depuis la précédente appréciation et des autres thérapies devenues disponibles depuis lors.

« Les spécialités génériques des spécialités de référence appartenant, en application du premier alinéa de l'article L. 601-6 du code de la santé publique, aux mêmes groupes génériques, sont présumées remplir la condition de service médical rendu prévue au premier alinéa ci-dessus, lorsque lesdites spécialités de référence figurent sur la liste prévue à l'article L. 162-17.

« II. – Le renouvellement de l'inscription d'un médicament est également soumis aux conditions prévues aux 1°, 3°, 4° et 5° du I et au II de l'article R. 163-5.

« III. – Lorsqu'une entreprise exploite plusieurs médicaments comportant la même composition qualitative en principes actifs sous des dosages, formes pharmaceutiques et présentations différents et inscrits sur la liste prévue à l'article L. 162-17, la validité de leur inscription sur cette liste expire à la date d'échéance de celle du médicament dont le renouvellement de l'inscription est sollicité en premier. L'entreprise doit adresser simultanément la même demande de renouvellement pour l'ensemble de ces médicaments.

« IV. – A l'occasion de l'examen du renouvellement de l'inscription d'un médicament sur la liste prévue à l'article L. 162-17, lorsque la Commission de la transparence propose de ne pas renouveler l'inscription ou propose de modifier le niveau de la participation de l'assuré, elle donne également un avis sur les médicaments appartenant à la même classe pharmacothérapeutique que le médicament dont le renouvellement de l'inscription est sollicité. Dans ce cas, la date fixée pour le renouvellement de l'inscription du médicament est reportée d'un mois pour permettre aux entreprises exploitant les médicaments de la même classe de présenter leurs observations sur l'avis qui leur est communiqué.

« *Art. R. 163-7.* – I. – Après avis de la commission mentionnée à l'article R. 163-15, peuvent être radiés de la liste prévue à l'article L. 162-17 par arrêté du ministre chargé de la sécurité sociale et du ministre chargé de la santé :

« 1° Les médicaments qui ne sont pas régulièrement exploités ;

« 2° Les médicaments dont la radiation est sollicitée par l'entreprise exploitant le médicament ;

« 3° Les médicaments qui ne peuvent plus figurer sur cette liste en vertu des dispositions prévues à l'article R. 163-3, aux 1°, 3°, 4° et 5° du I de l'article R. 163-5 et à l'article R. 163-6 ;

« 4° Les médicaments dont le conditionnement ne comporterait pas les informations destinées aux organismes d'assurance maladie, prévues en application de l'article L. 161-36 ;

« 5° Les médicaments pour lesquels l'entreprise exploitant le médicament n'a pas informé le ministre chargé de la sécurité sociale des modifications des données sur lesquelles l'inscription est fondée, en application de l'article R. 163-12.

« II. – Peuvent être radiés de la liste prévue à l'article L. 162-17, par arrêté du ministre chargé de la sécurité sociale et du ministre chargé de la santé, après avis de la commission mentionnée à l'article R. 163-15 et de celle mentionnée à l'article R. 5054 du code de la santé publique :

« 1° Les médicaments qui font l'objet d'une publicité auprès du public ;

« 2° Les médicaments dont la publicité auprès des professionnels de santé ne mentionne pas l'une des informations suivantes : le prix, la dénomination commune, les indications thérapeutiques retenues pour l'inscription sur la liste, signalées de manière spécifique, les modalités d'utilisation, le coût du traitement journalier ou, le cas échéant, le coût de cure, exprimé en prix de vente au public dans chacune de ces indications, le taux de participation des assurés à leurs frais d'acquisition, défini en application de l'article R. 322-1, l'inscription au titre de la clause mentionnée au troisième alinéa de l'article R. 163-2 ;

« 3° Les médicaments dont la publicité auprès des professionnels de santé n'est pas conforme au bon usage, au regard soit des références médicales opposables visées à l'article L. 162-12-15, soit des indications thérapeutiques ouvrant droit à la prise en charge ou au remboursement.

« Le directeur général de l'Agence française de sécurité sanitaire des produits de santé signale au ministre chargé de la sécurité sociale et au ministre chargé de la santé les médicaments dont la publicité ne serait pas conforme aux règles fixées ci-dessus.

« III. – Peuvent être radiées de la liste prévue à l'article L. 162-17, par arrêté du ministre chargé de la sécurité sociale et du ministre chargé de la santé, les spécialités figurant en qualité de génériques au répertoire mentionné à l'article R. 5143-8 du code de la santé publique, dont la dénomination est constituée d'un nom de fantaisie, lorsque cette dénomination n'est pas complétée par le suffixe prévu par l'article L. 162-17-1 du présent code dans l'étiquetage et la notice définis à l'article R. 5000 du code de la santé publique, dans le résumé des caractéristiques du produit prévu à l'article R. 5128-2 du même code, ainsi que dans toute publicité au sens de l'article L. 551 dudit code. »

V. – L'article R. 163-8 est ainsi modifié :

1° Au deuxième alinéa du I, les mots : « Pour l'application du présent article et des articles R. 163-7 à R. 163-17, ladite entreprise est celle... » sont remplacés par les mots : « A la présente section, ladite entreprise s'entend de celle... ».

2° Les mots : « articles R. 163-3 et R. 163-4 » et « article R. 163-14 » sont remplacés respectivement par les mots : « articles R. 163-3 et R. 163-5 » et « article R. 163-15 ».

VI. – Au II de l'article R. 163-9, au I de l'article R. 163-10 et aux articles R. 163-12 et R. 163-13, les mots : « article R. 163-14 » sont remplacés par les mots : « article R. 163-15 ».

VII. – Au I de l'article R. 163-9, les mots : « article R. 163-6 » sont remplacés par les mots : « article R. 163-8 ».

VIII. – L'article R. 163-10 est ainsi modifié :

1° Au I, les mots : « des articles R. 163-3 à R. 163-5 » sont remplacés par les mots : « de l'article R. 163-6 » ;

2° Le III est abrogé.

IX. – A l'article R. 163-12, les mots : « article R. 163-9 » sont remplacés par les mots : « article R. 163-11 » et les mots : « articles R. 163-11 et R. 163-12 » sont remplacés par les mots : « articles R. 163-13 et R. 163-14 ».

Art. 2. – La durée de validité de l'inscription des médicaments inscrits sur la liste prévue à l'article L. 162-17 du code de la sécurité sociale sans limitation de durée avant le 1er avril 1993 est fixée à cinq ans à compter de la date de publication du présent décret.

Art. 3. – Les dispositions du III de l'article R. 163-6 sont applicables aux médicaments ayant fait l'objet d'une inscription ou du renouvellement de leur inscription sur la liste prévue à l'article L. 162-17 à compter de la date d'entrée en vigueur du présent décret.

Art. 4. – A la section 2 du chapitre 3 du titre VI du livre Ier du code de la sécurité sociale (deuxième partie : Décrets en Conseil d'Etat), les articles R. 163-13 à R. 163-17 deviennent les articles R. 163-15 à R. 163-20 et sont ainsi rédigés :

« *Art. R. 163-15.* – La Commission de la transparence est composée de :

« 1° Un président et un vice-président nommés par arrêté du ministre chargé de la sécurité sociale et du ministre chargé de la santé pour une durée de trois ans renouvelable une fois ;

« 2° Trois membres de droit :

« – le directeur de la sécurité sociale ou son représentant ;

« – le directeur général de la santé ou son représentant ;

« – le directeur général de l'Agence française de sécurité sanitaire des produits de santé ou son représentant ;

« Chaque membre de droit peut se faire accompagner par une personne de ses services ;

« 3° Treize membres nommés dans les mêmes conditions que le président et le vice-président :

« *a)* Un médecin choisi sur une liste de deux noms proposés par l'ordre national des médecins ;

« *b)* Un pharmacien choisi sur une liste de deux noms proposés par l'ordre national des pharmaciens ;

« *c)* Le médecin-conseil national de la Caisse nationale de l'assurance maladie des travailleurs salariés et un médecin-conseil ou un pharmacien-conseil choisi sur une liste de deux noms proposés par la Caisse nationale de l'assurance maladie des travailleurs salariés ;

« *d)* Deux personnalités, médecins-conseils ou pharmaciens-conseils, choisies chacune sur une liste de deux noms proposés respectivement par la Caisse nationale d'assurance maladie et maternité des travailleurs non salariés des professions non agricoles et par la Caisse centrale de la mutualité sociale agricole ;

« *e)* Une personnalité choisie sur l'une des listes de deux noms établies par chacune des organisations syndicales les plus représentatives des fabricants de produits pharmaceutiques ;

« *f)* Six personnalités choisies en raison de leur compétence médicale, scientifique ou économique dans le domaine du médicament.

« Treize membres suppléants sont désignés dans les mêmes conditions que les membres titulaires ; le suppléant du médecin-conseil national de la Caisse nationale de l'assurance maladie des travailleurs salariés est un praticien-conseil choisi sur une liste de deux noms proposés par la Caisse nationale de l'assurance maladie des travailleurs salariés. Les membres suppléants peuvent remplacer les titulaires soit pour une ou plusieurs séances déterminées, soit s'il se produit une vacance au cours du mandat.

« *Art. R. 163-16.* – I. – Les délibérations de la commission mentionnée à l'article R. 163-15 ne sont valables que si au moins douze membres de la commission sont présents.

« II. – Les avis sont pris à la majorité des suffrages, le président ayant voix prépondérante en cas de partage égal des voix. Ils sont motivés.

« III. – Lorsque l'avis porte sur l'inscription, la modification des conditions d'inscription ou le renouvellement de l'inscription d'un médicament sur la liste prévue à l'article L. 162-17 ou sur l'inscription ou la modification des conditions d'inscription sur la liste prévue à l'article L. 618 du code de la santé publique, cet avis est immédiatement communiqué à l'entreprise qui exploite le médicament.

« L'entreprise peut, dans les huit jours suivant la réception de cet avis, demander à être entendue par la commission ou présenter ses observations écrites. La commission peut modifier son avis compte tenu des observations présentées.

« L'avis définitif est communiqué à l'entreprise, avec copie au Comité économique du médicament, et publié au *Bulletin officiel* du ministère chargé de la sécurité sociale. »

« *Art. R. 163-17.* – La commission mentionnée à l'article R. 163-15 se réunit sur convocation de son président, du ministre de la sécurité sociale, du ministre de la santé ou, pour l'exercice de ses compétences propres, du directeur général de l'Agence française de sécurité sanitaire des produits de santé. Son secrétariat est assuré par l'Agence française de sécurité sanitaire des produits de santé.

« La commission élabore son règlement intérieur.

« Son président peut faire appel à des rapporteurs extérieurs à la commission.

« Un rapporteur ou un expert intervenant dans l'examen d'un médicament devant la commission mentionnée à l'article R. 5140 du code de la santé publique ne peut intervenir comme expert représentant de l'entreprise exploitant le médicament pour l'examen du même médicament devant la commission mentionnée à l'article R. 163-15.

« Les membres de la commission, les personnes des services accompagnant les membres de droit et les rapporteurs doivent adresser à son secrétariat une déclaration mentionnant les liens directs ou indirects qu'ils peuvent avoir avec les titulaires d'autorisation de mise sur le marché et les entreprises dont les produits sont susceptibles de faire l'objet d'un examen par la commission, ainsi qu'avec les organismes professionnels ou les sociétés de conseil intervenant dans le secteur pharmaceutique. Ils s'engagent à signaler toute modification concernant ces liens. Ces déclarations sont publiées au *Bulletin officiel* du ministère chargé de la sécurité sociale.

« Les membres de la commission ne peuvent prendre part ni aux délibérations ni au vote s'ils ont un intérêt direct ou indirect à l'affaire examinée.

« *Art. R. 163-18.* – L'avis mentionné au premier alinéa de l'article R. 163-4, ainsi que celui rendu par la commission en application de l'article L. 619 du code de la santé publique, comportent notamment :

« 1° L'appréciation du bien-fondé, au regard du service médical rendu, de l'inscription du médicament sur les listes, ou l'une des listes, prévues à l'article L. 162-17 et à l'article L. 618 du code de la santé publique ;

« L'avis porte distinctement sur chacune des indications thérapeutiques mentionnées par l'autorisation de mise sur le marché, en distinguant, le cas échéant, des indications par groupes de populations pertinents au regard de l'appréciation du service médical rendu ;

« L'avis portant sur l'inscription du médicament sur la liste prévue à l'article L. 162-17 mentionne expressément les indications thérapeutiques pour lesquelles la commission estime fondée l'inscription. Il peut préconiser d'assortir l'inscription de la clause mentionnée au troisième alinéa de l'article R. 163-2 ;

« 2° Une comparaison du médicament, en termes de service médical rendu, avec ceux de la classe pharmaco-thérapeutique de référence ; pour les médicaments dont l'inscription sur la liste prévue à l'article L. 162-17 est sollicitée, cette comparaison est, sauf impossibilité signalée par la commission, effectuée au moins avec les médicaments inscrits venant en premiers par le nombre de journées de traitement, avec le médicament de cette classe dont le coût du traitement est le moins élevé et avec le dernier médicament inscrit dans la même classe ; le cas échéant, cette comparaison porte sur les médicaments à même visée thérapeutique ;

« L'avis comporte l'appréciation de l'amélioration du service médical rendu apportée par le médicament par rapport à ceux mentionnés ci-dessus et figurant sur la (ou les) liste(s) sur lesquelles l'inscription est sollicitée ; cette appréciation doit porter distinctement sur chacune des indications thérapeutiques mentionnées au 1° ci-dessus ;

« 3° Lors du renouvellement de l'inscription des médicaments sur la liste prévue à l'article L. 162-17, la réévaluation du service médical rendu dans les conditions prévues à l'article R. 163-6.

« 4° Une appréciation sur les modalités d'utilisation du médicament et notamment sur les durées de traitement, la posologie et les autres indications utiles à une bonne prescription du médicament ; pour les médicaments dont l'inscription ou le renouvellement de celle-ci sur la liste prévue à l'article L. 162-17 est demandée, ces modalités sont précisées à l'égard de chacune des indications thérapeutiques proposées ; à l'occasion du renouvellement de l'inscription, les modalités réelles d'utilisation et les indications thérapeutiques constatées sont comparées aux modalités d'utilisation et aux indications thérapeutiques retenues lors des avis précédents ;

« 5° L'estimation du nombre de patients relevant des indications thérapeutiques pour lesquelles la commission estime fondée l'inscription, selon les données épidémiologiques disponibles. Le cas échéant, l'avis mentionne l'impossibilité de réaliser des estimations précises ;

« 6° Pour les médicaments inscrits sur la liste prévue à l'article L. 162-17, leur classement au regard de la participation des assurés aux frais d'acquisition dans deux catégories déterminées en fonction de l'importance du service médical rendu ; l'avis précise, le cas échéant, si le médicament doit être considéré comme irremplaçable pour l'application du premier alinéa de l'article R. 322-1 ;

« 7° L'appréciation du conditionnement approprié au regard des indications thérapeutiques pour lesquelles la commission estime fondée l'inscription, de la posologie et de la durée de traitement ;

« La commission peut, en outre, indiquer les informations et études complémentaires indispensables à la réévaluation du service médical rendu par le médicament, qui devront être présentées par le demandeur à l'occasion du renouvellement de l'inscription sur la liste prévue à l'article L. 162-17.

« *Art. R. 163-19.* – A la demande du ministre chargé de la sécurité sociale ou du ministre chargé de la santé, la commission mentionnée à l'article R. 163-15 donne un avis sur :

« 1° Le bien-fondé de l'inscription, du renouvellement d'inscription ou de la modification des conditions d'inscription des spécialités génériques définies à l'article L. 601-6 du code de la santé publique, sur les listes prévues aux articles L. 162-17 du présent code et L. 618 du code de la santé publique ;

« 2° Le maintien du médicament sur les listes, ou l'une des listes, prévues aux articles L. 162-17 du présent code et L. 618 du code de la santé publique, compte tenu de la modification des données sur lesquelles est fondée l'inscription ; l'avis portant sur le maintien du médicament sur la liste prévue à l'article L. 162-17 peut préconiser d'assortir l'inscription de la clause mentionnée au troisième alinéa de l'article R. 163-2 ;

« 3° L'inscription des médicaments sur la liste mentionnée à l'article L. 595-7-1 du code de la santé publique ;

« 4° L'établissement de classifications des médicaments en fonction de leurs propriétés pharmacologiques et thérapeutiques ou de leurs indications ainsi que le classement des produits dans ces classifications ;

« 5° Les règles de conditionnement des médicaments par classe thérapeutique et la conformité à ces règles des conditionnements présentés ;

« 6° Toute question touchant à la consommation, au remboursement, à la prise en charge et aux conditions d'utilisation thérapeutique des médicaments figurant sur les listes prévues aux articles L. 162-17 du présent code et L. 618 du code de la santé publique.

« *Art. R. 163-20.* – I. – La commission mentionnée à l'article R. 163-15 donne un avis, à la demande du ministre chargé de la sécurité sociale, du ministre chargé de la santé, ou, pour l'exercice de ses compétences propres, du directeur général de l'Agence française de sécurité sanitaire des produits de santé, sur les documents suivants :

« 1° Les documents d'information à l'usage des praticiens portant sur la comparaison des médicaments de la même classe pharmaco-thérapeutique ou à même visée thérapeutique ;

« Ces documents doivent notamment rappeler les références médicales opposables visées à l'article L. 162-12-15 et les spécialités génériques commercialisées figurant au répertoire mentionné à l'article R. 5143-8 du code de la santé publique ;

« 2° Les fiches d'information thérapeutique préparées en vue d'être annexées aux arrêtés d'inscription des médicaments particulièrement coûteux et d'indications précises, prévues au troisième alinéa de l'article R. 163-2 ainsi que des fiches de même nature, publiées au *Bulletin officiel* du ministère chargé de la sécurité sociale, pour des médicaments dont les conditions d'utilisation nécessitent une information particulière des prescripteurs et notamment ceux qui sont soumis aux conditions de prescription restreinte prévues aux articles R. 5143-5-1 à R. 5143-5-6 du code de la santé publique ;

« 3° Des recommandations destinées aux prescripteurs et relatives à l'usage des médicaments.

« La publication et la diffusion de tous les documents précités ne peuvent intervenir qu'après accord du ministre chargé de la sécurité sociale et du ministre chargé de la santé.

« II. – La commission mentionnée à l'article R. 163-15 donne un avis sur les recommandations de bonne pratique et les références médicales établies par l'Agence française de sécurité sanitaire des produits de santé prévues à l'article L. 162-12-15.

« *Art. R. 163-21.* – La commission mentionnée à l'article R. 163-15 peut réévaluer le service médical rendu des médicaments inscrits sur les listes, ou l'une des listes, prévues à l'article L. 162-17 et à l'article L. 618 du code de la santé publique par classe pharmaco-thérapeutique ou à même visée thérapeutique, notamment lorsqu'elle propose l'inscription sur ces listes ou l'une de ces listes d'un médicament apportant une amélioration majeure du service médical rendu susceptible de modifier substantiellement les stratégies thérapeutiques antérieures. »

Art. 5. – Les dispositions prévues à l'article R. 163-15 entrent en vigueur à compter du 5 juin 2000.

Art. 6. – I. – L'article R. 322-1 du code de la sécurité sociale est ainsi modifié :

1° Au premier alinéa et au 5°, les mots : « article R. 163-8 » sont remplacés par les mots : « article R. 163-15 » ;

2° Au 5°, après les mots : « troubles ou affections sans caractère habituel de gravité », sont ajoutés les mots : « et pour les médicaments dont le service médical rendu, tel que défini au I de l'article R. 163-3, n'a pas été classé en application du 6° de l'article R. 163-18 comme majeur ou important ».

II. – A titre transitoire, les arrêtés en vigueur à la date de publication du présent décret, fixant la participation de l'assuré en ce qui concerne les médicaments aux taux prévus aux 5° et 6° de l'article R. 322-1, restent applicables jusqu'à l'intervention d'un arrêté modifiant cette participation en application du I ci-dessus et, au plus tard, jusqu'à l'expiration d'une période de cinq ans à compter de la publication du présent décret.

Art. 7. – I. – Le 3° du premier alinéa de l'article R. 5047-3 du code de la santé publique est ainsi rédigé :

« 3° De l'avis rendu en application de l'article R. 163-4 du code de la sécurité sociale par la Commission de la transparence mentionnée à l'article R. 163-15 du même code et le plus récemment publié dans les conditions prévues au dernier alinéa du III de l'article R. 163-16 du même code.

« Lorsque le médicament fait l'objet de plusieurs avis en raison d'une extension des indications thérapeutiques, la notion d'avis s'entend de l'ensemble des avis comportant une appréciation du service médical rendu dans chacune des indications thérapeutiques du médicament concerné. »

II. – Au 4° de l'article R. 5054 du code de la santé publique, les mots : « R. 163-9 » sont remplacés par les mots : « R. 163-15 ».

III. – L'article R. 5148 *bis* du code de la santé publique est ainsi rédigé :

« *Art. R. 5148* bis. – Toute ordonnance comportant une prescription de médicaments doit, pour permettre la prise en charge de ces médicaments par un organisme d'assurance maladie, indiquer pour chacun des médicaments prescrits :

« 1° La posologie ;

« 2° Soit la durée du traitement, soit le nombre d'unités de conditionnement.

« Si la durée du traitement est supérieure à un mois, l'ordonnance doit indiquer le nombre de renouvellements de la prescription par périodes maximales d'un mois dans la limite de six mois de traitement ou, pour les médicaments contraceptifs, par périodes maximales de trois mois dans la limite d'un an de traitement.

« Le pharmacien ne peut délivrer en une seule fois une quantité de médicaments correspondant à une durée de traitement supérieure à quatre semaines ou à trente jours selon le conditionnement. Toutefois, les médicaments contraceptifs peuvent être délivrés pour une durée de douze semaines.

« Le pharmacien est tenu de délivrer le conditionnement le plus économique compatible avec les mentions figurant sur l'ordonnance. »

Art. 8. – La ministre de l'emploi et de la solidarité, le ministre de l'économie, des finances et de l'industrie et la secrétaire d'Etat à la santé et à l'action sociale sont chargés, chacun en ce qui le concerne, de l'exécution du présent décret, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 27 octobre 1999.

LIONEL JOSPIN

Par le Premier ministre :

La ministre de l'emploi et de la solidarité,
MARTINE AUBRY

Le ministre de l'économie, des finances et de l'industrie,
DOMINIQUE STRAUSS-KAHN

La secrétaire d'Etat à la santé et à l'action sociale,
DOMINIQUE GILLOT

Arrêté du 26 octobre 1999 fixant la composition pour les organismes du régime général de sécurité sociale de la commission prévue à l'article R. 123-51 du code de la sécurité sociale

NOR : *MESS9923358A*

La ministre de l'emploi et de la solidarité,

Vu l'article R. 123-51 du code de la sécurité sociale ;

Vu l'arrêté du 26 mars 1966 modifié fixant les modalités d'application, en ce qui concerne les agents de direction et les agents comptables des organismes du régime général de sécurité sociale, des dispositions de l'article 19 du décret n° 60-452 du 12 mai 1960 modifié relatif à l'organisation et au fonctionnement de la sécurité sociale,

Arrête :

Art. 1er. – Sont nommés membres de la commission prévue à l'article R. 123-51 du code de la sécurité sociale :

1° Lorsque l'agent en cause est un agent de direction :

Représentants du ministre chargé de la sécurité sociale :

Un membre de l'inspection générale des affaires sociales, qui assure la présidence de la commission.

Le directeur de la sécurité sociale ou son représentant.

2° Lorsque l'agent en cause est un agent comptable :

Représentant du ministre chargé de la sécurité sociale :

Un membre de l'inspection générale des affaires sociales, qui assure la présidence de la commission.

Représentant du ministre chargé de l'économie et des finances :

Le directeur général de la comptabilité publique ou son représentant.

Art. 2. – Sont nommés membres de la commission prévue à l'article R. 123-51 du code de la sécurité sociale :

Représentants élus des agents de direction et agents comptables :

Premier groupe
(Directeurs)

Titulaires

M. Arcéga (Gérard), directeur de la caisse primaire d'assurance maladie de Vaucluse.

M. Delplanque (Jean-Jacques), directeur de la caisse d'allocations familiales de la Haute-Savoie.

Suppléants

M. Schaeffer (Daniel), directeur de la caisse primaire d'assurance maladie de la Corrèze.

M. Barry (Daniel), directeur de l'union régionale des caisses d'assurance maladie d'Auvergne.

M. Valenza (Claude), directeur de l'union de recouvrement des cotisations de sécurité sociale et d'allocations familiales de la Haute-Savoie.

M. Gilmant (Gérard), directeur de l'union de recouvrement des cotisations de sécurité sociale et d'allocations familiales de Rouen et du centre normand de formation et de perfectionnement.

M. Bussière (Alain), directeur de l'union de recouvrement des cotisations de sécurité sociale et d'allocations familiales de l'Indre.

M. Solé (Francis), directeur de la caisse primaire d'assurance maladie de l'Aude.

Deuxième groupe
(Agents comptables)

Titulaires

M. Henon (Dominique), agent comptable de la caisse primaire d'assurance maladie de Paris.

M. Challiol (Philippe), agent comptable de la caisse d'allocations familiales d'Anjou.

Suppléants

M. Bayard (Serge), agent comptable de la caisse d'allocations familiales de Lyon.

M. Quintana (Jacques), agent comptable de la caisse primaire d'assurance maladie de Valenciennes.

M. Audibert (Guy), agent comptable de la caisse d'allocations familiales du Puy-de-Dôme.

Mme Ravel (Hélène), agent comptable de la caisse d'allocations familiales des Alpes-Maritimes.

M. Cabot (Jean-Pierre), agent comptable de la caisse primaire d'assurance maladie du Gard.

M. Perros (André), agent comptable de la caisse primaire d'assurance maladie du Nord-Finistère, de la fédération de la caisse régionale d'assurance maladie de Bretagne et de la caisse primaire d'assurance maladie du Nord-Finistère et de l'union régionale des caisses d'assurance maladie de Bretagne.

Troisième groupe
(Directeurs adjoints)

Titulaires

M. Haurie (Jean-Louis), directeur adjoint de la caisse d'allocations familiales de la Gironde.

M. Louis (Daniel), directeur adjoint de la caisse d'allocations familiales de Meurthe-et-Moselle.

Suppléants

M. Lévèque (Claude), directeur adjoint de la caisse primaire d'assurance maladie de Roubaix.

M. Jourdan (Patrick), directeur adjoint de la caisse primaire d'assurance maladie du Havre.

M. Hoefman (Jacques), directeur adjoint de la caisse primaire d'assurance maladie de la Corrèze.

M. Dupont (Gilbert), directeur adjoint de la caisse régionale d'assurance maladie de Bretagne.

M. Rouvière (Daniel), directeur adjoint de la fédération des organismes de sécurité sociale du Sud-Est.

M. Emery (Michel), directeur adjoint de la caisse primaire d'assurance maladie des Hautes-Alpes.

Quatrième groupe
(sous-directeurs)

Titulaires

M. Guisgand (Pascal), sous-directeur de la caisse régionale d'assurance maladie du Centre-Ouest.

M. Gambier (Jocelyn), sous-directeur de la caisse primaire d'assurance maladie de Lens.

Suppléants

M. Lambert (Dominique), sous-directeur de la caisse primaire d'assurance maladie du Morbihan.

M. Pallarés (Jean-Pierre), sous-directeur de la caisse primaire centrale d'assurance maladie des Bouches-du-Rhône.

M. Dufour (Claude), sous-directeur de la caisse primaire d'assurance maladie du Cher.

M. Picaud (Jean-Pierre), sous-directeur de l'union de recouvrement des cotisations de sécurité sociale et d'allocations familiales de Charente-Maritime.

Mme Mollot-Derel (Martine), sous-directeur de la caisse primaire d'assurance maladie de la Côte-d'Or.

M. Auffret (Jean-Yves), sous-directeur de la caisse d'allocations familiales de Saint-Quentin.

Représentants élus des conseils d'administration :

Titulaires

M. Delorme (Jean), administrateur de l'union de recouvrement des cotisations de sécurité sociale et d'allocations familiales de la Manche, président du conseil d'administration.

LOIS

LOI n° 98-1194 du 23 décembre 1998 de financement de la sécurité sociale pour 1999 (1)

NOR : *MESX9800131L*

L'Assemblée nationale et le Sénat ont délibéré,

L'Assemblée nationale a adopté,

Vu la décision du Conseil constitutionnel n° 98-404 DC en date du 18 décembre 1998 ;

Le Président de la République promulgue la loi dont la teneur suit :

TITRE Ier

ORIENTATIONS ET OBJECTIFS DE LA POLITIQUE DE SANTÉ ET DE SÉCURITÉ SOCIALE

Article 1er

Est approuvé le rapport annexé à la présente loi relatif aux orientations de la politique de santé et de sécurité sociale, et aux objectifs qui déterminent les conditions générales de l'équilibre financier de la sécurité sociale pour l'année 1999.

TITRE II

DISPOSITIONS RELATIVES AUX RESSOURCES

Article 2

I. – Les dispositions du deuxième alinéa de l'article L. 651-2-1 du code de la sécurité sociale ne sont pas applicables au solde cumulé du produit de la contribution sociale de solidarité résultant de l'application du premier alinéa dudit article, constaté au 31 décembre 1998.

II. – Un prélèvement d'un milliard de francs est opéré en 1999 sur le produit de la contribution sociale de solidarité à la charge des sociétés, au profit du budget annexe des prestations sociales agricoles.

Les dispositions du *b* du 2° de l'article L. 139-2 du code de la sécurité sociale ne sont pas applicables, pour l'exercice 1999, au régime des exploitants agricoles.

III. – Le code de la sécurité sociale est ainsi modifié :

1° Au premier alinéa de l'article L. 651-1, les références : « aux articles L. 621-3, L. 721-1 et L. 723-1, » sont remplacées par les mots : « aux 1° et 2° de l'article L. 621-3, ainsi qu'au profit du Fonds de solidarité vieillesse mentionné à l'article L. 135-1, » ;

2° L'article L. 651-2-1 est ainsi modifié :

a) Le deuxième alinéa est ainsi rédigé :

« Le cas échéant, le solde du produit de la contribution résultant de l'application des dispositions de l'alinéa précédent est versé au Fonds de solidarité vieillesse mentionné à l'article L. 135-1. » ;

b) La première phrase du dernier alinéa est complétée par les mots : « et le Fonds de solidarité vieillesse » ;

3° Le premier alinéa de l'article L. 135-3 est complété par un 4° ainsi rédigé :

« 4° Une fraction, fixée par arrêté des ministres chargés de la sécurité sociale et du budget, du solde du produit de la contribution sociale de solidarité à la charge des sociétés visé au deuxième alinéa de l'article L. 651-2-1. »

Les dispositions du présent III entrent en vigueur à compter de l'exercice 1999.

IV. – Le code de la sécurité sociale est ainsi modifié :

1° L'article L. 135-1 est ainsi modifié :

a) Après le premier alinéa, il est inséré un alinéa ainsi rédigé :

« Le fonds a également pour mission de gérer un fonds de réserve pour les régimes d'assurance vieillesse visés à l'article L. 222-1 et aux 1° et 2° de l'article L. 621-3. » ;

b) Au deuxième alinéa, les mots : « qui est assisté d'un comité de surveillance composé notamment de membres du Parlement » sont remplacés par les mots : « qui est assisté dans les missions mentionnées aux premier et deuxième alinéas d'un comité de surveillance composé notamment de membres du Parlement, de représentants des assurés sociaux désignés par les organisations syndicales de salariés interprofessionnelles représentatives au plan national ainsi que de représentants des employeurs et travailleurs indépendants désignés par les organisations professionnelles d'employeurs et de travailleurs indépendants représentatives » ;

c) Avant le dernier alinéa, il est inséré un alinéa ainsi rédigé :

« Les opérations du Fonds de solidarité vieillesse correspondant à chacune des missions respectivement mentionnées au premier et au deuxième alinéas du présent article sont retracées en deux sections distinctes. » ;

2° Au premier alinéa de l'article L. 135-2, les mots : « Les dépenses prises en charge par le fonds visé à l'article L. 135-1 sont les suivantes » sont remplacés par les mots : « Les dépenses prises en charge par le Fonds de solidarité vieillesse au titre du premier alinéa de l'article L. 135-1 sont les suivantes » ;

3° L'article L. 135-3 est ainsi modifié :

a) Au premier alinéa, les mots : « Les recettes du fonds sont constituées par » sont remplacés par les mots : « Les recettes du fonds affectées au financement des dépenses mentionnées à l'article L. 135-2 sont constituées par » ;

b) Le dernier alinéa est ainsi rédigé :

« Les recettes et les dépenses du fonds de la première section doivent être équilibrées, dans des conditions prévues par les lois de financement de la sécurité sociale. » ;

4° Les articles L. 135-4, L. 135-5 et L. 135-6 deviennent respectivement les articles L. 135-1-1, L. 135-4 et L. 135-5 ;

5° Après l'article L. 135-1-1, il est créé une section 1 intitulée : « Opérations de solidarité » et comprenant les articles L. 135-2 à L. 135-5 ;

6° Après l'article L. 135-5, il est inséré une section 2 ainsi rédigée :

« Section 2

« Fonds de réserve

« *Art. L. 135-6.* – Les recettes du fonds affectées aux missions définies au deuxième alinéa de l'article L. 135-1 sont constituées par :

« 1° Une fraction, fixée par arrêté des ministres chargés de la sécurité sociale et du budget, du solde du produit de la contribution sociale de solidarité à la charge des sociétés visé au deuxième alinéa de l'article L. 651-2-1 ;

Rendue obligatoire, la formation médicale continue des médecins n'a pas connu les développements souhaitables. Le Gouvernement proposera au Parlement les dispositions législatives nécessaires pour lui donner une nouvelle impulsion. Une concertation est engagée sur ce thème avec les représentants des médecins libéraux mais également avec les médecins hospitaliers et salariés ;

Notre système de santé souffre de cloisonnements excessifs qui nuisent à la qualité des soins et sont source de dépenses inutiles. Le Gouvernement entend soutenir et favoriser les initiatives visant à une meilleure coordination des soins. Par ailleurs, le développement des réseaux pouvant associer médecine de ville et hôpital, professions médicales et paramédicales, permet d'améliorer la prise en charge des patients, de mieux concilier proximité et sécurité. La loi de financement ouvre, en ce domaine, des possibilités d'actions nouvelles aux partenaires conventionnels ;

L'exercice des professions paramédicales s'est profondément transformé au cours de ces dernières années pour répondre aux besoins de la population et à l'évolution de la science et des techniques. C'est pourquoi le Gouvernement entend clarifier les rôles respectifs des médecins et des professions paramédicales dans la prise en charge des malades par une adaptation des textes les rendant conformes aux pratiques et à leur évolution souhaitable. Le Gouvernement s'engage par ailleurs à doter les professions concernées de règles professionnelles et d'instances professionnelles propres permettant de favoriser les conditions d'un exercice de qualité ;

Notre système de santé est trop exclusivement centré sur l'acte curatif. La loi de financement ouvre la possibilité aux caisses de prendre en charge d'autres activités telles que la prévention, l'évaluation, l'éducation sanitaire. Il appartiendra aux caisses et aux professionnels de santé, dans le cadre conventionnel, de définir les dispositifs adaptés ;

La maîtrise de la démographie médicale est essentielle pour garantir le meilleur accès aux soins comme pour assurer la maîtrise des dépenses. Des dispositions législatives sont proposées au Parlement pour accroître la possibilité d'action des partenaires conventionnels en ce domaine et les autoriser à mener des politiques sélectives adaptées à la diversité des situations.

Des moyens sont nécessaires pour promouvoir l'ensemble de ces évolutions de notre système de soins ambulatoire. Un fonds d'aide à la qualité des soins de ville est créé et doté de 500 millions de francs.

b) Le médicament : rationaliser la prescription et les remboursements

La France se caractérise par un niveau global de consommation de médicaments très élevé, une surconsommation avérée pour certaines classes thérapeutiques telles que les antidépresseurs ou les antibiotiques, un faible développement des génériques. Cette situation est insatisfaisante au regard des exigences d'efficience de notre système de santé et préjudiciable en termes de santé publique. Les maladies iatrogènes représentent environ un million de journées d'hospitalisation.

Aussi le Gouvernement a-t-il engagé un ensemble de politiques structurelles visant à :

- lutter contre la surconsommation médicamenteuse. La taxe sur la promotion pharmaceutique a été augmentée dès 1998. La politique conventionnelle conduite par le Comité économique du médicament vise à obtenir une réduction du volume des classes où la surconsommation est avérée. Le développement des recommandations de bonnes pratiques permettra de réorienter les prescriptions ;
- développer les génériques. Un répertoire complet des génériques est disponible depuis juillet 1998. Le droit de substitution accordé aux pharmaciens, sauf refus explicite des médecins, permettra le développement de ce type de produit ;
- médicaliser le remboursement. La sécurité sociale doit concentrer ses efforts en matière de remboursement sur les médicaments dont l'efficacité médicale est avérée. Les critères de prise en charge des médicaments seront revus pour tenir compte tant de la gravité de la maladie que du service médical rendu. Une réévaluation de l'apport thérapeutique de l'ensemble des médicaments remboursables sera réalisée au cours des trois ans qui viennent.

Pour conduire l'ensemble de ces évolutions, le Gouvernement entend s'appuyer sur une politique conventionnelle active.

c) L'hôpital : promouvoir la qualité et adapter l'offre aux besoins

Promouvoir la qualité des soins, adapter notre offre hospitalière aux besoins, favoriser les coopérations entre établissements et, avec la médecine de ville, améliorer l'efficience globale du système hospitalier, tels sont les objectifs généraux de la politique hospitalière du Gouvernement.

En particulier, dans un souci d'accroissement de la sécurité sanitaire et de qualité des soins, la situation des professions hospitalières à forte pénibilité (anesthésistes, urgentistes, obstétriciens) doit être prise en compte. Des améliorations des conditions de travail de ces professions doivent être envisagées, en particulier au regard de la législation européenne (directive 93/104/CE) sur la question du temps de travail. Il importe d'augmenter l'attractivité de ces professions afin d'apporter une réponse allant dans le sens des conclusions du rapport Nicolas-Duret.

La promotion de la qualité à l'hôpital passe notamment par le développement de l'accréditation. Cette procédure permettra de vérifier sur la base d'une méthodologie fiable le niveau de performances sanitaires des établissements. L'ANAES a établi un référentiel d'accréditation. Il est en cours de test sur le terrain. Les premières démarches d'accréditation débuteront en 1999.

Notre offre hospitalière doit poursuivre son adaptation. C'est dans ce souci que la révision des schémas régionaux d'organisation sanitaire a été entreprise. Cet exercice de planification sanitaire est conduit avec le souci d'associer étroitement à la réflexion les établissements et leurs personnels, mais également les représentants des usagers et les élus locaux. Il permettra une meilleure prise en compte des besoins de santé.

La garantie offerte à tous d'un accès à des soins de qualité passe par l'organisation de réseaux entre établissements ou entre services qui garantiront à chacun une orientation vers une structure adaptée à son cas. Une telle organisation a été définie pour la sécurité périnatale et la cancérologie. Le Gouvernement entend poursuivre dans cette voie pour d'autres pathologies.

Le Gouvernement accentuera son effort de réduction des inégalités entre régions. Les dotations régionales seront différenciées à partir des besoins régionaux, des indicateurs sanitaires et des indicateurs d'efficience. La régionalisation de l'objectif clinique privé, entamée en 1998, sera accentuée. De même, la réduction des inégalités de dotation entre les hôpitaux, notamment à partir des indications fournies par le PMSI, sera poursuivie.

Le Gouvernement présentera un rapport sur l'évolution et la place des services de médecine non spécialisés à l'hôpital.

Le Gouvernement entend par ailleurs, en concertation notamment avec les caisses nationales d'assurance maladie et les syndicats médicaux, poursuivre sa réflexion sur l'adaptation de l'objectif des dépenses médicales par spécialité ou groupe de spécialités.

7. Assurer la régulation des dépenses

Le Gouvernement est convaincu que seules des politiques structurelles, destinées tant à accroître la qualité des soins

REPUBLIQUE FRANCAISE

Annexe 4-12

La Ministre de l'Emploi
et de la Solidarité
CabMA/BK/GD/CMO/D.9903417

Le Secrétaire d'Etat à la Santé
et à l'Action Sociale

Paris, le 13 AVR. 1999

Monsieur le Président,

Dans le cadre de la réforme engagée par le Gouvernement pour rationaliser les dépenses consacrées par la collectivité en matière de médicament et fonder leur prise en charge par l'assurance maladie sur des critères de santé publique, nous souhaitons aujourd'hui que la Commission de la Transparence engage la deuxième phase du programme triennal de réexamen du service médical rendu et procède à la réévaluation de l'ensemble des classes thérapeutiques et des médicaments remboursables par l'assurance maladie en ville, selon le calendrier joint.

Nous vous demandons pour ce réexamen d'apprécier par indication le service médical rendu par un médicament ou par une classe médicamenteuse au regard de leur efficacité et de leurs effets indésirables, de leur place dans la stratégie thérapeutique au regard notamment des autres thérapies disponibles, de la gravité de l'affection à laquelle ils sont destinés ainsi que du caractère préventif, curatif ou symptomatique du traitement médicamenteux et de son intérêt pour la santé publique.

Vous voudrez bien évaluer pour chaque médicament son niveau de service médical rendu en vous référant à l'un des trois niveaux suivants : majeur ou important, modéré, ou plus faible mais justifiant néanmoins une prise en charge.

Vous veillerez à ce que les procédures d'examen suivies par la Commission comportent toutes les garanties d'objectivité et d'impartialité requises et à ce que les entreprises pharmaceutiques qui contesteraient l'avis de la commission concernant leurs propres spécialités puissent faire connaître leur position selon les modalités que vous jugerez appropriées.

Les dates du calendrier triennal que nous avons retenu et rendu public récemment ont été arrêtées au plus tard. Nous ne verrions que des avantages à ce que la réévaluation soit menée plus rapidement et aboutisse dans les meilleurs délais.

Nous vous prions d'agréer, Monsieur le Président, l'expression de nos sentiments les meilleurs.

Martine AUBRY

Bernard KOUCHNER

Monsieur Bernard DUPUIS
Président de la Commission de la Transparence
Agence Française de Sécurité Sanitaire des produits de santé
143/147, boulevard Anatole France
93285 SAINT-DENIS CEDEX

c.c. : M. P. DUNETON, Directeur Général de l'AFSSAPS.

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RÉPUBLIQUE FRANÇAISE

REUNION DE LA COMMISSION DES COMPTES DE LA SECURITE SOCIALE

21 septembre 2000

Discours de Martine AUBRY,
Ministre de l'Emploi et de la Solidarité
COMMISSION DES COMPTES
DE LA SECURITE SOCIALE

retour au sommaire

Mesdames, Messieurs,

Le Secrétaire général vient de vous présenter la situation des comptes pour 2000 et 2001. Je remercie une fois de plus François MONIER pour la qualité de son travail. Il a confirmé le retour à l'équilibre des comptes dès 1999, et il vient de vous indiquer que l'excédent prévu en 2000 s'élève à 3,3 MdF et que l'excédent tendanciel devrait s'élever à 15,4 MdF en 2001.

Je note que sur 2000, nous aurions respecté les prévisions de mai (5 MdF d'excédent) si la sécurité sociale n'avait dû prendre en charge 2 MdF supplémentaires au titre de l'ARS.

Pour 2001, les mesures nouvelles arrêtées par le Gouvernement ramènent l'excédent tendanciel à 3,4 MdF.

Pour bien mesurer l'évolution il faut raisonner à structure constante. Ceci revient à neutraliser les conséquences de la budgétisation de l'Allocation Rentré Scolaire et des transferts au fonds de réserve des retraites. Pour 2000, à structure constante, l'excédent du régime général est ainsi de 16,2 MdsF. Il atteint 17,7 MdsF en 2001.

Vous le voyez, le redressement des comptes se poursuit et s'amplifie.

Si l'on considère non plus le seul régime général, mais l'ensemble des régimes sociaux (UNEDIC et protection sociale) l'excédent atteint 0.5 % du PIB, c'est à dire 45 MdsF environ en 2001. Les comptes sociaux aident désormais puissamment à la réduction des déficits publics.

Je crois que ces chiffres doivent être rappelés, sans triomphalisme mais d'abord pour montrer le chemin parcouru depuis les 54 MdsF de déficit du régime général en 1996 ou encore les 33 MdsF en 1997. Ces chiffres sont par ailleurs transparents car la situation des comptes sociaux fait l'objet, deux fois par an, grâce à la commission des comptes, d'un examen très attentif. J'en profite pour signaler que nous progressons dans la présentation des comptes puisque cette année, comme nous nous y étions engagés l'an dernier, nous présentons les comptes en encaissements–décaissements et en droits constatés et qu'une disposition du PLFSS prévoit la mise en place d'un plan comptable unique des organismes de sécurité sociale.

Les raisons de ce redressement des comptes, je tiens à les rappeler brièvement : la croissance économique bien sûr, que le Gouvernement a encouragée et qui est forte et riche en emplois, en particulier grâce à la réduction de temps de travail ; des mesures de redressement ensuite, prises dès l'automne 1997 et qui ont amélioré les comptes de 20 MdsF ; enfin des mesures structurelles concernant la dépense qui ont des effets positifs dans certains secteurs et qui restent insuffisants dans d'autres. Effets qui ont tout de même permis à la croissance des dépenses d'assurance maladie de rester inférieure à celle du PIB, contrairement à bien d'autres pays. De plus, ce redressement s'accompagne d'une amélioration du niveau de la protection sociale.

Si nous avons tant travaillé à ce redressement, si je me réjouis qu'il soit là et qu'il se confirme et s'amplifie, ce n'est pas pour le plaisir de constater des excédents, c'est parce qu'ils garantissent d'abord la pérennité de nos systèmes de protection sociale et nous permettent de mener à bien des politiques indispensables pour que la protection sociale de nos concitoyens aujourd'hui et demain soit améliorée. **La sécurité sociale, ce n'est plus un trou à boucher, c'est un instrument puissant pour améliorer la vie de nos concitoyens et mieux préparer leur avenir.**

Le projet de loi de financement de la sécurité sociale pour 2001, dont je vais vous présenter les grandes lignes, s'inscrit pleinement dans ces perspectives.

1 Accélérer la rénovation de la politique familiale, en faveur des jeunes enfants et du logement social

Lorsque nous sommes arrivés en 1997, la branche famille accusait un déficit de 14,5 MdsF. Grâce aux mesures de redressement qui ont été prises, la branche famille est redevenue excédentaire de 4,8 MdsF en 1999 et de 6,8 MdsF en prévisionnel pour 2000.

Ces mesures de redressement, tout en introduisant plus de justice sociale au niveau des prestations familiales, ont permis de dégager des marges de manœuvre pour mener une véritable politique familiale de grande ampleur. Chaque année la Conférence de la famille marque les étapes de cette rénovation, destinée à mieux répondre aux besoins des familles.

Toutes les mesures décidées depuis 1997 l'ont été en concertation avec la CNAF et le mouvement familial, dont je salue le rôle constructif.

Je ne citerai pas toutes les mesures qui ont été prises, j'en rappellerai seulement quelques unes :

- tout d'abord, l'extension de 18 à 19 ans puis à 20 ans de l'ensemble des prestations familiales,
- l'extension à 21 ans en 2000 du complément familial et des aides au logement,
- l'amélioration des loyers plafonds pour l'allocation de logement familiale,
- l'extension à toutes les familles de un enfant sous condition de ressources de l'allocation de rentrée scolaire,
- la forte progression du budget du FNAS afin d'aider les modes de garde collectifs (1 MdsF en 1999, 700 Millions en 2000).

Cette année encore, les actions décidées en faveur des familles à la Conférence de la famille du 15 juin dernier montrent la volonté du Gouvernement de poursuivre et accélérer la rénovation de la politique familiale. Deux axes principaux ont été privilégiés : les mesures en faveur de la petite enfance et les aides au logement. Ainsi, le Gouvernement a décidé, en concertation avec les mouvements familiaux :

1.1 En ce qui concerne la petite enfance

- la création d'un fonds d'investissement pour les crèches doté de 1,5 MdF, permettant d'accélérer la réalisation de places de crèches afin de répondre à la demande des familles,

- l'augmentation de 1,7 MdF du budget du FNAS pour améliorer l'aide au fonctionnement des crèches et des centres de loisirs,

- l'augmentation de l'AFEAMA pour les familles modestes qui souhaitent avoir recours à une assistante maternelle agréée,

2 En ce qui concerne les aides au logement, nous engageons une réforme fondamentale car elle conjugue trois objectifs :

- simplifier des aides pour les allocataires grâce à l'unification des barèmes des trois aides au logement (APL, ALF, ALS),

- éviter que la reprise d'activité pour un bénéficiaire du RMI ne se traduise par une diminution de son aide au logement,

- introduire plus de justice en améliorant le montant d'aide attribuée aux ménages modestes : à titre d'exemple, pour un couple avec deux enfants ayant un revenu égal au SMIC, l'aide va augmenter de 600 F par mois.

Je n'oublie pas non plus la création d'un congé assorti d'une allocation pour permettre aux parents de suspendre leur activité pour accompagner un enfant gravement malade. Cela constitue une véritable avancée sociale.

L'ensemble de ces mesures annoncées par le Premier ministre le 15 juin dernier représente un effort de

10,5 MdsF en faveur des familles (3,7 MdsF supportés par l'Etat et 6,8 MdsF par la branche famille).

Je me félicite de voir qu'à nouveau les décisions difficiles prises par le Gouvernement en 1997 et 1998 ont porté leurs fruits et permettent désormais d'envisager l'avenir avec sérénité.

1. Mieux indemniser les victimes d'accidents du travail et de maladies professionnelles

Depuis que ce gouvernement est en place, nous avons fait un important travail pour améliorer la reconnaissance et la réparation des accidents du travail et des maladies professionnelles. Je pense au raccourcissement des délais de réponse des caisses, à la réforme du tableau des maladies professionnelles, aux garanties sur les délais de réponse aux victimes.

Nous avons déjà pris un certain nombre de mesures particulières en faveur des victimes de l'amiante, comme le dispositif de cessation anticipée d'activité pour les travailleurs de l'amiante. Cette année, nous allons au-delà. Nous savons tous les souffrances qu'endurent les victimes de l'amiante et le drame que vivent ceux qui leur sont proches.

Il nous apparaît fondamental d'accorder à ces victimes une juste réparation. La législation sur les accidents du travail et les maladies professionnelles n'y parvient que partiellement et les victimes n'obtiennent actuellement qu'une indemnisation insuffisante après de longues années de procédure. En outre, certaines victimes ne disposent pas d'une couverture sociale contre les maladies professionnelles. Je pense notamment aux artisans mais aussi aux victimes dites " environnementales ", celles qui sans jamais avoir été en contact avec l'amiante en milieu professionnel, souffrent de pathologies liées à l'exposition à l'amiante.

Le gouvernement a donc décidé de créer un fonds d'indemnisation des victimes de l'amiante. Il assurera aux victimes et à leur famille la réparation intégrale des préjudices subis, quel que soit le statut de la personne ou les conditions de son exposition. Nous avons cherché à mettre en place une procédure simple, efficace dans le souci d'éviter que la recherche de l'indemnisation ne soit un véritable parcours du combattant.

Le fonds sera financé par les employeurs, via la branche accidents du travail et par le budget de l'Etat. Il sera doté de 2 MdsF dès 2001.

Le drame de l'amiante appelait une réponse rapide et forte mais je sais aussi qu'il a démontré les limites de la législation sur les accidents du travail et les maladies professionnelles en matière d'indemnisation ou de lourdeur des procédures. C'est pourquoi je vais demander au président de la commission spécialisée du Conseil supérieur de prévention des risques professionnels, en charge des maladies professionnelles, de lancer dans les plus brefs délais une réflexion large sur la réparation des risques professionnels, en concertation étroite avec l'ensemble des partenaires concernés.

1. **Améliorer la couverture maladie, amplifier les actions de santé publique tout en modérant l'évolution globale des dépenses grâce à la poursuite des politiques structurelles engagées.**

Depuis trois ans nous conduisons une politique déterminée d'amélioration de la couverture maladie des Français.

La loi du 27 juillet 1999 portant création d'une **Couverture Maladie Universelle,** permet depuis le 1er janvier 2000 à l'ensemble des résidents en France d'accéder à une couverture maladie de base.

De plus, elle a ouvert le droit à une couverture complémentaire gratuite pour les plus modestes de nos citoyens : 6 millions de personnes sont concernées. D'ores et déjà, l'accès à ce nouveau droit a été ouvert pour 4,3 millions de personnes. Je me félicite à ce propos de la mobilisation de l'ensemble des acteurs: professionnels de santé, caisses d'assurance maladie, collectivités locales, organismes de couverture complémentaire et associations humanitaires. Ils contribuent chaque jour sur le terrain à mettre en œuvre cette réforme ambitieuse.

Dans le secteur hospitalier, notre priorité, c'est d'améliorer la qualité de l'accueil et des soins des malades et des conditions de travail du personnel hospitalier. Dans le cadre des protocoles que nous avons conclus, nous avons notamment dégagé 10 MdsF dont 2 MdsF pour répondre aux remplacements.

Nous améliorons l'équipement sanitaire de la France en IRM. Rattraper notre retard en ce domaine est une priorité, car la demande des malades, c'est un accès à des examens plus faciles et des délais d'attente raccourcis.

C'est dans la durée que peut se mettre en œuvre efficacement la politique de santé publique. Le programme national de lutte contre le cancer que nous avons arrêté avec Dominique GILLOT le 1er février dernier propose pour la première fois une approche intégrée organisant la mobilisation de tous les acteurs, de la recherche à la prise en charge des personnes malades et de leurs familles.

Ce plan, qui représente un engagement de 1,8 MdsF, permettra de développer le dépistage systématique des cancers les plus dangereux : cancers du sein, de l'utérus et cancers colo-rectaux.

A la suite des Etats généraux de la santé, qui ont montré la forte attente de la population vis à vis de notre système de santé, le Gouvernement proposera dans les semaines qui viennent un **projet de loi de modernisation du système de santé qui s'articulera autour de cinq axes** : renforcer les droits fondamentaux de la personne et associer les citoyens à la gestion du système de santé, améliorer les mécanismes de pilotage du système de santé, améliorer la qualité du système de santé, renforcer la politique de prévention et instaurer une politique nationale d'éducation pour la santé, instaurer un dispositif de prise en charge des risques thérapeutiques.

Ce sera l'occasion d'un grand débat sur l'organisation et les priorités de notre système de santé. Ceci est nécessaire pour compléter une vision souvent présentée comme essentiellement financière du PLFSS.

3.1 Des dépenses de santé qui évoluent encore rapidement

En 2000, le dépassement de l'ONDAM devrait atteindre 1,6% par rapport à l'objectif fixé de 658,3 MdsF, en prenant en compte les reports de dépenses de la fin 1999. Le dépassement pour 2000 s'élèvera à 11 MdsF, déduction faite de la contribution de l'industrie pharmaceutique.

Quelles sont les raisons de ce dépassement ?

Ce sont les soins délivrés en ville qui sont, cette année encore, responsables du dépassement, puisque leur progression sera cette année de 5,5%.

Les dépassements sont principalement imputables à quatre postes de dépenses : le médicament à hauteur de 6,2 MdsF, les honoraires de certaines professions de ville pour 3,8 MdsF, les indemnités journalières pour 1,7 MdsF et les dispositifs médicaux (TIPS) pour 1,6 MdsF.

En revanche, pour les hôpitaux les objectifs ont été maintenus.

Quant aux dépenses des cliniques privées et les établissements médico-sociaux, elles progresseront en 2000 de 2,2% et de 4,9%, conformément, là aussi, aux objectifs qui leur avaient été impartis.

Au total, les dépenses d'assurance maladie de l'ONDAM se situeront sur un rythme un peu supérieur à 4% en 2000.

Tout en notant que les dépenses de santé continuent à évoluer à un rythme moins élevé que celui de la richesse nationale, je ne me satisfais pas d'une évolution qui, pour la deuxième année consécutive, reste supérieure aux objectifs fixés.

Il me paraît cependant plus que jamais nécessaire que les objectifs votés par le Parlement soient respectés. C'est en maîtrisant mieux les dépenses que nous trouverons les marges

de manœuvre permettant de couvrir de nouveaux besoins et d'améliorer le niveau de protection de nos concitoyens. Chaque franc dépensé doit l'être à bon escient. Les dépenses qui ne répondent pas aux besoins réels, ce sont des cotisations en trop ou des dépenses justifiées en moins : là aussi on pourrait dire que la mauvaise dépense chasse la bonne.

2. **Poursuivre les politiques structurelles engagées.**

C'est tout d'abord le cas dans le secteur de l'hôpital, dans lequel nous menons une politique active de recomposition du tissu hospitalier au service d'objectifs de santé publique.

L'hôpital connaît une réorganisation de grande ampleur :

Un mouvement de réorganisation sans précédent est aujourd'hui engagé dans toutes les régions. Cette politique volontariste menée depuis 1997 par le secteur hospitalier s'articule autour de trois priorités : la réduction des inégalités dans l'accès aux soins, l'adaptation de l'offre de soins aux besoins de la population et la promotion de la qualité et la sécurité des soins.

La réflexion pour fonder la tarification des établissements de santé sur les pathologies traitées est engagée. L'expérimentation de nouvelles modalités de tarification pour les établissements de santé doit reposer sur des données d'activité hospitalière fiables et rapidement disponibles. A cette fin, une agence technique de l'information sur l'hospitalisation sera créée afin d'améliorer le traitement des données et faciliter leur diffusion.

La politique de réduction des inégalités de dotation entre régions et entre établissements de santé se poursuit. L'ampleur de la redistribution est significative : ce sont près de 2.7 MdsF qui ont été apportés aux régions les plus en retard. Cette politique sera poursuivie.

Les schémas régionaux d'organisation sanitaire, adoptés dans toutes les régions à la fin de l'année 1999, fixent désormais les priorités sanitaires de la politique hospitalière. Pour faciliter la mise en œuvre de ces objectifs de santé publique, les établissements de santé ont particulièrement développé leur coopération. En juillet 2000, on recense 370 opérations importantes de coopération hospitalière. Les fusions juridiques d'établissement publics ainsi que le partage d'activités entre établissements publics et privés se sont intensifiées depuis 1998.

L'évolution des techniques médicales et de la demande des patients conduit à une transformation en profondeur des structures hospitalières. Les durées de séjours continuent de diminuer. Les hospitalisations d'un jour ou à domicile augmentent. Cela s'est traduit depuis 1997 par la fermeture de plus de 9500 lits de courts séjours.

Cette réorganisation améliore la qualité de la prestation offerte à la population

En effet, elle permet aux établissements de santé de mieux prendre en compte les priorités de santé publique définies par le gouvernement. Cette année la priorité est donnée au plan cancer arrêté par le gouvernement en 2000 avec notamment la poursuite du programme de développement de soins palliatifs ; l'augmentation du nombre de places d'hospitalisation à domicile ; l'installation de nouveaux appareils d'imagerie par résonance magnétique et de radiothérapie et la prise en compte des innovations thérapeutiques. Le parc des appareils IRM autorisés aura ainsi doublé entre 1997 et 2000 passant de 137 à 276.

La réorganisation des services de périnatalité qui s'achèvera au cours de l'année 2001 permettra, par la mise en réseaux des établissements de santé, d'améliorer la sécurité de la naissance pour la mère et l'enfant. Cette réorganisation se traduira par la transformation de 52 maternités en centre périnatal de proximité.

De même la réorganisation des urgences répond à la nécessité d'un meilleur traitement des urgences vitales. Les sites d'urgences autorisés vont passer de 820 à 600 sites organisés en un réseau gradué d'orientation et de prise en charge. Le gouvernement a renforcé les moyens des services d'urgence. Les établissements de santé renforcent leur coopération avec les médecins de ville.

Conformément au plan greffe présenté par le gouvernement le 22 juin 2000, les moyens des

établissements de santé seront renforcés de manière à favoriser l'accès à la greffe par le développement de réseaux des établissements pour le prélèvement de greffons.

En matière de sécurité sanitaire, des mesures importantes seront prises en 2001 pour améliorer la qualité des procédures de désinfection et de stérilisation et développer l'utilisation de dispositifs médicaux à usage unique. Ces actions se traduiront notamment par le renouvellement et l'achat de matériels.

L'ANAES a rendu publics en juin 2000, les premiers compte rendus d'accréditation. En juillet 2000 : 186 établissements de santé étaient engagés dans la procédure d'accréditation. 650 professionnels de santé seront formés d'ici le début de l'année 2001 permettant à l'ANAES d'assumer pleinement sa mission d'accréditation.

Le gouvernement accompagne de manière significative ce mouvement de recomposition de l'offre hospitalière.

Grâce aux accords conclus avec les représentants des personnels hospitaliers, une nouvelle dynamique a été créée. Les contrats d'amélioration des conditions de travail, la définition d'un projet social au sein du projet d'établissement ainsi que les mesures sans précédent prises pour favoriser la promotion sociale et professionnelle des agents dans les établissements publics de santé contribueront au progrès du système de santé dans son ensemble.

Ces efforts seront soutenus par le fonds de modernisation des établissements de santé (FMES) dont la création est proposée dans le projet de loi de financement de la sécurité sociale pour 2001.

Je n'oublie pas par ailleurs l'important chantier qui va s'ouvrir dans les prochaines semaines sur la réduction du temps de travail à l'hôpital et qui donnera lieu à une réflexion sur les modes d'organisation actuels, leur amélioration et qui se traduira par des créations d'emplois.

Je n'oublie pas que les cliniques privées participent activement à cet effort de recomposition de l'offre de soins. Désormais, la réforme de la fixation des tarifs au niveau régional et en concertation avec les professionnels de ce secteur permet de mieux valoriser l'activité de chaque établissement.

Le fonds de modernisation des cliniques privés est désormais en place. Les ARH instruisent actuellement les premiers projets déposés par les établissements.

L'ensemble de ces mesures structurelles et pérennes créent des conditions nouvelles permettant aux établissements d'évoluer et de mieux prendre en compte les objectifs de santé publique du gouvernement au plus grand bénéfice de la population.

Nous devons aussi modérer notre dépense de médicaments par des dispositifs structurels efficaces.

Les dépenses de médicament remboursées progressent de 6 à 7% en 2000, soit une évolution très proche de celle de l'année précédente. La France ne constitue pas, dans ce domaine, une exception puisque la plupart des pays occidentaux connaissent une évolution encore plus rapide de ces dépenses, mais le niveau de notre consommation médicale est plus élevé que dans nombre de pays voisins.

Nous ne pouvons nous satisfaire d'une telle situation. En 2000, les dépenses de médicament sont, avec plus de 6 milliards sur 11 au total, le premier motif de dépassement de l'ONDAM. Les politiques structurelles que nous avons décidées n'ont pas encore fait sentir leur plein effet. Elles doivent être poursuivies et amplifiées.

Le développement des génériques s'amorce. Il n'était pas normal que ces médicaments, dont le principe actif est aussi efficace que celui de leur princeps, mais qui sont 30% moins coûteux, soient moins utilisés en France que dans d'autres pays. En accord avec les représentants de la profession, avec lesquels nous avons signé un protocole l'année dernière, les pharmaciens disposent désormais d'un droit de substitution.

Nous ferons dans les premiers jours d'octobre un bilan précis de la progression des médicaments génériques et des économies dont la sécurité sociale a bénéficié. Le résultat est encourageant : la prescription et la substitution des médicaments génériques bousculent les mentalités tant des prescripteurs que des assurés. Il faut amplifier l'effort. Les économies tirées des génériques peuvent être évaluées à 500 millions de Francs.

La politique conventionnelle menée par le Comité économique des produits de santé porte elle aussi ses fruits. Le Comité a entrepris des campagnes d'harmonisation des prix sur les veinotoniques, les vasodilatateurs, les magnésium et les calcium que, dans le cadre de la négociation, les laboratoires ont accepté.

L'année 2000 marque une nouvelle étape. J'avais rappelé, l'année dernière, devant cette même commission, la nécessité d'adapter les niveaux de remboursement et les prix en fonction du service médical rendu (SMR). Je rappelle que le SMR prend en compte le rapport efficacité /sécurité du médicament, sa place dans la stratégie thérapeutique, la gravité de la maladie considérée, le caractère curatif, préventif ou symptomatique de l'action du médicament ainsi que son intérêt pour la santé publique. Ces éléments permettent de définir trois niveaux de SMR : majeur ou important, modéré ou faible, insuffisant. A chacune de ces catégories est associé un niveau de prise en charge : remboursement à 65%, remboursement à 35%, absence de remboursement.

La procédure d'évaluation est pratiquement achevée aujourd'hui. Au total, près de 2.663 spécialités ont été évaluées par la Commission de la transparence, soit plus des deux tiers des spécialités pharmaceutiques françaises. 60% ont été classées en SMR majeur ou important, 15% en SMR modéré ou faible, 25% en SMR insuffisant.

Nous avons, sans tarder, tiré les conséquences de cette évaluation et j'ai annoncé, en juillet dernier, les mesures que nous entendions mettre en œuvre. Le taux de remboursement des vasodilatateurs a été uniformisé : toutes les spécialités de cette classe sont désormais remboursées à 35%. Parallèlement, le Comité économique a conduit avec les laboratoires concernés des négociations pour faire baisser les prix des spécialités dont le SMR a été jugé insuffisant. Avec ces deux mesures, c'est plus d'un milliard de francs qui sera économisé sur l'année 2001.

Il faut souligner que ces économies, et c'était là tout l'objet de la politique que nous avons menée depuis deux ans, ne sont pas réalisées au détriment des patients ou de la santé publique. On ne fait pas du déremboursement " en aveugle ", par simple souci d'économies. C'est au contraire une mesure qui va dans le sens d'une amélioration de l'efficacité de la dépense de santé, donc de la santé elle même. Ce que nous ne dépensons plus ici, pour des produits qui n'améliorent pas l'état de santé de nos concitoyens, nous pourrons le consacrer à des produits plus efficaces, plus innovants mais aussi souvent plus onéreux. Nous ne pouvons en effet laisser à la porte du remboursement des médicaments dont on estime qu'ils apportent un plus en termes de santé publique, parce que nos habitudes en matière de prescription ne nous en laissent pas les moyens. C'est aussi cela la maîtrise structurelle de la dépense.

En effet, comme je l'ai annoncé en juillet dernier, les spécialités dont le service médical rendu a été jugé insuffisant ne seront, à terme, plus remboursées. Ceci ne doit cependant pas se faire dans la précipitation. Il importe de donner aux patients, aux prescripteurs mais aussi aux laboratoires, le temps de s'adapter aux changements qui s'annoncent. A l'issue d'une période transitoire de trois ans (2000,2001,2002), les médicaments à SMR insuffisant sortiront du remboursement.

J'avais également annoncé que je souhaitais apporter aux prescripteurs une autre information que celle dont ils disposent aujourd'hui et qui, nous le savons tous, est essentiellement diffusée par l'industrie pharmaceutique. Depuis trois ans, nous avons largement réformé le contrôle de la promotion des laboratoires. Rappelons que, chaque année, ce sont près de 12 milliards qui sont dépensés ainsi. Nous avons réformé la taxe sur la promotion pharmaceutique, introduit des sanctions financières conventionnelles en cas d'infraction constatée par rapport à la réglementation sur la publicité et encadré les dépenses promotionnelles dans le cadre des conventions signées par le comité économique des produits de santé.

Aujourd'hui nous souhaitons aller plus loin en cherchant les moyens d'apporter une information neutre, validée scientifiquement sur le bon usage du médicament. Un groupe confraternel

d'information des prescripteurs sera prochainement mis en place. Il diffusera auprès des prescripteurs une information objective et facilement utilisable sur les prescriptions, leurs coûts et leur stratégie thérapeutique. Il rassemblera notamment des médecins qui sont proches du terrain et proches des préoccupations des prescripteurs. Dès cette année, nous lui donnerons les moyens de fonctionner. A cette fin, la loi va créer un fonds de promotion de l'information médicale alimenté par une fraction de la taxe sur la promotion pharmaceutique.

Par ailleurs, je voudrais saluer l'action de la CNAM en faveur de l'information des usagers, que ce soit sur la surconsommation de certains médicaments ou sur les génériques.

La progression forte des ventes de médicaments a bénéficié à ses distributeurs. Il est normal que l'assurance maladie corrige les conséquences de cette croissance sur la marge de ces entreprises. J'ai donc souhaité que soient revus les taux de marges de la vente directe et de la répartition pharmaceutique. Après avoir reçu leurs représentants, j'ai décidé de procéder à un ajustement de la marge des distributeurs qui rapportera à l'assurance maladie 450 Millions de Francs en année pleine.

Enfin, nous allons modifier, par la loi, la contribution de l'industrie pharmaceutique que l'on appelle la " clause de sauvegarde ". Créée il y a deux ans, elle a permis de récupérer une partie du dépassement sur les dépenses de médicaments : près d'un milliard en 1999 et 2000. Mais son mode de calcul a aujourd'hui besoin d'être revu, car il comporte des effets de seuil peu lisibles. Aussi, la loi de financement pour 2001 va-t-elle retenir un mode de calcul plus simple, linéaire, avec pour objectif de récupérer 70 % du dépassement.

Pour les matériels médicaux (prothèses, accessoires, pansements), nous connaissons encore une forte croissance, de l'ordre de 15%. Ce résultat s'explique par un certain nombre de facteurs objectifs : réduction des durées de séjour, développement de l'hospitalisation à domicile... mais il nous faut, là comme ailleurs, expertiser la pertinence de ces dépenses.

C'est pourquoi, la loi de financement de la sécurité sociale pour 2000 avait prévu un changement fondamental dans la procédure d'inscription au TIPS. Celle-ci devrait très prochainement se mettre en œuvre. Le mode de régulation de ce secteur sera alors identique à celui qui existe pour le médicament et qui, comme nous venons de le voir, porte ses fruits.

Dans quelques semaines, l'Agence française de sécurité sanitaire débutera un processus d'évaluation du service rendu. Le Comité économique des produits de santé lancera, quant à lui, avec les industriels du secteur une politique conventionnelle.

La croissance des honoraires et des prescriptions autres que le médicament est également trop rapide en 2000.

Comme la majorité de gestion de la CNAM l'avait souhaité, la régulation de ces dépenses repose depuis la LFSS 2000 sur une large délégation de gestion aux caisses d'assurance maladie. Elles doivent ainsi gérer de façon concertée et négociée, les dépenses d'honoraires, de biologie et de transport sanitaire.

Dans ces secteurs aussi , la maîtrise structurelle doit s'appliquer.

Nous avons mis en place en trois ans les outils permettant d'assurer une meilleure qualité des soins dispensés. Car je crois profondément que c'est seulement grâce à ces instruments structurants mis à la disposition des professionnels et des caisses que nous résoudrons le problème récurrent de la progression trop rapide des dépenses de soins de ville.

Pour la première fois la CNAM a pris des mesures de redressement en juin qui ont validées. Il s'agissait d'une première application du nouveau dispositif dont j'espère que, dans l'avenir, il fera l'objet d'une application plus concertée.

Les médecins demandaient la possibilité de s'engager avec les caisses sur des objectifs permettant de sortir d'une régulation qui serait purement financière.

Nous avons donc donné en 1999 la possibilité aux partenaires conventionnels d'inclure dans les

conventions des outils permettant d'améliorer la qualité des soins et de déroger aux règles de tarification.

Depuis cette année, à travers les accords de bons usages des soins et les contrats de bonne pratique, les caisses et les professionnels libéraux peuvent s'entendre pour prévoir des incitations financières en contrepartie d'engagements sur la formation et la qualité des soins. Il faut maintenant que ces mécanismes fonctionnent.

Les dispositifs d'évaluation et d'entretien des connaissances des médecins sont désormais en place. Ainsi, le décret sur l'évaluation des médecins est paru en décembre 1999. L'ANAES travaille actuellement avec les syndicats de médecins aux modalités de sa mise en œuvre. Le fonctionnement de l'organisme de gestion conventionnel de la formation médicale continue des médecins a été fixé par un décret sorti le mois dernier.

Mais nous avons également donné aux caisses les moyens de mieux contrôler les prescriptions.

Les formulaires demandant aux médecins de mentionner la justification médicale de la prescription des arrêts de travail et des transports de malades ont été validés et sont d'ores et déjà en application.

Le mécanisme de contrôle des patients ayant une consommation excessive de soins est prévu dans un décret qui devrait être publié dans les jours qui viennent.

Concernant les professionnels paramédicaux, les orientations que j'ai décidées suite au rapport Brocas sont suivies. Ainsi, l'arrêté de 1962 fixant les règles de la prescription des soins a été aménagé pour permettre une plus grande responsabilisation de ces professionnels. Les décrets de compétence de ces derniers seront également adaptés – celui des masseurs-kinésithérapeutes a déjà été modifié en conséquence. Vous savez que je tiens également à donner aux paramédicaux une instance de réflexion et de gestion de leur exercice professionnel. L'office des professions paramédicales sera créé par la loi de modernisation du système de santé.

Le fonctionnement des soins de ville doit être décloisonné. De plus en plus, il faudra travailler en réseau non seulement entre professionnels de ville, mais aussi avec l'hôpital et les cliniques.

Le fonds d'aide à la qualité des soins de ville, créé à cet effet, a commencé à fonctionner.

Les réseaux de soins vont faire l'objet d'une refonte dans le sens de la simplification et de la régionalisation dans le cadre du projet de loi de modernisation du système de santé.

Enfin, l'informatisation du système de santé a fortement progressé en 2000. Plus du tiers de médecins envoient des feuilles de soins électroniques aux caisses – on monte à 50 % pour les généralistes. Les autres professions de santé montent très vite en puissance.

Nous devons également sanctionner les comportements abusifs d'une minorité de professionnels, qui, de ce fait, font du tort non seulement à leur profession mais aussi à la collectivité. Un nouveau dispositif de sanction des abus et des fraudes sera mis en place par la LFSS 2001. Trois principes devront nous guider : nous allons favoriser la conciliation préalable aux poursuites, nous allons garantir le droit à la défense des professionnels mis en cause, nous allons enfin permettre de sanctionner efficacement les professionnels dont la faute sera avérée. Ces dispositions feront l'objet d'une étroite concertation avec les professionnels concernés.

Les non salariés non agricoles bénéficient d'une amélioration de la couverture maladie.

Le projet de loi de financement de la sécurité sociale pour 2001 sera aussi l'occasion de mettre en œuvre les propositions faites par le conseil d'administration de la caisse nationale d'assurance maladie des professions indépendantes (CANAM). Elles permettront d'améliorer sensiblement la couverture sociale de ses professions en alignant le niveau des prestations en nature sur celles du régime général. Il y a donc désormais un socle commun entre le régime général, les régimes des exploitants agricoles et des salariés agricoles et ceux des professions indépendantes. L'amélioration des prestations maladie et maternité sera financée par un relèvement, à due concurrence, du taux de cotisation.

J'en viens à la fixation de l'ONDAM pour 2001

L'objectif pour 2001 doit être fixé en ayant pour but de renforcer l'efficacité de notre système de santé, de permettre aux acteurs du système de dispenser des soins de qualité tout en tenant compte à la fois de l'impact des politiques structurelles que nous avons lancées et du cadre économique et financier de la Nation.

Le gouvernement a retenu un objectif national des dépenses d'assurance maladie 2001 de 694,6 MdsF, en progression de 3,5 % par rapport à 2000.

Cet objectif permettra de répondre aux priorités de santé identifiées par les conférences et le Haut comité de la santé publique. Je pense également aux grandes politiques de santé qu'il faut poursuivre comme le plan Cancer ou le plan Greffes mais également à la nécessité de tenir compte des progrès de la connaissance médicale notamment en matière de réduction des risques sanitaires. Je pense en particulier à la maladie de Creutzfeld-Jacob et à son nouveau variant.

Un effort particulier sera fait, comme les années précédentes, en faveur des établissements médico-sociaux, pour accompagner le développement du nombre de place pour les personnes handicapées et la médicalisation des établissements pour personnes âgées dépendantes.

De plus le Gouvernement proposera pour 2001 un taux d'évolution des dépenses identique pour les hôpitaux et les cliniques privées.

Cet objectif, les caisses d'assurance maladie et les professionnels de santé devront le gérer de façon responsable en s'inscrivant dans la volonté d'infléchir durablement les tendances en matière de dépenses de ville. Les outils structurels de maîtrise des dépenses et d'amélioration de la qualité des soins existent, je l'ai dit. Il faut qu'ils s'en saisissent.

2. Associer les retraités aux fruits de la croissance et préparer l'avenir des régimes de retraite

Nous avons trouvé la branche vieillesse en déficit de 5 MdsF en 1997. Elle renoue dorénavant avec les excédents : 3,7 MdsF en 1999 et 3,4 MdsF en 2000 avant versement au fonds de réserve des retraites.

Ces excédents retrouvés permettent d'associer les retraités aux fruits de la croissance, tout en préparant l'avenir des régimes de retraite

4.1 Associer les retraités aux fruits de la croissance

Pour 2001, le Gouvernement propose de revaloriser les pensions de 2,2 %, alors que l'inflation prévisionnelle est de 1,2 %. Ce coup de pouce porte à 1,3 % le gain de pouvoir d'achat des retraités par rapport à l'inflation depuis 1997.

Par ailleurs, pour les retraités qui ne sont pas imposables à l'impôt sur le revenu, le Gouvernement souhaite leur accorder un gain de pouvoir d'achat supplémentaire grâce à la suppression de la CRDS (0,5%). Cette mesure devrait concerner près de 5 Millions de retraités.

4.2 Préparer l'avenir

Conformément à ce que le Premier ministre a annoncé lors de sa déclaration sur l'avenir des retraites le 21 mars dernier, le Gouvernement travaille pour préparer l'avenir, en abondant le fond de réserve et en engageant la concertation sur les réformes nécessaires de nos régimes de retraite.

- le fonds de réserve

Pour assurer les retraites des Français sur le long terme, le Gouvernement a créé le fonds de réserve en 1998 et y a affecté des ressources nouvelles dès 1999 : excédents de la CNAV et du fonds de solidarité vieillesse, la moitié du prélèvement de 2 % sur les revenus du patrimoine, contributions des Caisses d'Epargne et de la Caisse des Dépôts et Consignations, auxquels s'ajoute la majeure partie du produit de la vente des licences de téléphonie mobile de troisième génération.

Fin 2001, le fonds de réserve disposera de plus de 50 milliards de francs. Que de chemin parcouru depuis trois ans !

Avec les sources de financement actuelles, le fonds de réserve devrait disposer de 1.000 milliards de francs en 2020, dont 300 milliards proviendront des intérêts financiers. Cette somme correspond à la moitié des déficits prévisionnels des régimes de retraite entre 2020 et 2040.

Compte tenu des enjeux forts liés à la gestion du fonds de réserve et afin de lui donner plus de lisibilité, le Gouvernement propose d'en faire un établissement public séparé du FSV dont il faisait jusqu'à présent partie. Un conseil de surveillance aux pouvoirs renforcés, associant notamment des parlementaires et des représentants des partenaires sociaux, sera garant de la bonne gestion de ce fonds.

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Nous pouvons nous réjouir de la poursuite de l'assainissement financier de la sécurité sociale. Après plus de 15 années de déficit, l'excédent des comptes se confirme et s'amplifie : 700 MdF en 1999, 3,4 MdF en 2000 et 4,4 MdF en 2001. Mais le redressement des comptes est aussi le fruit des réformes structurelles que nous avons patiemment engagées, et qui doivent se poursuivre. C'est ce qui nous permettra de continuer à faire progresser les acquis sociaux et, par la mise en réserve d'une partie de ces excédents, de garantir l'avenir de notre système de retraite et au-delà de notre protection sociale.

retour au sommaire

La politique du médicament

Discours de M. Jean-François MATTEI, le 17 juillet 2003

Je souhaite pouvoir aborder avec vous trois thèmes :

- la présentation des produits susceptibles de faire l'objet de la première vague de déremboursements,
- les grandes lignes de la réforme de la commission de la transparence
- et enfin les conséquences de l'arrêt récent du conseil d'Etat sur les vasodilatateurs.

Comme vous le savez, j'ai annoncé à l'automne, lors du projet de loi de financement de la sécurité sociale pour 2003, mon intention de procéder au déremboursement des médicaments n'ayant pas un service médical rendu suffisant pour justifier un remboursement. Cette décision est la conséquence directe de la réévaluation des 4.500 médicaments de la pharmacopée qui avait été commandée par Martine Aubry en 1999. Elle avait d'ailleurs publiquement annoncé son intention de procéder au déremboursement puis est revenue sur sa décision.

Dérembourser pour favoriser l'innovation

Je ne pouvais laisser la situation en l'état. Vous le savez, l'assurance maladie connaît un déficit important qui résulte d'une progression rapide des dépenses et d'une croissance ralentie des recettes conséquence du ralentissement actuel de la conjoncture économique. Pendant ce temps, nous devons admettre au remboursement de nouveaux produits dont les patients ont besoin. Depuis mon arrivée, nous avons notamment inscrit au remboursement des produits importants pour les malades tels que Ebixa, Prévenar, Lantus ou Keppra...

Ces décisions coûtent cher. Il est légitime d'essayer de les financer en partie au moins par le déremboursement de produits dont l'utilité est devenue moindre. C'est la concrétisation de ce qu'un ancien président du comité économique des produits de santé, Jean Marmot, qualifiait de "respiration de la liste des médicaments". En outre, ces produits pouvaient, juridiquement être déremboursés sur simple décision du ministre. Il n'était pas sain de laisser leurs laboratoires continuer à les commercialiser sans offrir la moindre visibilité.

Le plan que j'ai annoncé est étalé sur 3 ans afin de permettre tant aux médecins qu'aux industriels de se préparer à cette évolution. Ces déremboursements doivent intervenir en trois étapes correspondant chacune à une des catégories de médicaments suivantes : en 2003, les produits dont l'utilisation n'est médicalement pas souhaitable, en 2004 les produits qui relèvent d'un choix d'automédication et, enfin, en 2005, les produits médicalement peu efficaces mais, pour l'heure, sans alternative thérapeutique.

Dérembourser : une procédure longue

Nous avons donc procédé en fin d'année dernière à une relecture de la liste des produits à SMR insuffisant pour retenir ceux qui portaient la mention "n'a pas de place dans la stratégie thérapeutique". 95 spécialités ont alors été identifiées dont 2 n'étaient plus commercialisées à cette date. Restaient 93. En février, les laboratoires exploitant ces spécialités ont été informés individuellement de notre intention de procéder au déremboursement de leur spécialité. Ils ont été en même temps avertis qu'ils disposaient d'un mois pour faire valoir leurs observations à la commission de la transparence. Les laboratoires n'ont fait usage de ce droit que pour 10 produits. Les réexamens de la commission de la transparence ont eu lieu en mai et juin. A l'issue de cette phase, nous étions en mesure de procéder aux déremboursements pour le 1° juillet comme prévu.

Un délai supplémentaire nous a toutefois été imposé du fait de l'intervention récente de la décision du 20 juin du conseil d'Etat, qui, saisi par 2 laboratoires, a annulé les arrêtés pris par mon prédécesseur qui abaissaient de 65% à 35% le taux de remboursement de 2 médicaments vasodilatateurs. En effet, le Conseil d'Etat a mis en évidence l'insuffisante motivation des avis de la commission de la transparence sur lesquels le ministre s'appuie pour décider d'un déremboursement. J'ai donc demandé pour les produits concernés que la rédaction des avis motivés soit reprise de façon plus explicite et dans le sens d'une plus grande rigueur. Ce travail a mobilisé la commission de la transparence et son secrétariat jusqu'à ce jour. La commission de la transparence s'est réunie mercredi 16 pour adopter les nouveaux avis. Ceux-ci ont été transmis aux laboratoires qui disposent

de 8 jours pour faire part de leurs observations. A l'issue de ce délai, je serai en mesure de procéder au déremboursement.

Dérembourser : une procédure complexe

Toutefois, dans un souci de transparence et pour anticiper une annonce de déremboursements qui, juridiquement du fait des délais de procédure, ne pourra se faire qu'en août, j'ai souhaité vous communiquer dès maintenant les produits que j'ai demandés à la commission de réexaminer en vue d'un éventuel déremboursement. Vous trouverez la liste dans le dossier de presse. Cette liste précise pour chaque produit, ses indications, une brève description des raisons qui m'ont conduit à interroger la commission de la transparence une dernière fois sur l'opportunité d'un déremboursement et une présentation des alternatives thérapeutiques. Je ne doute pas que ce tableau devrait répondre à l'ensemble de vos interrogations.

Je profite de cette occasion pour faire le point sur 2 produits qui ne figurent pas dans cette liste alors qu'ils avaient été évoqués dans les journaux comme devant en faire partie. Le Toplexil est un sirop dont la commission de la transparence a estimé lors de la réévaluation qu'il rendait un service médical insuffisant car il associait un anti tussif et un expectorant. Chaque médecin sait que cette association est illogique. Suite à cette évaluation, l'entreprise a choisi de modifier la composition de ce produit. Comme pour tout médicament, elle a déposé un nouveau dossier d'autorisation de mise sur le marché ; ce nouveau sirop a été évalué en octobre 2002 par la commission de la transparence et a été crédité à cette occasion d'un "smr faible". Il n'est donc plus question de dérembourser ce produit. Nous n'avons pas de base légale pour le faire. Je vous rappelle que nous ne pouvons dérembourser que les médicaments susceptibles d'entraîner des dépenses injustifiées ou ceux qui ont un service médical rendu insuffisant. Dimetane, autre produit anti tussif, a choisi de procéder de la même manière.

Comme je vous l'ai dit, je ne pourrai procéder au déremboursement qu'au vu de l'avis définitif de la commission de la transparence. L'avis rendu mercredi n'est qu'un avis provisoire. Nous devrions donc être à même de publier l'arrêté officialisant la décision et la liste des produits concernés au début du mois d'août, une fois les avis devenus définitifs. La liste que je vous communique fournit toutefois une bonne indication des produits qui, sauf avis contraire de la commission, devraient être déremboursés.

Vous le voyez, un déremboursement nécessite une procédure longue et juridiquement complexe. Il ne saurait en être autrement. Il s'agit en effet d'une décision lourde de conséquences pour les médecins, leurs patients et l'industriel qui exploite ce médicament. La commission de la transparence a la charge de la majeure partie du travail d'instruction des dossiers de déremboursement. Je souhaite aujourd'hui lui rendre hommage pour le travail qu'elle a fourni. C'est un travail difficile, exigeant, technique. Il est légitime de remercier aujourd'hui tout spécialement les membres bénévoles et le tout premier d'entre eux son président, le professeur Bernard Dupuis.

Réformer la commission de la transparence

Il reste que cette commission doit évoluer pour assumer l'ensemble des charges que j'entends lui confier. La commission de la transparence doit en effet non seulement évaluer les nouveaux produits afin d'aider le politique à déterminer si le produit doit être admis au remboursement. Cette évaluation sert ensuite à la fixation des prix. Elle doit aussi le conseiller dans la gestion quotidienne de la liste des médicaments remboursés. Ces missions doivent être exercées dans le cadre d'un certain formalisme juridique. Cela implique des équipes et des savoir faire multiples, médicaux et juridiques. Elle a enfin un rôle à jouer capital dans l'information des professionnels de santé au quotidien. L'administration ne peut travailler dans son coin, elle doit informer et expliquer ses décisions auprès des praticiens et peut-être même auprès des patients. J'ai demandé au professeur Gilles Bouvenot (voir son C.V dans le dossier de presse) de me faire des propositions sur les évolutions souhaitables de cette commission. A partir de ses suggestions, j'ai décidé de faire évoluer la commission de la transparence dès maintenant selon trois axes : un changement de sa composition, une modification des procédures et un renforcement de son autonomie financière.

Cette évolution ne préjuge naturellement pas de la création de la commission du service médical rendu étendu à l'ensemble des conduites et procédés diagnostiques et thérapeutiques qui aura lieu dans l'année qui vient après une large concertation.

1 - La modification de sa composition vise à renforcer le caractère médical de cette commission. Je souhaite que ses avis soient, d'un point de vue médical, le plus incontestable possible. C'est pourquoi j'ai décidé d'augmenter le nombre de cliniciens qui y participent. Parallèlement, les représentants des administrations ou des caisses n'auront plus qu'une voix consultative. Il s'agit de mettre fin aux

soupçons, même injustifiés, qui pèsent actuellement sur le fonctionnement de cette commission. Les avis seront purement médicaux. Le mandat des actuels membres de la commission arrive à échéance fin juillet. La modification de la composition que je souhaite faire nécessite un décret en conseil d'Etat. Ce texte sera transmis au cours de l'été au Conseil d'Etat afin de le publier dès septembre pour assurer la continuité de cette commission essentielle au bon fonctionnement de notre dispositif d'admission au remboursement. Je peux d'ores et déjà vous annoncer que le professeur Gilles Bouvenot sera le président de cette commission de la transparence rénovée. C'est un choix logique. Il a une grande connaissance du médicament développée lors de ses nombreuses participations aux instances travaillant sur le médicament en France. Il était en outre cohérent de lui confier la charge de la commission après lui avoir demandé d'en tracer les évolutions.

2 - Nous devons aussi donner plus de clarté aux procédures qui régissent le fonctionnement de la commission de la transparence. Les modifications porteront sur la procédure telle qu'elle est décrite dans le code de la sécurité sociale. Le texte actuel est complexe, d'une interprétation délicate et source de contentieux. Le commissaire du gouvernement chargé du dossier vasodilatateur au conseil d'Etat le juge lui même difficile à appliquer. Les changement affecteront aussi le cheminement du dossier au sein de la commission. Nous devons être en mesure de mieux suivre les différentes étapes d'analyse d'un dossier. Cela permettra un travail plus approfondi et cela constituera un atout important dans le respect des délais qui nous sont fixés par l'Union Européenne. Les changements affecteront enfin le choix des experts qui peuvent être amenés à contribuer au travail de la commission. Les enjeux financiers qui découlent de cette commission sont considérables, la pression n'est pas absente. Les conditions de déontologie doivent donc être irréprochables. Cet axe de la réforme nécessite plus de temps, la réforme devrait pouvoir être mise en place à la fin de l'automne.

3 - Le troisième axe de la réforme de la transparence concerne le renforcement de la structure administrative sur laquelle est adossée cette commission. La Cour des Comptes a de nombreuses fois déploré le manque de moyens qui était accordé à la commission de la transparence. Le positionnement ambiguë de cette commission (elle est placée auprès du ministre mais rattachée à l'AFSSAPS) n'est pas de nature à faciliter la dotation en moyens administratifs de cet organisme. Il est temps de lui donner plus d'indépendance.

Il n'est pas raisonnable de confier à cette commission une tâche aussi lourde sans lui accorder les moyens nécessaires. J'ai obtenu du ministère de l'économie et des finances que nous indemnisions les experts libéraux. C'est un début, il faudra sans doute aller plus loin. Je souhaite aussi doter la commission d'un secrétaire général chargé du suivi de l'ensemble des taches administratives. Je souhaite enfin conférer une certaine autonomie budgétaire à cette commission. Les modalités ne sont pas encore fixées. La solution retenue pour le comité économique des produits de santé peut nous inspirer. Cette dimension devra aussi être considérée dans le cadre plus large de la mise en place de la commission du service médical rendu.

L'arrêt du conseil d'Etat sur les vasodilatateurs

Je faisais référence, il y a quelques instants à la nécessaire qualité juridique des avis. Vous le savez, le conseil d'Etat a annulé deux décisions prises par Madame Guigou en mettant en évidence le caractère insuffisant de la motivation des avis rendus par la commission de la transparence préalablement aux décisions du ministre de la santé.

Cette décision de justice fragilise l'ensemble des décisions de baisse de taux ou de déremboursement prises depuis 2001. Les enjeux financiers sont importants. Nous ne pouvons laisser un problème formel remettre en cause une politique dont aucun scientifique ne conteste le bien fondé.

Il fallait agir rapidement pour mettre fin à l'instabilité juridique née de cet arrêt. J'ai donc décidé de proposer au parlement une validation législative qui consolidera l'ensemble des décisions qui ont été prises et qui, à l'heure de leur annonce, n'avaient fait l'objet d'aucune contestation. Ce texte revêt la forme d'un amendement à un texte (voir fiche du dossier de presse) que le gouvernement fait actuellement discuter au parlement. J'espère qu'il pourra être promulgué dans les meilleurs délais.

Comme vous le voyez, malgré les imprévus qui font partie de tout quotidien, je maintiens le cap de la politique du médicament que j'avais définie à l'automne dernier.

Une politique du médicament au service des malades

J'avais souhaité faciliter l'accès de nos concitoyens aux innovations. Pour ce faire, j'ai mis en place une nouvelle procédure de dépôt de prix, et consacré 200 millions à l'innovation à l'hôpital.

J'ai souhaité pouvoir faire des économies sur les molécules plus anciennes, nous avons fait une campagne sur le générique, nous sommes en train de finaliser la mise en place des tarifs forfaitaires de remboursement et obtenu des laboratoires une baisse de prix conséquente sur le paracétamol équivalent à un prix générique.

Je désirais une gestion plus active de la liste des déremboursements : nous avons baissé la prise en charge de produits dont la prise en charge à 65% n'était pas justifiée, et nous allons procéder au déremboursement de la première phase du déremboursement des produits à SMR insuffisant. Il me semblait enfin nécessaire d'améliorer nos procédures : la modification de la commission de la transparence est en cours.

Les mesures que j'ai prises dès mon arrivée avec le soutien des professionnels de santé ont incontestablement concouru à ralentir la croissance des dépenses de médicaments en ville et à l'hôpital. Alors que le taux de croissance se situait à 7,7% par an en 2000 et 2001, il a été de 5,7% en 2002 et tout porte à croire que cet infléchissement se poursuivra en 2003.

C'est donc, avec constance et malgré les difficultés, que je trace un chemin pour assurer les meilleurs traitements aux coûts les plus justes pour les malades. C'est à eux seuls que je pense en définissant la politique du médicament car notre système de sécurité sociale doit rester ce qu'il a toujours été, juste et solidaire. Et tout le monde peut comprendre l'importance d'une prise en charge des meilleurs traitements, les plus innovants pour tous ceux qui en n'ont besoin lors des maladies graves. Le Ministre de la santé est d'abord le Ministre des malades et je veux que ceux-ci sachent ma détermination à leur assurer le meilleur, au meilleur coût pour nous tous. Ne l'oublions pas, nous payons tous pour que chacun soit pris en charge selon ses besoins.

La réévaluation mode d'emploi

1/ Pourquoi " réévaluer " les médicaments ?

L'objectif de la réévaluation, demandé en 1999 par le précédent gouvernement, était d'apprécier pour chaque médicament le bien fondé de son maintien au remboursement. En effet, avant cette date, il n'existait pas de procédure permettant de réviser périodiquement la liste des produits remboursés.

Pour ce faire, l'ensemble des médicaments remboursables par l'assurance maladie en ville s'est vu attribuer un service médical rendu (SMR).

Le SMR est un critère composite, défini à l'article R-163-3 du code de la sécurité sociale, qui prend en compte , d'une part la gravité de la pathologie dans laquelle le médicament est indiqué, d'autre part des données propres au médicament lui-même, dans l'indication considérée : efficacité, sécurité d'emploi, place dans la stratégie thérapeutique, et, le cas échéant, intérêt en termes de santé publique.

2/ Qui a réévalué les médicaments?

La commission de la transparence a été chargée de cette mission. Elle a pris en compte l'avis de groupes d'experts cliniciens dans chaque discipline thérapeutique. Elle s'est également appuyée sur les ressources de l'Agence française de sécurité sanitaire des produits de santé (Afssaps), qui assure le secrétariat de la commission.

3/ Comment s'est déroulée la procédure ?

La réévaluation comportait les phases suivantes :
- Regroupement des spécialités par classe pharmaco-thérapeutique
- Analyse des données et proposition de SMR par les groupes d'experts
- Examen des propositions par la Commission de la transparence et rédaction des avis
- Notification aux laboratoires concernés
- Examen par la commission des observations et des données déposées par les laboratoires qui le souhaitaient
- Nouvel avis de la commission
- Phase contradictoire avec possibilité pour la firme d'être entendue une nouvelle fois par la commission
- Avis définitif de la Commission de la transparence

4/ Les laboratoires ont-ils eu l'occasion de présenter leurs observations ?

Oui, les entreprises ont bénéficié de multiples occasions d'échanges avec la commission.

La réévaluation a fourni aux entreprises une première occasion de venir défendre le service médical rendu (SMR) par leur produit. Ensuite, chaque décision prise a donné lieu à une nouvelle possibilité d'échange.

Ainsi, lorsque le ministre a informé par courrier en février 2003 les entreprises de son intention de dérembourser certains médicaments en juillet 2003, il leur a offert la possibilité de présenter leurs observations. Sur les 95 présentations concernées par cette première phase de déremboursement, les laboratoires n'ont souhaité faire des observations que sur 10 d'entre elles. Ces observations orales ou écrites ont été examinées lors de réunions de la commission en mai et juin.

5/ Comment ont été classés les médicaments ?

Au terme de cette procédure, la Commission a qualifié le SMR de chacune des spécialités :
- SMR majeur ou important
- SMR modéré ou faible
- SMR insuffisant pour justifier d'une prise en charge par l'assurance maladie.

6/ Combien ont été concernés par cette réévaluation ?

Au 7 juin 2001, **4.490** spécialités avaient été réévaluées :
- **2.815** spécialités à SMR majeur ou important
- **840** spécialités à SMR modéré ou faible
- **835** spécialités à SMR insuffisant

7/ Si les médicaments à SMR insuffisant sont inefficaces, pourquoi maintenir leur autorisation de mise sur le marché ?

Pour qu'un médicament reçoive une autorisation de mise sur le marché (AMM) il est nécessaire que le bénéfice qu'il apporte (efficacité) soit supérieur au risque qu'il entraîne (effets indésirables). Cette évaluation du rapport bénéfice/risque se fait par indication, c'est à dire dans le cadre de la maladie auquel le médicament est destiné. L'AMM est accordée selon les standards scientifiques et médicaux en vigueur au moment où le laboratoire dépose sa demande. Elle peut être réévaluée, modifiée, ou retirée à tout moment si des données nouvelles laissent penser que le rapport bénéfice/risque n'est plus positif. Ceci est en particulier le cas s'il existe des effets indésirables nouveaux, ou plus graves que ce qui était attendu. Un problème de santé publique, comme le développement de la résistance aux antibiotiques, peut également justifier la révision ou le retrait d'une AMM.

Une réévaluation des AMM des médicaments contenant des antibiotiques pour usage local est ainsi en cours par l'Agence française de sécurité sanitaire des produits de santé, et s'est déjà traduit par le retrait récent du marché de médicaments contenant des antibiotiques pour administration par voie nasale.

Cependant, le fait qu'un médicament ait un SMR jugé insuffisant ne signifie pas pour autant qu'il existe un motif de santé publique justifiant son retrait du marché. Les médicaments les plus anciens ont été mis sur le marché à une époque où il n'était pas exigé du laboratoire d'apporter les preuves incontestables d'une efficacité clinique selon les standards actuels. Ces médicaments peuvent ainsi progressivement perdre leur place dans la stratégie thérapeutique, en raison de l'évolution des connaissances et de l'existence de nouvelles alternatives. Cependant, si le médicament en question est bien toléré (effets indésirables rares et bénins), il n'existe pas de motivation suffisante pour justifier un retrait de l'autorisation de mise sur le marché.

En revanche, il est légitime que, dans le cadre d'une politique de santé publique, les pouvoirs publics cherchent à réorienter les médecins et les patients vers des produits plus efficaces et mieux tolérés.

Les mesures prises à la suite de la réévaluation

1/ 2001 : baisse des taux de prise en charge des médicaments à SMR insuffisant

Le précédent gouvernement a baissé le taux de prise en charge des produits à SMR insuffisant et obtenu des baisses de prix de la part des laboratoires.

- **Les baisses de taux de prise en charge :** les baisses ont été organisées par un arrêté d'Août 2000 prévoyant la **baisse du taux de remboursement pour les vasodilatateurs périphériques et les nootropiques.** Ce texte a été abrogé en raison d'un vice de forme sanctionné par le Conseil d'Etat mais les baisses de taux ont été reprises par un arrêté du 14 septembre 2001. Un arrêté publié le 30 décembre 2001 a complété la baisse du taux de remboursement des autres médicaments dont

le SMR a été qualifié d'insuffisant et qui étaient encore remboursables à 65%.
- **Les baisses de prix** : L'Etat a demandé aux entreprises des baisses de prix sur les produits à SMR insuffisant selon un plan sur trois ans. Les baisses ont été obtenues en 2000, 2001 et 2002 respectivement de 7%, 8%, 7% en moyenne. Elles ont dans certains cas été remplacées par des déremboursements volontaires.

2/ Avril 2003 : 617 médicaments à SMR modéré ou faible font l'objet d'une baisse de taux de remboursement.

Les baisses de taux de remboursement de ces spécialités ont été mises en application en avril 2003, après que les laboratoires concernés ont été invités à présenter leurs observations à la commission de la transparence. La Commission a ainsi examiné des recours pour 68 spécialités. Pour 11 spécialités correspondant à 8 principes actifs, la commission a modifié son avis et considéré que le SMR était important.
L'arrêté de baisse de taux du 19 avril 2003 a concerné 617 présentations de médicaments correspondant 204 principes actifs.

3/ Juillet 2003 : présentation d'une liste préliminaire de médicaments à SMR insuffisant déremboursés

Jean-François Mattei a décidé de programmer le déremboursement des médicaments à SMR insuffisant en trois vagues (2003 à 2005). La première année concerne les médicaments dont la commission avait jugé, d'une part que le SMR était insuffisant, et d'autre part qu'ils n'avaient aujourd'hui pas de place dans la stratégie thérapeutique, d'autres moyens de prise en charge leur étant préférable (le plus souvent parce que ces derniers sont plus efficaces et mieux tolérés ou d'administration plus facile). En 2004 seront déremboursés les produits qui relèvent d'un choix d'automédication. Ils auront ainsi disposé d'environ 2 ans pour se préparer au passage à l'automédication. Enfin, en 2005, le déremboursement concernera des produits médicalement peu efficaces mais, pour l'heure, sans alternative thérapeutique.

4/ Combien de médicaments sont concernés ?

La liste initiale comptait 95 présentations.
- 2 produits ne sont plus commercialisés et ont déjà été radiés.
- 3 produits ont vu leur déremboursement reporté à une année ultérieure (2 formes de Sterlane et Covatine).
- 2 produits sont en attente d'un nouvel examen à la commission d'AMM (2 formes d'Isoprinosine)
- 4 produits sont maintenus au remboursement dont 3 suite à un changement de formule Toplexil et 2 formes de Dimetane et 1 suite à la réévaluation du SMR par la commission de la transparence (Orbenine).

Au total, 84 présentations seront déremboursées.

5/ Combien espérez-vous économiser avec cette mesure ?

Les déremboursements auxquels il est procédé cette année n'ont pas qu'un objectif financier. Ils répondent aussi à **un objectif de santé publique**. Ils visent des spécialités dont l'utilisation n'est plus souhaitable par les médecins et leurs patients. C'est pour cela que le tableau récapitulatif du dossier de presse indique les alternatives possibles. Il est possible que certains produits viennent se substituer aux produits que déremboursés.
Quelques repères financiers permettent toutefois d'apprécier l'ordre de grandeur de l'économie potentielle si l'on fait l'hypothèse que l'ensemble des produits de cette liste seront effectivement déremboursés. Le chiffre d'affaires TTC des spécialités déremboursées est de 82 millions d'€.

Une nouvelle politique du médicament : donner la priorité à l'innovation

1) État des lieux

Les dépenses de médicaments progressent à un rythme élevé : **depuis 1990**, elles ont plus que **doublé**. Les Français sont parmi les plus grands consommateurs mondiaux de médicaments (**3 milliards de boîtes consommés par an**, soit un peu moins d'une boîte par personne et par semaine).

Cependant, les patients souffrent d'un accès encore insuffisant à certaines innovations. Chaque année sont mis sur le marché des médicaments apportant des améliorations majeures. Ces produits sont de plus en plus coûteux : la recherche est longue et hasardeuse, les techniques employées de plus en plus sophistiquées, le nombre de patients en bénéficiant peut être faible. Le traitement par le Glivec revient à 30 000 €par an (pour la leucémie myeloïde chronique) par patient, Kineret utilisé dans la polyarthrite rhumatoïde se situe au même niveau de coût, le traitement par l'Herceptine pour certaines formes de cancer du sein coûte plus de 12 800 €...

La gestion du médicament se caractérisait jusqu'à présent par une absence de vision d'ensemble et par des opérations ponctuelle pour sortir de situations financières délicates.

2) Actions du gouvernement

Une politique du médicament lisible centrée sur l'innovation

Trois axes structurent la politique du médicament mise en place : le soutien à l'innovation, la recherche d'une efficience accrue pour les dépenses existantes et la simplification des dispositifs de régulation.

A - Garantir à tous l'accès aux médicaments les plus innovants :
- Fournir un effort supplémentaire pour le médicament innovant à l'hôpital. **200 M€** supplémentaires vont ainsi être consacrés à des médicaments particulièrement coûteux. **15 médicaments** sur les **4400 utilisés** représentent **25 % des dépenses** en médicaments à l'hôpital. Le Fabrazyme utilisé dans le traitement de la maladie de Fabri coûte **152 500 €**par an et par patient.
- Accélérer la mise sur le marché en pharmacie des médicaments les plus innovants. Le délai moyen actuel de mise sur le marché est de **240 jours**, il devrait pouvoir être réduit à environ **100 jours**.

B - Optimiser les dépenses sur les médicaments existants :
En réduisant les coûts supportés par l'assurance maladie sur des molécules existantes, il est possible de dégager des marges de manœuvre pour prendre en charge les innovations nécessaires à la santé des Français.

- Favoriser le développement du générique. Ces médicaments, copies fidèles de médicaments qui ne sont plus protégés par un brevet, sont de 30 à 40 % moins coûteux que les originaux. Ils n'occupent **qu'un peu plus de 6%** du marché français alors qu'ils dépassent plus de 20% chez certains de nos voisins. Quatre mesures ont été prises pour aider au développement des génériques.
a) L'accord du 5 juin entre les médecins et la caisse d'assurance maladie a permis d'impliquer le médecin dans la politique de promotion des génériques.
b) Une campagne de publicité grand public a été menée pour rappeler aux patients l'intérêt de ces produits.
c) La loi de financement pour la sécurité sociale pour 2003 a créé les forfaits de remboursement. Cette mesure vient en complément des politiques déjà déployées pour favoriser le développement du générique. Lorsque le forfait sera appliqué, le

patient sera libre du choix de la marque du médicament qu'il souhaite mais il ne sera remboursé qu'à hauteur du forfait.
d) La loi de financement pour la sécurité sociale pour 2003 prévoit enfin la possibilité de baisser les coûts supportés par l'assurance maladie pour des molécules anciennes comme le paracétamol ou l'aspirine.

La progression du générique a été spectaculaire ces derniers mois. Auparavant, lorsqu'un patient avait le choix d'un générique, il n'acceptait de le prendre que dans un cas sur trois. Désormais, il accepte une fois sur deux.

- Mener une politique de gestion active des produits remboursés. La réévaluation initiée en 1999 a permis de mettre en évidence 800 produits ne justifiant plus une prise en charge par les pouvoirs publics et 800 autres ne présentant pas un service médical rendu (SMR) suffisant pour une prise en charge à 65 %. En octobre 2002, le ministre a annoncé le déremboursement sur 3 ans de l'ensemble des produits à SMR insuffisants. Les produits à SMR modéré ou faible qui n'étaient pas pris en charge à 35 % viennent d'être ramenés à ce taux.

C - Simplifier et améliorer les dispositifs de régulation :
- **Évolution des taxes** dans le domaine pharmaceutique. Les assiettes varient d'une taxe à l'autre et sont contestées par les entreprises. La loi de financement pour la sécurité sociale 2003 a fait un premier pas dans le sens de la simplification en supprimant une des taxes, la taxe additionnelle sur les ventes directes. Elle a aussi été l'occasion de simplifier le calcul de l'assiette de la taxe sur la promotion.
- **Réforme de la commission de la transparence** : cette commission est chargée d'évaluer les médicaments qui pourraient être admis au remboursement. Malgré son rôle essentiel dans le dispositif, elle souffre d'un manque de moyens. Une première étape a consisté à rémunérer les experts qui participent activement au fonctionnement de cette commission. Une réforme plus globale aura lieu à l'occasion de son renouvellement.

3) Perspectives

La politique définie pour les médicaments sera poursuivie. D'autres économies sur les molécules anciennes peuvent être réalisées en accélérant le rythme d'apparition des génériques et en favorisant l'automédication.
Il faudra, avec l'aide de l'ensemble des acteurs du système de santé, trouver des solutions pour s'assurer que les Français n'utilisent que le strict nécessaire. La politique de développement de l'innovation sera poursuivie.

Présentation de la commission de la transparence

1/ Ses missions :

- donner un avis sur l'inscription, le renouvellement et la radiation des médicaments inscrits sur la liste d'admission au remboursement
- procéder aux réévaluations des listes de produits admis au remboursement lorsque nécessaire
- donner un avis sur les documents d'information à destination des praticiens et notamment les fiches d'information thérapeutiques ou les recommandations sur l'usage des médicaments.

2/ Sa composition : (article R.163-15 du code de la sécurité sociale)

- Un président et un vice-président
- Trois membres de droit : le directeur de la sécurité sociale ou son représentant ; le directeur général de la santé ou son représentant ; le directeur général de l'Agence

française de sécurité sanitaire des produits de santé ou son représentant ;
- Treize membres :
  - 7 représentants institutionnels: Un médecin au titre de l'ordre national des médecins ; un pharmacien choisi au titre de l'ordre national des pharmaciens ; deux représentants de la Caisse nationale de l'assurance maladie des travailleurs salariés ; un représentant de la Caisse nationale d'assurance maladie et maternité des travailleurs non salariés des professions non agricoles et un de la Caisse centrale de la mutualité sociale agricole ; un représentant de l'industrie pharmaceutique
  - Six membres choisis en raison de leur compétence médicale, scientifique ou économique dans le domaine du médicament.

Le président et le vice président et les membres (hors membres de droit) sont nommés par arrêté du ministre chargé de la sécurité sociale et du ministre chargé de la santé pour une durée de 3 ans renouvelable une fois.
La très grande majorité des membres de cette commission est soit médecin soit pharmacien. En dehors des représentants de l'administration, les membres de cette commission sont des bénévoles. Ils prennent sur leur temps de travail pour participer aux travaux de cette commission.

3/ Son fonctionnement :

La commission se réunit deux fois par mois pour une séance de 4 heures. Le secrétariat technique, administratif et scientifique de la commission est assuré par l'Agence Française de Sécurité Sanitaire des Produits de Santé.
La commission est assistée dans son travail, pour tous les dossiers qui le nécessitent, par des rapporteurs externes, notamment des médecins spécialistes du domaine pathologique concerné par le médicament évalué.
Elle se prononce en rendant des avis où elle détaille 2 critères :
- le service médical rendu : ce critère composite, (article R-163-3 du code de la sécurité sociale) prend en compte, d'une part la gravité de la pathologie dans laquelle le médicament est indiqué, d'autre part des données propres au médicament lui-même, dans l'indication considérée : efficacité, sécurité d'emploi, place dans la stratégie thérapeutique, et, le cas échéant, intérêt en termes de santé publique. Il permet une évaluation dans l'absolu de l'intérêt médical d'une spécialité au vu d'un éventuel remboursement. Il est aussi utilisé pour fixer le taux de prise en charge d'un produit. Cet indice est gradué de majeur à insuffisant.
- l'amélioration de service médical rendu (ASMR) évalue l'apport d'un nouveau médicament par rapport aux produits existants dans une indication. Ce critère est gradué de 1 (progrès majeur) à 5 (n'apporte rien par rapport aux produits existants). L'ASMR est utilisée par le Comité économique des produits de santé (CEPS) pour fixer le prix d'une spécialité.

Petit glossaire du médicament

Médicament
La définition réglementaire du médicament est la suivante :
(Art. L. 5111-1 du code de la santé publique)
"On entend par médicament toute substance ou composition présentée comme possédant des propriétés curatives ou préventives à l'égard des maladies humaines ou animales, ainsi que tout produit pouvant être administré à l'homme ou à l'animal, en vue d'établir un diagnostic médical ou de restaurer, corriger ou modifier leurs fonctions organiques."
Cette définition est assez générale, les autres termes utilisés ont des définitions plus précises.

Principe actif
Le principe actif est la substance responsable de l'action pharmacologique, ex : le paracétamol. Un même principe actif peut être présent dans de multiples spécialités et présentations.

Spécialité
La réglementation précise (Art. L. 5111-2 du code de la santé publique) :
"On entend par spécialité pharmaceutique, tout médicament préparé à l'avance, présenté sous un **conditionnement particulier et caractérisé par une dénomination spéciale**."
En pratique, les spécialités ont une autorisation de mise sur le marché.
Par exemple " Voltarène comprimés 50mg " et " Voltarène suppositoire 100 mg " et " Voltarène comprimés 25 mg " sont des spécialités différentes contenant un même médicament ou principe actif, le diclofénac.

Présentation
Une spécialité pharmaceutique peut être commercialisée sous différentes présentations, selon la taille ou la contenance du conditionnement.
Par exemple "ADVIL comprimés 400mg, Boîte de 20" et "ADVIL comprimés 400mg, Boîte de 30" sont des présentations différentes d'une même spécialité.

Annexe 4-15

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RÉPUBLIQUE FRANÇAISE

Xavier Bertrand

Ministre de la Santé et des Solidarités

Discours

Sous réserve du prononcé

« 3ième vague de Médicaments Réévalués»

Mercredi 25 octobre 2006

CONTACT Service de Presse : 01 40 56 40 14 /12
www.sante.gouv.fr

Annexe 4-15

▪ Jeudi dernier, la Haute autorité de santé m'a recommandé de dérembourser 89 médicaments à service médical rendu insuffisant. **J'ai décidé de ne pas suivre l'avis de la HAS**. Je vais vous dire ce que j'ai décidé. Je veux vous dire pourquoi j'ai pris cette décision.

▪ Vous le savez, en 1999, le service médical rendu de l'ensemble des médicaments (soit 4 500) a été réévalué.
La prise en charge des médicaments doit s'apprécier en fonction du service médical rendu, et lui-même s'évalue et se réévalue en tenant compte notamment de l'évolution des connaissances scientifiques.

La prise en charge des médicaments nécessite donc **une gestion dynamique et rigoureuse**. Elle doit fournir à nos concitoyens l'ensemble **des médicaments dont ils ont besoin et seulement ceux là**. Elle doit aussi être capable de fournir des solutions pour l'ensemble des pathologies qui le nécessitent. Elle doit être en mesure d'assurer la prise en charge **des médicaments les plus innovants, même quand ce sont aussi les plus coûteux.**

• Je sais aussi que, **quand il n'y a rien, un médicament même faiblement efficace est un progrès pour les patients.**

• **Je souhaite donc qu'on ne parle plus de médicaments inefficaces ou inutiles.** C'est incompréhensible pour des patients qui prennent ces médicaments depuis des années. Ca l'est également pour les médecins qui ont prescrit ces médicaments. **Je préfère que l'on insiste sur le caractère prioritaire des médicaments remboursés** ; c'est pourquoi, je compte **modifier le décret sur la transparence prochainement.**

▪ La troisième et dernière vague de médicaments au service médical rendu jugé insuffisant vient d'être réévaluée par la Haute autorité de santé, autorité scientifique indépendante Elle porte sur des **médicaments à prescription obligatoire, c'est-à-dire sur des médicaments que seul un médecin peut vous autoriser à prendre**.

▪ La décision que je vais vous présenter prend compte plusieurs approches :
- la **recommandation scientifique** de la HAS
- l'existence d'**alternatives** thérapeutiques
- la capacité des patients concernés à **modifier leur comportement**
- **l'absence d'étude sur les reports** éventuels sur d'autres médicaments. Je demande d'ailleurs à l'Assurance maladie de procéder à ces études.
- **l'évolution des prix à la sortie du déremboursement**

Vous comprendrez qu'en tant que ministre de la santé, je dois non seulement fonder ma décision sur des recommandations scientifiques mais aussi **anticiper les conséquences d'un déremboursement sur les prix et voir très concrètement comment les patients et les professionnels de santé vont pratiquer ces changements.** La HAS est dans son rôle quand elle regarde l'appréciation scientifique, mon rôle c'est de tenir compte de la réalité sociale. Je suis convaincu que médical ne peut en aucun cas rimer avec brutal. Pour autant, je ne veux pas de statu quo.

▪ Sur la base d'éléments scientifiques **nouveaux**, la HAS a considéré que **5** des médicaments réévalués ont un service médical rendu suffisant pour être **pris en charge dans toutes leurs indications thérapeutiques** et **50 dans une partie de leurs indications**. Ces médicaments méritent donc d'être pris en charge, et continueront à l'être à hauteur de **65 ou 35 %, selon leur service médical rendu**.

▪ Pour 89 autres médicaments, la HAS a confirmé que le service médical rendu était insuffisant et a recommandé leur déremboursement selon des modalités adaptées à chaque type de médicament.

▪ Mais c'est aussi aux laboratoires, et non seulement aux patients, d'assumer les conséquences du service médical rendu insuffisant, je demande donc que soient appliqués à ces médicaments des **baisses de prix significatives. L'explosion des prix seraient incompréhensibles et inacceptables.**

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▪ Elle a en effet distingué **un premier groupe de 48 médicaments dit « vasodilatateurs »**, utilisés dans les troubles cognitifs des sujets âgés pour lesquels il n'existe **pas, à ce jour, d'alternative**. Et **un deuxième groupe de 41 médicaments** utilisés dans des pathologies diverses et souvent bénignes, pour lesquels **il existe**, en revanche, **d'autres traitements**.

▪ En ce qui concerne **le groupe dit des vasodilatateurs** pour lesquels il n'existe pas d'alternative, j'ai décidé de conserver leur prise en charge à hauteur de **35% tout en leur appliquant une baisse de prix allant jusqu'à 20%.** Je sais que des études importantes sont en cours sur certains de ses produits. Je souhaite que selon les vœux exprimés par le Collège de la Haute autorité de santé, **des nouveaux résultats cliniques** permettent de modifier comme cela a été fait pour d'autres médicaments l'évaluation de leur service médical rendu.

▪ En ce qui concerne **les 41 médicaments pour lesquels il existe une alternative**, j'ai décidé de conserver leur prise en charge, mais seulement **à 15%, et ce pendant un an avec une baisse de prix allant jusqu'à 15%.** Les patients qui le souhaitent pourront bénéficier d'une période de transition pendant laquelle la charge est répartie entre les patients, l'Assurance maladie et les laboratoires.

▪ Le maintien au remboursement, ne serait ce qu'à hauteur de 15%, permettra **aux patients de bénéficier d'un temps d'adaptation et aux professionnels de santé d'un temps de pédagogie**. Je suis par ailleurs très attaché à ce les prix ne flambent pas au moment du déremboursement. C'est pourquoi je souhaite aussi utiliser cette période **pour formaliser avec les industriels des accords de modération de prix à la sortie de leur déremboursement.**

▪ Je tiens à préciser que **les complémentaires santé vont également bénéficier de ces baisses de tarifs** et qu'elles n'auront donc aucune raison d'augmenter leurs tarifs, bien au contraire.

▪ **J'ai donc saisi le Comité des produits de santé pour que l'ensemble de mes décisions soient appliqués dès la fin du mois de janvier.**

▪ Enfin, je tiens à préciser que nous n'avons pas besoin de ce type de mesure pour réussir la réforme de l'Assurance maladie. Ce qui m'intéresse d'avantage, c'est l'évolution des comportements. Je suis fier qu'aujourd'hui un milliard d'euros soient consacrés chaque année à la prise en charge de médicaments nouveaux. Les 70 à 100 millions d'euros d'économie attendus sont bien loin de compte là.

Annexe 4-16

Comité Economique du Médicament
Le Président

République Française

Le 17 février 2000

COURRIER ARRIVÉ LE : 22/02/2000
Le Conseiller
N° : 00001204O
Transmis à :
Le

NOTE

pour la ministre de l'emploi et de la solidarité

à l'attention d'Hervé Le Louët, conseiller technique

Objet : Conséquences de la réévaluation des médicaments.

Conformément à la demande de la ministre, j'ai consulté les entreprises pharmaceutiques les plus concernées par la réévaluation des médicaments afin d'examiner avec elles selon quelles modalités on pouvait envisager de donner suite aux avis rendus par la commission de la transparence. Parallèlement à ces discussions particulières, une concertation a été engagée avec le SNIP, comme cela avait été prévu dans l'accord sectoriel de juillet dernier.

La ministre trouvera ci-après successivement un compte rendu de ces consultations (A) et des propositions d'action (B).

A- Compte rendu de consultations

1- Outre la concertation avec le SNIP, des discussions approfondies ont eu lieu avec les 18 entreprises les plus concernées, représentant à elles seules plus de 90 % du chiffre d'affaires total des médicaments à SMR insuffisant (Aventis, Sanofi Synthélabo, Servier, Pierre Fabre, Beaufour Ipsen, Merck AG, Negma, Lafon, BASF, Chiesi, Innothéra, Expanscience, Mayoly, Médiolanum, Pharmapharm, Roche-Nicolas, Wyeth et Novartis.

2- Ni les entreprises consultées ni le SNIP ne se déclarent hostiles au principe même de la réévaluation. Beaucoup sont en revanche critiques sur certains aspects de la procédure suivie. Toutes dénoncent avec vigueur les fuites constatées et médiatisées depuis l'été, y compris sur les travaux préparatoires de la commission. Au-delà des questions de principe, nombreuses sont les entreprises à contester le traitement infligé à leurs propres produits, cette contestation m'ayant paru particulièrement forte pour les veinotoniques et ceux des vaso-dilatateurs qui détiennent une indication dans l'artérite des membres inférieurs. Il faut s'attendre à des contentieux sans doute assez nombreux.

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3- La perspective d'un déremboursement immédiat est considérée comme difficilement soutenable, à des degrés divers selon ce que représentent ces produits dans leur chiffre d'affaires, par toutes les entreprises consultées sauf une (il s'agit d'Innothéra, qui produit des bas de contention, et qui estime qu'en cas de déremboursement des veinotoniques, la progression des ventes de bas pourrait rapidement compenser ce qu'elle perdrait à l'occasion du passage de son veinotonique en non-remboursable).

De fait, un déremboursement immédiat serait catastrophique pour Beaufour Ipsen (près d'un millier d'emplois), Negma, Lafon et un grand nombre de petites entreprises. Servier et Pierre Fabre s'en sortiraient, mais au prix d'un ralentissement sévère du développement de leurs futurs produits et sans doute, bien qu'ils ne l'aient pas évoqué devant moi, de réductions d'effectifs ou de non-création d'emplois. Aventis et Sanofi Synthélabo seraient fortement handicapées, en termes de ressources à consacrer au développement de leurs innovations, par rapport à leurs concurrents mondiaux.

Pour les filiales françaises de groupes étrangers, qui sont souvent d'anciennes PME indépendantes rachetées au fil du temps, les dégâts seraient importants en termes d'emplois (usines de fabrication et visiteurs médicaux). Je dois cependant signaler, pour sa valeur symbolique, l'exception de Mediolanum, petit groupe italien qui est menacé pour 70 % de son chiffre d'affaires, et qui m'a néanmoins indiqué que, quoiqu'il arrive en termes de déremboursement, il ne supprimerait aucun emploi en France.

4- Encore que sans enthousiasme, toutes les entreprises m'ont paru estimer qu'un déremboursement différé pouvait être géré par elles sans trop de dégâts pour autant que le délai soit suffisant.

5- Pour échapper à un déremboursement immédiat, et tant que le risque de déremboursement reste crédible, la plupart des entreprises seraient prêtes à accepter des baisses de prix, à l'exception notable de Beaufour.

6- Le SNIP ne serait pas opposé à des baisses de prix, tout en revendiquant qu'elles soient aussi modérées que possible et en rappelant que pour les médicaments remboursés à 35 %, compte tenu des dispositions de l'accord sectoriel, les ristournes sont plus avantageuses pour le sécurité sociale que les baisses de prix. Il estime que les déremboursements, différés ou non, devraient être sélectifs. Selon lui, un déremboursement peut être rapidement envisagé pour les magnésiums, pour peu que l'AFSSAPS leur confère une indication exploitable auprès du grand public, pour les bains de bouche ou pour certains produits d'ophtalmologie. Le SNIP juge, en revanche que le déremboursement est, même à terme, difficilement envisageable pour les vaso-dilatateurs à indication « artérite des membres inférieurs », pour lesquels il n'existe pas d'alternative thérapeutique et qui ne peuvent en aucun cas être exploités en automédication. Sa position est intermédiaire pour les veinotoniques pour lesquels, à s'en tenir au plan technique et commercial, un passage à l'automédication lui paraît concevable, dès lors qu'il serait laissé aux entreprises le temps de s'y préparer.

Le SNIP souhaite, de manière générale, qu'on privilégie les baisses de taux de remboursement en indiquant qu'elles ont un effet important de réduction des volumes prescrits.

B- Propositions d'action

1- **Annoncer un déremboursement à terme** (le 31 décembre 2003 ?) en indiquant que pourront y échapper les médicaments pour lesquels la commission de la transparence aurait avant cette date réévalué le SMR attribué sur la base d'un nouveau dossier d'essais cliniques. Pour pouvoir bénéficier de ce délai, les laboratoires devraient avoir accepté des baisses de prix conventionnelles (cf. 3 ci dessous).

Commentaire : c'est le nœud du dispositif. Il me paraît clair qu'on ne peut pas tout dérembourser tout de suite, ce qui serait dévastateur à tous égards, et pas seulement pour des raisons d'emplois ou de maintien du potentiel industriel français dans ce secteur, encore que ces raisons soient sérieuses.

Ce sont avant tout des raisons d'ordre sanitaire et social qui s'opposent à un déremboursement massif et brutal, étant rappelé que les médicaments contestés s'adressent, pour la plus grande part, aux personnes âgées (vaso-dilatateurs cérébraux) ou aux femmes qui souffrent des jambes (veinotoniques) et que, même si ces médicaments ne sont pas d'une grande efficacité, ils répondent incontestablement à une demande et à une douleur et on ne leur connaît pas d'alternative thérapeutique crédible. Il est vrai que l'usage, en cette quantité, de ces médicaments constitue une exception française et on peut sans doute légitimement soutenir, d'un point de vue rationaliste, que les gens ne se porteraient pas plus mal et, a fortiori, ne mourraient pas plus vite s'ils s'abstenaient d'en consommer, mais cette exception française constitue une donnée culturelle lourde, et je crois périlleux de prétendre en venir à bout sans délai ni pédagogie préalable.

Secondairement, on ignore tout des reports de prescription qui se produiraient en cas de déremboursement immédiat. Il faut cependant redouter, la maladie ou la plainte ne disparaissant pas avec le déremboursement du médicament, que ces reports ne se portent sur des produits plus coûteux et inutilement –voire dangereusement- plus actifs : anti-alzheimer et anti agrégants plaquettaires à la place des vaso-dilatateurs, anti-inflammatoires accompagnés d'antiulcéreux à la place des veinotoniques, benzodiazépines à la place des sédatifs à base de plantes, etc. Dans une stricte perspective d'équilibre des comptes de l'assurance maladie, il n'est pas certain que le déremboursement immédiat soit une bonne affaire.

En sens inverse, il ne me paraît pas non plus possible de ne rien faire en matière de déremboursement, ce qui décrédibiliserait durablement le processus de réévaluation et serait en opposition avec les orientations de la politique du médicament annoncées par la ministre et qui, je le répète, ne m'ont paru contestées par aucun de ceux que j'ai rencontrés.

On ne peut pas davantage, enfin, se contenter d'annoncer qu'on déremboursera plus tard, sans fixer précisément les conditions et les délais de ce déremboursement.

Les avantages de la formule proposée sont :

- Qu'elle ne discrédite ni les médecins ni les malades dans leurs usages respectifs de prescription et de consommation, tout en validant clairement l'avis de la commission de la transparence, qui ne peut se prononcer que sur des preuves scientifiques ;
- Qu'elle se traduit néanmoins par des mesures immédiates ou d'effet prochain, et permet de ne pas encourir le reproche d'avoir en pratique enterré un élément important de la politique du médicament.

On aurait pu imaginer de subordonner le différé de déremboursement au lancement de nouveaux essais cliniques mais, outre qu'un tel processus saturerait très rapidement les possibilités d'essais françaises, cela risquerait de créer un effet d'aubaine pour les plus grandes entreprises, qui bénéficieraient de l'inévitable renonciation des petites, et, paradoxalement, de relancer la promotion et la prescription de ces médicaments.

2- **Publier sans délai l'avis de la commission de la transparence et organiser l'information des professionnels de santé**, par exemple par une lettre de la ministre à l'ensemble des médecins et des pharmaciens (ci-joint en annexe, à toutes fins utiles, un projet de lettre).

Cette information devrait être relayée par l'assurance maladie qui pourrait à cette fin chercher à passer au niveau national ou régional des accords de bon usage du médicament avec les représentants des médecins.

Commentaire : On peut attendre de cette mesure trois effets :

- Une incidence directe sur la prescription en faisant appel à la responsabilité des médecins ;
- L'occasion d'expliquer clairement la différence entre un médicament dont le SMR ne justifie pas la prise en charge collective et un médicament inutile ;
- Une caution apportée au travail de la commission de la transparence, qui me paraît avoir grand besoin d'être soutenue dans cette affaire.

3- **Baisser les prix** en deux étapes à l'été 2000 et à l'été 2001, ce qui reviendra, pour les plus importantes des classes de médicaments concernées, à accélérer le processus de baisse engagé à l'été 1999. Je n'ai évidemment pas ouvert de négociation explicite sur ce point avec les entreprises, dans l'attente de la décision de la ministre sur le dispositif d'ensemble, mais il est raisonnable de penser que ces baisses, ou les déremboursements volontaires qui s'y substitueraient (cf. 4 ci-dessous) pourraient représenter 500 MF (en CA annuel) à l'été 2000 et autant à l'été 2001.

Commentaire : Comme prévu dans l'accord sectoriel, ces baisses feraient l'objet d'une compensation forfaitaire dans le calcul des remises quantitatives de fin d'année dues en cas de dépassement de l'ONDAM. Le rendement net immédiat serait donc considérablement plus faible (au mieux 200 MF) mais aurait son plein effet dès l'année suivante. Surtout, la mesure serait très visible pour les médecins et pour le public et constituerait une compensation pour l'assurance complémentaire pour les baisses de taux de remboursement (cf. 5 ci-dessous).

4- **Accepter, et même encourager les déremboursements, même isolés** et les accompagner en aménageant les règles de la publicité grand public. On peut espérer

aboutir rapidement à des déremboursements collectifs sur quelques classes, et notamment les magnésiums.

Commentaire : Les déremboursements isolés de médicaments substituables à des produits qui resteraient remboursés n'entraînent bien sûr que peu d'économies pour l'assurance maladie dans la mesure où les prescriptions sont massivement reportées. Je crois cependant qu'il y a intérêt à les encourager, pour leur portée symbolique lorsque ces médicaments sont impropres à une exploitation en non remboursable, et pour amorcer le mouvement de passage à l'automédication dans le cas contraire.

Le projet de loi de modernisation de la santé pourrait être l'occasion d'autoriser la publicité grand public au cours des quelques mois précédant un déremboursement décidé.

5- **Faire sans délai les passages de 65% à 35%** pour les produits actuellement pris en charge à 65 % et dont le SMR est faible ou modéré ainsi que, dans l'attente d'un éventuel déremboursement, pour ceux dont le SMR est insuffisant.

Commentaire : Dans le contexte du dispositif d'ensemble ci-dessus, cette mesure deviendrait parfaitement naturelle. Il ne pourrait en particulier pas être reproché à l'Etat de faire supporter aux seules mutuelles les conséquences de la réévaluation puisque celles-ci bénéficieraient directement des baisses de prix et, en perspective, des déremboursements annoncés. Du point de vue des comptes de l'assurance maladie, je rappelle que ces changements de taux devraient permettre une économie de plus de 1 milliard en année pleine.

*

Il y a à mon avis urgence à ce que la ministre fasse connaître sa décision, et ceci pour deux raisons essentielles :

D'abord parce que plus le temps passera, plus s'installera l'opinion que le gouvernement n'est en aucun cas prêt à dérembourser, ce qui rendra très difficile à mettre en œuvre toute autre mesure alternative. Spécifiquement, on ne peut espérer de baisses de prix significatives dans un cadre conventionnel que si le risque du déremboursement reste crédible.

En second lieu parce que le respect de l'ONDAM 2000 dépend très directement de la rapidité avec laquelle on aura tiré les conséquences de la réévaluation, sachant que, même hormis l'épidémie de grippe qui va coûter assez cher en dépenses remboursées de médicaments, la tendance actuelle du marché n'est pas à la décélération et qu'il va être difficile de maintenir durablement la croissance française des dépenses à un niveau aussi inférieur à celui constaté chez ses principaux voisins.

Pour ces motifs, il me semble en particulier qu'il n'y a pas intérêt à surseoir en annonçant que les conséquences de la première série d'avis de la commission de la transparence ne seront tirées qu'à l'achèvement du processus général de réévaluation. Je souligne à cet égard que, quoiqu'on entende parfois dire, il n'y a pas de réel enjeu d'égalité de traitement entre entreprises dans une décision immédiate portant sur la seule première phase

de réévaluation, car la concurrence dans le secteur du médicament s'exerce entre produits partageant les mêmes indications thérapeutiques. On sait, de surcroît, que les entreprises qui seront vraisemblablement touchées par les phases à venir seront pour l'essentiel les mêmes que celles de la première phase.

Noël Renaudin

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Noël Renaudin
20 décembre 2010

Fiche sur le Médiator établie à la demande de la mission de l'IGAS

P.J. copie des JO des 11 octobre 2000, 20 octobre 2001 et 12 octobre 2002

1) Prix

Sur la période antérieure à 1991, le CEPS ne dispose d'aucune information. A cette date, le prix du Médiator était de 26,70F en prix fabricant hors taxes.

A la suite de la réévaluation générale du SMR des médicaments remboursables de 1999, la ministre de l'époque (Martine Aubry), qui avait demandé cette réévaluation, a décidé de maintenir au remboursement l'ensemble des produits auxquels la commission de la transparence avait attribué un SMR insuffisant (dont le Médiator).
En contrepartie, il a été demandé au CEPS (alors comité économique du médicament) de baisser les prix de ces médicaments. L'orientation donnée au comité était d'obtenir, en moyenne, une baisse de 20% en trois ans.
Le comité a aussitôt engagé une négociation conventionnelle avec l'ensemble des entreprises concernées avec comme objectif d'obtenir pour l'année 2000 une première baisse équivalente, en moyenne, à 7% du chiffre d'affaires total de ces produits.
Les médicaments appartenant à des catégories homogènes, comme les veinotoniques, les mucolytiques ou les vasodilatateurs ont fait l'objet de demandes de baisses à des taux variables, et d'autant plus grands que leur coût de traitement journalier était élevé. Les autres, c'est-à-dire ceux qui étaient seuls de leur espèce, comme le Médiator se sont vu demander uniformément 7% de baisse.
Le comité a accepté des contrepropositions de la part des entreprises, soit sous la forme d'une modulation des baisses entre médicaments exploités par le même laboratoire, soit sous forme de déremboursements volontaires, dès lors que le résultat économique recherché était atteint.
Le prix du Médiator a ainsi été baissé de 10%, passant, en PFHT, de 26,70F à 24,03F. Par cette baisse plus élevée que celle qui lui était demandée, le laboratoire obtenait de moins baisser le prix d'un autre médicament, le Daflon (veinotonique).

Deuxième étape en 2001, et nouvelle baisse conventionnelle du Médiator, dont le prix fabricant passe de 24,03F à 22,35F (soit 7% de baisse).

Pour la troisième étape de 2002, le laboratoire Servier a refusé la baisse conventionnelle qui lui était proposée pour le Médiator comme pour tous les autres produits concernés qu'il exploitait. Afin de maintenir l'égalité de traitement entre entreprises, le comité, qui ne pouvait pas encore, à l'époque, prendre de décisions unilatérales, a demandé aux ministres (santé et finances) de prendre un arrêté de baisse. Cet arrêté, publié au JO du 12 octobre 2002, baissait le prix de Médiator de 5% (de 3,41€ à 3,24€) ainsi que ceux de 5 autres médicaments exploités par Servier. L'entreprise a fait un recours contre cet arrêté et l'a perdu.

2) Taux de remboursement

Le CEPS n'est pas compétent en matière de taux de remboursement et n'a pas été associé aux procédures. Il en a en revanche été tenu étroitement informé, mais je ne peux donc que rappeler les souvenirs que j'ai conservés de ces évènements.

La baisse (de 65% à 35%) du taux de remboursement des vasodilatateurs a été décidée la première au vu du caractère emblématique de cette classe de médicaments. Il faut se souvenir qu'à l'époque, les journaux qui se penchaient sur le sujet alternaient deux types d'articles. Ceux qui dénonçaient le gaspillage consistant à continuer à rembourser des médicaments « inutiles » ; ceux qui alarmaient patients et médecins sur l'éventualité d'un déremboursement de médicaments que, pour les uns, ils avaient durablement prescrits et qui, pour les autres, leur faisaient – pensaient-ils - depuis longtemps le plus grand bien.

La décision de passer les vasodilatateurs à 35% a été un compromis sur cette alternative : on ne causait aucun tort aux patients ni aux médecins puisque l'assurance complémentaire prenait le relais mais on réduisait la dépense injustifiée de l'assurance maladie obligatoire.

Il me semble que le train suivant de baisses de taux a été arrêté dans le même esprit, par classes de médicaments.

Le fait que le Médiator, et sans doute un ou deux autres produits, aient échappé à ces mesures tient, me semble-t-il, probablement à ce qu'il constituait une classe à lui tout seul. Ce qui est en revanche certain, c'est que son cas n'a à aucun moment été évoqué devant le CEPS au cours de ces procédures, ni sur le registre des économies à réaliser, ni a fortiori sur celui de la sécurité.

3) déremboursements

Là encore, le CEPS, juridiquement incompétent, n'a été qu'informé des mesures engagées. J'ai cependant, intuitu personae, été consulté par les ministres qui se sont successivement saisis de cette question dans la mesure où les déremboursements, à la différence des baisses de taux, ne sont évidemment pas sans conséquences sur la situation des entreprises concernées.

En 1999, j'avais indiqué à Mme Aubry que le comité pouvait faire son affaire, au plan industriel, des déremboursements recommandés par la commission de la transparence, pour peu qu'on accepte que cela soit très progressif. Il m'a paru clair que la décision qu'elle a prise de ne rien dérembourser a été exclusivement inspirée par le souci de ne pas priver les patients ni les médecins de médicaments auxquels, à tort ou à raison, ils étaient très majoritairement attachés.

Il faut noter que les déremboursements opérés à cette époque, et notamment ceux décidés par arrêté du 4 septembre 2001, l'ont été à l'initiative des laboratoires, en lieu et place des baisses de prix qui leur étaient demandées, et non à l'initiative de l'Etat.

La répartition en trois catégories des médicaments dont la commission de la transparence avait estimé le SMR insuffisant a été opérée, dans mon souvenir, à la demande de M. Mattéi lorsque celui-ci était ministre de la santé. Les critères de la répartition étaient les suivants :

Devaient être classés dans la catégorie 1 (médicaments à dérembourser sans délai) les spécialités qui disposaient d'indications communes avec des médicaments à SMR suffisant, et

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dont on pouvait donc considérer sans ambigüité que leur maintien au remboursement exposait les patients à une perte de chances. Ceux-ci risquaient en effet de se voir prescrire un médicament avec un rapport bénéfice risque moins bon que celui d'un autre médicament disponible pour la même indication. A ma connaissance, le cas du Médiator n'a pas été évoqué lors de ce travail de classement dans la mesure où ce médicament disposait d'une indication exclusive.

La catégorie 2 était constituée de ceux des médicaments non classés dans la catégorie 1 et non soumis à prescription obligatoire. Il s'agissait donc de médicaments dont le déremboursement pouvait être envisagé dans la perspective d'un passage à l'automédication.

La catégorie 3 était constituée des médicaments n'appartenant à aucune des deux premières. Elle incluait donc naturellement le Médiator, produit de prescription obligatoire. Le déremboursement de cette dernière catégorie était considéré comme plus difficile.

La catégorie 1 a été effectivement déremboursée à cette époque.

Après la réforme de l'assurance maladie de 2004, M. Bertrand, devenu ministre de la santé, a demandé à la nouvelle HAS de se prononcer sur les médicaments des catégories 2 et 3. Celle-ci a, pour l'essentiel, confirmé le caractère insuffisant du SMR de ces spécialités sans établir de distinction entre les catégories.

Les mesures prises à la suite de cet avis l'ont été sans considération pour leurs conséquences industrielles, mais exclusivement en fonction de leur acceptabilité par les patients. Il va de soi que, comme dans les épisodes précédents, la question de la dangerosité intrinsèque de produits, le Médiator ou un autre, n'a jamais émergé lors de la préparation des décisions.

Ministère de l'Emploi
et de la Solidarité

Le Conseiller

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RÉPUBLIQUE FRANÇAISE

Le 24 MAR. 2000

127, rue de Grenelle 75700 Paris 07 SP
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NOTE

A l'attention de Madame la Ministre
S/C de Monsieur Dominique MARCEL
Directeur du Cabinet
et de Monsieur Pierre-Louis BRAS
Directeur-adjoint du Cabinet

OBJET : Réforme du remboursement/Conséquences à tirer de la réévaluation

I - RAPPEL

La réforme du remboursement prévoit que l'admission sur la liste des médicaments remboursables sera dorénavant fondée sur le service médical rendu. Celui-ci sera apprécié en tenant compte de l'efficacité et des effets indésirables du médicament, de sa place dans la stratégie thérapeutique, la gravité de l'affection à laquelle le médicament est destiné, ainsi que du caractère préventif, curatif ou symptomatique du traitement médicamenteux et de son intérêt pour la santé publique.

Le décret fixant les nouvelles conditions d'admission au remboursement a été publié le 27 Octobre 1999.

Parallèlement, une opération de réévaluation du service médical rendu de l'ensemble des médicaments remboursés a été initiée en mars 1999. Celle-ci se déroule en 3 phases. Les résultats définitifs de la première phase sont connus, de même pour les résultats préliminaires de la seconde phase.

Il faut noter que la troisième phase ne concerne que peu de médicaments ; ses résultats ne seront pas de nature à remettre en cause les décisions qui pourraient être prises au vu des résultats des deux premières phases.

Lors de la transmission des résultats définitifs de la première phase, vous avez souhaité que tous les acteurs concernés (syndicats des médecins et de pharmaciens, ordres professionnels, industriels, mutualité) soient consultés, afin de connaître leurs propositions sur les conséquences à tirer de cette réévaluation. Vous trouverez en annexe I les résultats de cette concertation.

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II – PROPOSITION D'ACTION

Vous trouverez en annexe :

- les données économiques concernant les déremboursements, les hausses de prix et les baisses de taux (annexe II)
- les données démographiques relatives aux principales classes de médicament concernées (annexe III)
- la position de la DGS (annexe IV)
- Les mesures à adopter sur les dispositifs médicaux (annexe V)

D'une façon générale, ne rien faire serait catastrophique puisqu'il s'agirait là d'une décrédibilisation durable d'un axe important de la politique du médicament, que vous avez initiée il y a maintenant 3 ans. De plus, hormis quelques exceptions, je vous rappelle que le principe même de cette démarche n'a été remise en question par personne.

Appliquer immédiatement les avis de la Commission de la Transparence serait à l'inverse suicidaire, tant l'impact d'une telle mesure serait catastrophique pour nombre d'entreprises d'une part, en terme d'emploi (pour les plus petites), mais également en terme de ressources à consacrer au développement de leurs innovations (pour les plus grandes.). D'autre part, parce que nous mettrions en péril l'organisation sanitaire et sociale en déstabilisant sans information les praticiens, et en s'exposant à un report de prescriptions massif coûteux et dangereux (anti-alzheimer et anti-agrégants à la place des vasodilatateurs, benzodiazépine à la place des sédatifs à base de plantes).

Bien évidemment, nous sommes à peu près certains que le fait de ne plus utiliser ces médicaments ne remettraient pas en cause les données de la morbi-mortalité dans notre pays, mais cette hyper consommation est une donnée culturelle de notre pays, qu'il nous faudra gérer à plus long terme grâce à des mesures de formation et d'information appropriées.

Quatre outils sont à notre disposition pour gérer de façon efficace et équilibrée ce dossier avec le minimum « d'effets secondaires » possibles. Il s'agit :

1°) d'un déremboursement à terme de 2 ou 3 ans
2°) des baisses de prix
3°) des baisses de taux
4°) d'une campagne de formation et d'information active

2 scénarios sont possibles :

Le premier consiste à :

- annoncer à terme de 2 ou 3 ans,

  • le déremboursement des spécialités dont le SMR a été jugé insuffisant,
  • la baisse du taux de remboursement (65 % → 75 %) pour les spécialités dont le SMR a été jugé faible ou modéré,

- effectuer immédiatement des baisses de prix d'environ 5 % par an sur les médicaments dont le SMR a été jugé insuffisant, et, ce jusqu'au déremboursement.

Ce scénario permet de tirer les conséquences de la réévaluation, sans impact immédiat sur les assurés, et sans prendre le risque d'un conflit majeur avec l'un des protagonistes. En revanche, le gain pour les comptes de l'exercice 2000 sera faible (environ 150 MF), et d'environ 500 MF pour 2001 (cf. annexe II). Ce gain faible pour l'année 2000 s'explique par le fait que la baisse des prix ne concernerait en pratique que le dernier trimestre de l'année. En effet, la loi nous impose que toute baisse de prix soit négociée dans le cadre conventionnel. Ce n'est qu'en cas d'échec éventuel de cette négociation que des arrêtés peuvent être pris. Cela prendra donc quelques mois.

Le 2ème scénario consiste à :

- Annoncer les déremboursements à terme de 2 à 3 ans des médicaments dont le SMR a été jugé insuffisant.

- Effectuer immédiatement

  • des baisses de taux pour les médicaments dont le SMR a été jugé insuffisant mais aussi pour ceux dont le SMR à été jugé mineur ou modéré,
  • des baisses de prix d'environ 5 % par an pour les médicaments dont le SMR a été jugé insuffisant.

Le risque de conflit notamment avec la mutualité est réel, toutefois les gains pour l'assurance maladie seront beaucoup plus significatifs puisque en sus des baisses de prix, cette mesure rapporterait 525 MF en 2000 et 2,1 MdF en 2001.

Commentaires

1°) Déremboursement à terme :

Cette annonce présente un triple avantage. Tout d'abord, c'est la seule mesure qui crédibilise l'ensemble du dispositif, et qui permettra d'inciter les différents partenaires -notamment les industriels-, à accepter les autres dispositions.

De plus, cette mesure, si elle est accompagnée d'une information intelligente des praticiens et du public, ne discréditera ni les malades, ni les médecins dans leurs usages respectifs de prescription et de consommation.

Enfin, cette solution pourrait être gérée sans trop de dégâts par les entreprises pour autant que le délai soit adapté. Bien évidemment, le terme du remboursement sera à évaluer au cas par cas. Il peut être rapide pour les magnésiums, dans la mesure où ceux-ci font l'objet d'un consensus scientifique très large et d'un consensus quasi total au niveau industriel, ainsi que pour les médicaments appartenant à des classes où il demeure des médicaments à SMR important. Dans ce dernier cas, il existe une meilleure alternative thérapeutique au sein de la classe (ex : hypnotiques). Le patient est donc mieux soigné .

Il peut être délayé à 2 ou 3 ans pour les médicaments appartenant à des classes thérapeutiques où l'ensemble des produits a un SMR insuffisant. Il n'y a donc pas d'alternative possible au sein de la classe (ex : les veinotoniques, les vasodilatateurs...), de façon à prendre en compte les données socio-culturelles et économiques.

Sur le plan financier, les déremboursements suivant les avis de la Commission de la Transparence génèreraient une économie brute (c'est-à-dire hormis l'effet report) de 9,6 MdF pour l'assurance maladie et de 5,5 MdF pour la mutualité.

A l'évidence, les effets du déremboursement seront différents selon qu'il s'agit d'un médicament appartenant à une classe où subsiste un nombre important de produits à SMR important, ou d'un médicament appartenant à une classe dont tous les médicaments ont vocation à être déremboursés.

Dans le premier cas, l'effet report serait de 100 % vers les autres médicaments de la même classe, mais le bilan en volume serait neutre.

Dans le second cas, l'attitude des prescripteurs et des patients est difficile à prévoir et dépendra de la capacité du produit à passer en automédication. Dans cette hypothèse, le gain brut du déremboursement ne serait plus que de 2,3 MdF.

L'aménagement du déremboursement nécessite que soient adoptées des mesures favorisant le passage en automédication. Sur le plan du statut même de l'automédication, un simple toilettage des AMM est nécessaire, mais aucune disposition législative n'est à envisager. A l'inverse, nous pourrions faire adopter lors de la loi santé une disposition visant à permettre aux produits ayant demandé le délistement de faire de la publicité deux mois avant la date effective du délistage.

2°) Baisses de prix

Les simulations qui vous sont proposées sont basées sur une baisse de prix globale de 5%. On peut discuter de l'opportunité d'annoncer une baisse de prix homogène sur l'ensemble des firmes. En effet, le nombre de produits soumis à une baisse de prix est très variable dans le CA total des entreprises. Ainsi, le taux de 5% pourrait être difficile à gérer pour les entreprises qui ont une forte proportion de produits à baisser, et ne pourrait être dépassé pour celles qui, au contraire, peuvent supporter une baisse plus élevée.

3°) Baisse des taux (de 65 à 35 % pour tous les produits à SMR insuffisant, modéré ou faible

Elle est évidement récusée par la mutualité puisque le coût supplémentaire assuré par celle-ci serait de 1,8 MdF (en année pleine). Cette somme pourrait être diminuée par le déremboursement de quelques classes et par les baisses de prix. Enfin, il s'agirait d'un surcoût transitoire puisque nombre des médicaments concernés s'inscrivent dans une procédure de déremboursement à terme.

Enfin, le transfert de charge des mutuelles à l'assurance maladie à l'occasion de la réforme de la marge des officines est estimé à 300 MF, et le surcoût dû à l'augmentation tendancielle du taux moyen de remboursement est estimé à 600 MF (soit près de 1 MdF).

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4°) Campagne d'information et de formation

Une campagne d'information et de formation, éventuellement relayée par l'assurance maladie, devra être conduite. Elle permettra d'avoir une incidence directe sur la prescription. La forme que celle-ci doit revêtir est à discuter. Cette information devrait permettre de réexpliquer la différence entre l'AMM et le SMR.

De façon immédiate, une synthèse des avis de la Commission de la Transparence en attente pourrait être diffusée sous une forme qui reste à déterminer. Vous trouverez en (annexe VI) ? un projet de lettre aux médecins et pharmaciens.

III - CONCLUSION

D'une façon générale, cette réforme doit avoir un habillage le plus « santé publique possible ». Elle permet essentiellement, d'une part, de mieux soigner les patients, d'autre part, de dégager des sommes qui seront immédiatement réinvesties dans la prise en charge des dispositifs médicaux (annexe V). Aucune économie n'est donc réalisée sur la santé de la population.

Je vous remercie de me donner vos instructions sur la démarche à adopter.

Hervé LE LOUËT

ANNEXE I

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ANNEXE I
RESULTAT DE LA CONCERTATION
(SYNTHESE)

De façon globale, les différents acteurs consultés réagissent de façon corporatiste. Vous trouverez, ci-joint, les comptes-rendus des différentes réunions.

1. Les syndicats de médecins

Les médecins ont peu d'idées sur les conséquences à tirer de la réévaluation. Ils se réfugient derrière une critique souvent non étayée de la procédure de réévaluation (c'est-à-dire du fonctionnement de la Commission de la Transparence). Bien évidemment, ils n'osent pas remettre en cause le principe même de réévaluation (hormis la CSMF qui considère qu'il s'agit là d'un simple habillage d'une politique uniquement budgétaire), mais l'on sent très clairement, bien que tout cela soit du domaine du non dit, que les médecins ont peur qu'on ne les prive du support de la relation thérapeutique avec les malades. Il s'agit là d'une attitude bien française où chaque consultation doit être sanctionnée d'une prescription médicamenteuse.

De plus, beaucoup de praticiens ne se voient pas expliquer à leurs patients qu'ils leur prescrivent depuis des années des médicaments « inutiles » (la confusion entre SMR et utilité est omniprésente chez les médecins).

2. Les pharmaciens

Si les pharmaciens ne remettent pas en cause le principe, les deux syndicats se livrent à une critique véhémente des procédures de la Commission de la Transparence, et agitent le spectre d'une médecine à deux vitesses.

En réalité, la grande peur des pharmaciens est qu'un déremboursement massif conduise à une sortie des produits concernés du pan pharmaceutique. Ceci représente, évidemment, une perte substantielle pour leur chiffre d'affaires (8 à 11 %).

3. Les ordres professionnels

- *L'Ordre national des Médecins* : le message essentiel de l'Ordre national des Médecins est que, quelles que soient les mesures adoptées, l'Ordre ne s'engagera pas dans un conflit sur la liberté de prescription. M. DETILLEUX a préféré placer le débat sur l'évolution du système de protection sociale. Lui aussi confond les procédures d'AMM et d'accès au remboursement.

- *L'Ordre national des Pharmaciens* : M. PARROT s'est livré à une critique des procédures de fonctionnement de la Commission de la Transparence. Il s'était déjà livré par voie de presse à ce type d'exercice dans sa « lettre à mes confrères ».

M. PARROT se prononce pour une baisse des taux de remboursement des médicaments à SMR insuffisant, et insiste sur la nécessité de mesures pédagogiques d'accompagnement dont le support pourrait être le réseau des pharmaciens

4. La Mutualité :

Les deux fédérations consultées (FNMF et FMF) ont souligné leur attachement à la réévaluation. Bien évidemment, ils manifestent l'un et l'autre une opposition farouche à toute baisse des taux ou à la création d'un taux intermédiaire soulignant qu'une telle mesure les mettraient en péril sur le plan financier, mais, surtout, n'aurait aucune influence sur le contenu de la prescription. Ils soutiennent en revanche les déremboursements

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COMPTE-RENDU DES REUNIONS AVEC LES SYNDICATS SUR LES CONCLUSIONS A TIRER DE LA REEVALUATION DES CLASSES THERAPEUTIQUES

MG-France (M. R BOUTON, Président)

M. BOUTON, à qui l'on demandait de réagir sur les conséquences à tirer du travail de réévaluation des classes thérapeutiques, a plaidé en faveur d'une « médicalisation de la prescription ».

Celui-ci pense qu'il faut éviter les déremboursements massifs, et redéfinir des sous-populations de patients susceptibles de bénéficier des thérapeutiques dont le SMR a été jugé insuffisant. Les questions sur les modalités selon lesquelles de telles populations seraient définies sont restées sans réponse. De plus, M. BOUTON dénonce la volonté des pouvoirs publiques d'imposer aux médecins, en plus de leur raisonnement sémiologique et thérapeutique, une prise en compte du « rapport qualité/prix ».

A l'évidence, la position adoptée par M. BOUTON est purement circonstancielle et dénote une mauvaise compréhension du processus et de la méthodologie de la réévaluation (mais ceci est sans doute de notre responsabilité).

En réalité, ces termes pour le moins équivoques sous-tendent l'angoisse des généralistes de devoir se passer de médicaments dont ils ne remettent pas en cause l'unique intérêt placebo, mais qui sont le support de leur relation thérapeutique avec le patient.

Toutefois M. BOUTON a soulevé 2 problèmes réels :

- Le premier problème concerne l'information thérapeutique dont disposent les médecins généralistes. Celle-ci est quasi-uniquement dispensée par l'industrie pharmaceutique, et il est évident que des mesures devront êtres prises pour remédier à cela. M. BOUTON

est cependant resté fort discret sur les formes que celle-ci pourrait revêtir.

- Le deuxième problème, plus difficile à régler, est qu'en ce qui concerne le tiers-payant, pour les généralistes, la prescription justifie l'acte.

En conclusion la position de M BOUTON manque de clarté. Hormis une opposition de principe, on ne relève pas de réelles contre-propositions.

U.C.C.S.F

Compte-tenu de la nature de l'exercice des praticiens représentés par ce syndicat, le Pr WINISDOEMFER n'a émis aucun avis sur le processus de réévaluation et fait confiance à la commission de la transparence.

Il a simplement fait remarquer que le déremboursement des veinotoniques, qu'il considère inutiles, inciteraient les patients à subir une intervention au niveau de leurs vamiles et de leurs hémorroïdes (et comme chirurgien, il s'en félicite !).

C.S.M.F.

La CSMF représentée, par son Président, M. MAFFIOLI, s'est montrée extrêmement virulente sur le processus de réévaluation.

M. MAFFIOLI considère qu'il n'a aucune proposition à faire sur les conséquences à tirer de la réévaluation, dans la mesure où il remet en cause les travaux de la commission de la transparence.

Les critiques alléguées sont :

- une mauvaise distinction entre l'utilité et le Service Médical Rendu par le médicament
- une commission comportant trop d'hospitalo-universitaires
- des experts partiaux et n'ayant aucun sens du vécu quotidien et de la relation thérapeutique
- une commission qui travaille trop vite et sur des critères non validés

Il propose donc que la commission soit réellement transparente tant au niveau de ses membres que de sa méthodologie et qu'elle associe un peu plus de praticiens de terrain.

Enfin, M. MAFFIOLI considère que cette opération n'est qu'un habile habillage d'une politique essentiellement guidée par l'impératif budgétaire.

Syndicat des Médecins Libéraux (SML - Dr CABRERA)

L'entretien avec M. CABRERA a été bref. Il souligne son attachement au principe de la réévaluation dans la mesure où il est convaincu que la société doit opérer des choix.

Il formule, cependant moins violemment, les mêmes critiques vis-à-vis de la commission de la transparence que C. MAFFIOLI. Le Dr CABRERA met en garde contre une politique de déremboursement rapide et mal conduite, ce qui génèrerait un effet de report de prescriptions vers des classes médicamenteuses plus coûteuses et plus dangereuses.

En terme de proposition, M. CABRERA est favorable à une baisse de taux pour certaines classes et à un déremboursement à terme.

Annexe 4-17

COMPTE-RENDU DE LA REUNION AVEC LES SYNDICATS DE PHARMACIENS SUR LES CONSEQUENCES A TIRER DE LA REEVALUATION DE L'ENSEMBLE DES CLASSES THERAPEUTIQUES

Personnes présentes :

- Messieurs BERAS et JAPHET, respectivement Président et Vice-président de l'Union nationale des pharmacies de France (UNPF).
- Monsieur CAPDEVILLE, Président de la Fédération syndicale des Pharmacies de France.

Monsieur BERAS à qui l'on demandait son avis sur les conséquences à tirer de la réévaluation de l'ensemble thérapeutique, nous a répondu qu'il s'agissait là d'un mauvais dossier.

Il a critiqué, de façon véhémente, la notion de service médical rendu, le fonctionnement de la commission de transparence et a souligné l'absence de représentation, au sein de cette même commission, de pharmaciens d'officine.

De façon générale, Monsieur BERAS s'est opposé à toute mesure de baisse de taux ou de déremboursement arguant du fait que l'on allait pénaliser les personnes les plus défavorisées.

Il s'est, en revanche, prononcé en faveur d'une baisse de prix progressive effectuée par le comité économique du médicament.

Cette appréciation générale a été confirmée par son Vice-président, Monsieur JAPHET qui, toutefois, ne s'est pas opposé à une baisse de taux de 65 à 35 % pour les vasodilatateurs. Monsieur JAPHET a également voulu nous mettre en garde contre le risque de transfert de prescription notamment en ce qui concerne les veinotoniques et les vasodilatateurs.

Il insiste sur la nécessité d'un vaste travail pédagogique avant que de prendre une quelconque mesure. En réalité, l'angoisse majeure de Monsieur JAPHET est que, selon lui, le déremboursement massif d'un certain nombre de classes thérapeutiques conduirait, comme cela a été le cas avec les vitamines, à une sortie de ces produits du pan pharmaceutique avec une perte financière substantielle.

Monsieur CAPDEVILLE a repris les critiques vis-à-vis de la Commission de transparence dénonçant : « un cénacle hospitalo-centriste ». Il a également regretté l'absence de pharmaciens au sein de cette Commission. Il se dit d'accord avec le président de l'ordre des pharmaciens qui dénonce une manipulation de la part de la Commission de transparence.

Toutefois, Monsieur CAPDEVILLE, conscient de la nécessité de réformer, nous a fait un certain nombre de propositions.

Monsieur CAPDEVILLE pense qu'un déremboursement brutal des spécialités telles que préconisées par la Commission de transparence, serait suicidaire et ouvrirait la porte aux assureurs privés type AXA. Cet avis est largement repris par ses confrères.

Ceci étant, Monsieur CAPDEVILLE se dit prêt à soutenir une démarche qui consisterait à opérer des baisses de prix progressives sur les produits dont le SMR a été estimé insuffisant, pour arriver à terme, à un déremboursement de ces spécialités.

Annexe 4-17

Compte-rendu de la réunion avec M. DUTILLEUX

Ordre National des Médecins

Monsieur DUTILLEUX ne remet en cause ni la démarche, ni la procédure de réévaluation. Il insiste sur l'importance du pouvoir discrétionnaire de la ministre.

Il craint toutefois un problème de lisibilité du message en évoquant une crainte diffuse parmi nos concitoyens d'une médecine à 2 vitesses.

Selon lui, il ne faut évidement pas tout médicaliser, et plutôt que d'agir sur l'accès au remboursement, retirer purement et simplement l'AMM aux médicaments à SMR insuffisant.

Toutefois M. DUTILLEUX souligne que les problèmes posés par la réévaluation dépassent largement le cadre du médicament, mais interrogent sur l'avenir de la protection sociale.

Il nous fait part de ses craintes de voir dans les années qui viennent se développer le recours aux assureurs privés, et s'interroge sur le rôle à jouer par la mutualité.

Enfin, M. DUTILLEUX nous informe que quelles que soient les mesures, l'Ordre ne s'engagera pas dans un conflit sur la liberté de prescription.

Annexe 4-17

Compte-rendu de la réunion avec

M. PARROT, Président de l'Ordre national des Pharmaciens

Interrogé sur les conséquences à tirer de la réévaluation, M. PARROT a essentiellement critiqué les procédures de fonctionnement de la Commission de la Transparence à laquelle il appartient depuis plusieurs années (à noter qu'il s'est déjà livré à ce type d'exercice par voie de presse dans sa « lettre à mes confrères »).

Ainsi, M. PARROT regrette ;

- la lourdeur de la rédaction des avis, qui selon lui ne mettent pas assez en évidence les données les plus pertinentes,

- la main mise d'une administration toute puissante conduisant à un manque d'indépendance de la commission,

- le rôle « délétère » des caisses qui ne raisonnent qu'en termes économiques (il remet en cause le droit de vote accordé aux caisses dans cette instance).

Enfin, il déplore que l'idéal scientifique de la Commission de la Transparence ne soit tourné que vers les produits majeurs, et dénonce les « maltraitances » dont sont victimes les petits médicaments.

Il propose d'enrichir la Commission de la Transparence des praticiens de terrain, et de faire participer plus souvent les sociétés savantes (il critique ainsi la médecine basée sur les faits).

Selon M. PARROT, les avis de la Commission de la Transparence ne sont pas applicables en l'état.

Il préconise une baisse de taux pour les médicaments à SMR insuffisant, et un passage progressif en automédication pour certaines classes comme les veinotoniques.

Il insiste sur la nécessité des mesures d'accompagnement pour expliquer cette démarche aux prescripteurs et aux publics, l'outil idéal étant pour lui d'utiliser le maillage du territoire du réalisé par le réseau officinal.

Annexe 4-17

Compte-rendu de la réunion avec LA FNMF

Mr DAVAN et le Pr. BERAS ont été reçus pour nous livrer leur réflexions sur les conséquences tirer de la réévaluation.

Ils ont souligné l'importance qu'ils attachaient à la redéfinition du panier de soins et ne contestent pas les travaux effectués par la Commission de la Transparence.

Ils regrettent toutefois de n'être associés à aucune commission, et donc de ne pouvoir peser dans la négociation.

A cet égard, une place pourrait être accordée à la mutualité au sein de l'Observatoire national de la Prescription.

Sur les outils disponibles pour mettre en œuvre les conclusions de la Commission de la Transparence, il ont émis les avis suivants :

- opposition farouche à toute baisse de taux ou à la création d'un petit taux. Ceci pour des raisons financières évidentes mais également parce que cette mesure ne modifie pas le contenu de la prescription.

- baisse de prix : avis favorable à des baisses de prix significatives et progressives pour les médicaments à SMR insuffisant. Ceci devait à terme conduire à un déremboursement.

Ces baisses doivent être associées à une homogénéisation des prix dans certaines classes thérapeutiques.

- déremboursement : nos interlocuteurs sont bien évidemment favorables à cette mesure. Celle-ci doit être progressive, et doit s'accompagner d'une large information des médecins et du grand public auquel ils sont prêts à s'associer.

Ils insistent sur le bien fondé de cette mesure qui permettra de renforcer la prise en charge sur le nécessaire (réparation, prévention).

A titre d'exemple, la mutualité se dit prête, en cas de déremboursement des veinotoniques, à réévaluer la prise en charge de la contention.

Pour étayer cette volonté, M. DAVANT évoque la possibilité pour la mutualité de se désengager de la prise en charge des veinotoniques.

Annexe 4-17

Compte-rendu de la réunion avec LA FMF

L'entretien avec M. ZAMICHIEI fut plus bref.

Celui-ci ne remet pas en cause le processus de réévaluation. Il s'oppose fermement à une éventuelle baisse de taux de remboursement qui, selon lui, conduirait à un conflit dur avec la mutualité.

M. ZAMICHIEI nous met en garde contre une mesure de déremboursement trop large et trop rapide qui ouvrirait la voie à une médecine à 2 vitesses, et à un effet de report de prescriptions incontrôlable.

Enfin, il évoque la nécessité d'une large information des prescripteurs et du grand public.

ANNEXE II

DSS/FOS

Impact des propositions de la commission de la transparence - première phase de réévaluation

01/08/2000

Variable :FRS (Milliers)	CMA/8/99 FRS										
Total deux phases	CAHT	estimation CA PPTTC (CAHT *1,5)	taux de remboursement actuel	montant théorique des remboursements	taux d'exonération TM estimé	montant réel des remboursements	économie passage à 35%	économie dérembourse ment	économie totale	économie passage à 35% et baisse des prix de 10%	économie supplémentaire liée à la baisse des prix
TOTAL sans déremboursement	**15 369 474**	**23 054 210**		**12 014 039**		**15 383 757**	**2 163 586**	**0**	**2 163 586**	**3 485 603**	**1 322 017**
TOTAL proposition de la commission	**15 369 474**	**23 054 210**		**12 014 039**		**15 383 757**	**1 261 377**	**9 602 943**	**10 864 319**		
Première phase de réévaluation											
déremb cardiologie	5 653 039	8 479 559		4 261 461		5 710 885	592 926	5 710 885		1 104 722	511 796
C5C0 VASOPROTECTEURS V GENER	2 678 016	4 017 024	35%	1 405 958	23%	2 013 113	0	2 013 113		201 311	201 311
C4A1 VASODIL.CEREB+PERIP-C4A2	2 415 986	3 623 979	65%	2 355 586	55%	3 050 685	491 395	3 050 685		747 324	255 929
N6D0 NOOTROPIQUES	223 409	335 114	65%	217 824	51%	277 695	49 216	277 695		72 064	22 848
C6A0 AUTRES CARDIOVASCULAIRES	84 949	127 424	65%	82 825	49%	104 564	19 594	104 564		28 091	8 497
C5B0 ANTIVARIQUEUX V.LOC.	65 200	97 800	35%	34 230	26%	50 517	0	50 517		5 052	5 052
C10B0 ANTI-ATHEROM.ORIG.NATUR	67 772	101 658	65%	66 078	46%	82 582	16 351	82 582		22 974	6 623
C1D0 THERAPIE CORON.SF C1E+C8	50 192	75 288	65%	48 937	63%	65 608	8 297	65 608		14 028	5 731
C1C1 STIMUL.CARD.SF.DOPAMIN.	23 984	35 976	65%	23 384	44%	28 871	6 090	28 871		8 368	2 278
G4B3 DYSFONCTION.ERECTION	10 132	15 198	35%	5 319	32%	8 476	0	8 476		848	848
G2X9 AUT.PROD.GYNECOLOGIQUES	10 258	15 387	35%	5 385	19%	7 310	0	7 310		731	731
C4A2 ANTAGONIST CA VIS.CEREB	5 724	8 586	65%	5 581	39%	6 748	1 576	6 748		2 093	517
S1X1 AUT.PRDTS OPHT.V.GENER	4 753	7 130	35%	2 495	22%	3 517	0	3 517		352	352
C5A1 ANTIHEMORROID.LOC.+CORT	4 656	6 984	35%	2 444	19%	3 315	0	3 315		331	331
A11H3 AUTRES VITAMINES SEULES	2 997	4 496	35%	1 573	31%	2 471	0	2 471		247	247
C1B0 ANTIARYTHMIQUES	2 364	3 546	65%	2 305	65%	3 106	377	3 106		650	273
B2G0 HEMOSTIPTIQUE	2 326	3 489	35%	1 221	28%	1 861	0	1 861		186	186
B1C0 INHIBITEUR AGGRE PLAQUET	321	482	65%	313	79%	446	30	446		72	42
35% cardiologie	1 541 109	2 311 664		1 502 581		1 989 760	275 917	0		447 301	171 384
C1D0 THERAPIE CORON.SF C1E+C8	796 547	1 194 821	65%	776 633	63%	1 041 203	131 672			222 625	90 953
C2A1 ANTIHYPERTENS.SEUL.CENTR	382 849	574 274	65%	373 278	56%	486 736	75 032			116 203	41 170
C2A2 ANTIHYPERTENS.SEUL.PERIP	307 688	461 532	65%	299 996	57%	391 358	60 149			93 270	33 121
C1B0 ANTIARYTHMIQUES	49 965	74 948	65%	48 716	65%	65 650	7 969			13 737	5 768
C10A9 AUT.REDUCT.CHOLEST&TRIGL	4 060	6 090	65%	3 959	40%	4 812	1 095			1 467	372
35% rhumatologie hors myorelaxant	768 660	1 152 990		749 444		882 633	231 734	0		296 824	65 090
M1A1 ANTIRHUMAT NON STER SEUL	336 574	504 861	65%	328 160	27%	376 373	110 133			136 757	26 624
M5X0 AUT PRDT PR APP LOCO-MOT	175 339	263 009	65%	170 956	30%	198 705	55 118			69 476	14 359
A12A0 CALCIUM	149 171	223 757	65%	145 442	43%	179 336	38 074			52 201	14 126
H4A0 CALCITONINES	105 348	158 022	65%	102 714	41%	125 139	28 185			37 881	9 695
M1C0 ANTIRHUMAT SPECIFIQUES	2 228	3 342	65%	2 172	78%	3 080	225			510	286
déremb metabolisme	678 578	1 017 867		430 326		533 266	44 396	533 266		93 283	48 887
A12C1 MAGNESIUM	500 771	751 157	35%	262 905	14%	329 517	0	329 517		32 952	32 952
C10A9 AUT.REDUCT.CHOLEST&TRIGL	164 606	246 909	65%	160 491	40%	195 114	44 396	195 114		59 468	15 072
A12C2 AUTRES SUPPLEMENTS MINER	12 204	18 306	35%	6 407	12%	7 820	0	7 820		782	782
A15A0 OREXIGENES	997	1 496	35%	523	30%	815	0	815		82	82
déremb rhumatologie hors myorelaxant	282 189	423 284		152 430		204 212	2 228	204 212		22 427	20 198
M5X0 AUT PRDT PR APP LOCO-MOT	210 548	315 822	35%	110 538	19%	149 244	0	149 244		14 924	14 924
M1A1 ANTIRHUMAT NON STER SEUL	65 737	98 606	35%	34 512	17%	45 285	0	45 285		4 529	4 529

M2A0 REVULSIFS ANTIRHUMATISM	25 890	38 835	35%	13 592	23%	19 390	0	19 390		1 939	1 939
M6A0 ENZYMES ANTI INFLAMMAT.	23 528	35 292	35%	12 352	15%	15 764	0	15 764		1 576	1 576
A12C2 AUTRES SUPPLEMENTS MINER	12 711	19 067	35%	6 673	12%	8 145	0	8 145		815	815
M4A0 ANTI GOUTTEUX	6 132	9 198	65%	5 979	51%	7 605	1 365	7 605		1 989	624
A12A0 CALCIUM	3 380	5 070	65%	3 296	43%	4 064	863	4 064		1 183	320
N5A9 ANTIPSYCHOTIQUES CONVNTL	0	0	65%	0	79%	0	0	0		0	0
déremb psychiatrie	361 663	542 495		317 977		377 484	85 173	377 484		114 404	29 231
N5B2 HYPNOT ASS DE NON BARBIT	143 329	214 994	65%	139 746	35%	166 216	41 810	166 216		54 250	12 441
C1X0 AUT PRODUITS CARDIOLOG.	88 853	133 280	65%	86 632	24%	98 022	30 221	98 022		37 001	6 780
A12C2 AUTRES SUPPLEMENTS MINER	47 596	71 394	35%	24 988	12%	30 499	0	30 499		3 050	3 050
A12C1 MAGNESIUM	29 392	44 088	35%	15 431	14%	19 340	0	19 340		1 934	1 934
N5B1 HYPNOT NON BARBIT SEULS	20 454	30 681	65%	19 943	52%	25 538	4 408	25 538		6 521	2 113
N5B4 HYPNOT.+BARBITURIQUES	23 148	34 722	65%	22 569	31%	26 286	7 231	26 286		9 136	1 906
C1B0 ANTIARYTHMIQUES	7 267	10 901	65%	7 085	65%	9 548	1 159	9 548		1 998	839
N5C0 TRANQUILLISANTS	1 341	2 012	65%	1 307	50%	1 662	300	1 662		436	136
N5B3 HYPNOT.BARBITUR. SEULS	283	425	65%	276	65%	373	45	373		77	33
déremb myorelaxants	29 484	44 225		28 746		33 277	9 384	33 277		11 773	2 389
M3B0 MYORELAXANTS ACT.CENTRAL	29 484	44 225	65%	28 746	29%	33 277	9 384	33 277		11 773	2 389
35% métabolisme	139 120	208 680		135 642		189 868	16 124	0		33 499	17 374
V3A0 MEDICAMENTS DIVERS	139 120	208 680	65%	135 642	74%	189 868	16 124			33 499	17 374
35% psychiatrie	144 247	216 371		140 641		174 459	35 924	0		49 778	13 853
N5C0 TRANQUILLISANTS	60 115	90 173	65%	58 612	50%	74 490	13 443			19 547	6 105
N5B2 HYPNOT ASS DE NON BARBIT	48 043	72 065	65%	46 842	35%	55 714	14 014			18 184	4 170
N6A0 ANTIDEPRESSEURS	27 735	41 603	65%	27 042	46%	33 810	6 679			9 392	2 713
N5B1 HYPNOT NON BARBIT SEULS	8 354	12 531	65%	8 145	52%	10 445	1 788			2 654	866
35% myorelaxants	439 290	658 935		428 308		496 014	139 647	0		175 284	35 637
M3B0 MYORELAXANTS ACT.CENTRAL	439 290	658 935	65%	428 308	29%	496 014	139 647			175 284	35 637
Total première phase	CAHT	PPTTC estimé	taux de remboursement actuel	montant théorique des remboursements	taux d'exonération TM estimé	montant réel des remboursements	économie passage à 35%	économie déremboursement	économie totale	économie passage à 35% et baisse des prix de 10%	économie supplémentaire liée à la baisse des prix
sans déremboursement (les déremboursé	**10 037 379**	**15 056 068**		**8 147 555**		**10 591 859**	**1 433 454**	**0**	**1 433 454**	**2 349 294**	**915 841**
proposition de la commission (déremboursé	**10 037 379**	**15 056 068**		**8 147 555**		**10 591 859**	**699 347**	**6 859 124**	**7 558 471**		
Deuxième phase de réévaluation											
déremb ORL	1 901 453	2 852 180		1 023 749		1 340 353	17 247	1 340 353		149 557	132 311
R5C0 EXPECTORANTS	808 931	1 213 397	35%	424 689	22%	595 887	0	595 887		59 589	59 589
R2A0 ANTIINF.DECONGES.PHARYNX	263 131	394 697	35%	138 144	17%	182 200	0	182 200		18 220	18 220
J7C0 AUTRES VACCINS	262 380	393 570	35%	137 750	11%	166 414	0	166 414		16 641	16 641
R1A4 ANTIINF.RHINOL.SS.CORTIC	194 572	291 858	35%	102 150	13%	126 997	0	126 997		12 700	12 700
R1A3 CORTIC.RHINOL.AV.ANTIINF	157 845	236 768	35%	82 869	10%	97 884	0	97 884		9 788	9 788
J1X9 AUT.ANTIBIOTIQUES	56 398	84 597	65%	54 988	32%	64 517	17 211	64 517		21 942	4 731
R1A7 DECONGESTIONNANTS NASAUX	51 914	77 871	35%	27 255	14%	34 133	0	34 133		3 413	3 413
		0	35%	0						0	0
R5F0 AUTRES ANTITUS+P BR.PULM	25 804	38 706	35%	13 547	15%	17 304	0	17 304		1 730	1 730
R1A9 AUT.PREP.RHINOL.TOPIQUES	20 897	31 346	35%	10 971	19%	14 930	0	14 930		1 493	1 493
R5D2 AUTR.ANTITUSSIFS +ASSOC.	19 934	29 901	35%	10 465	14%	13 236	0	13 236		1 324	1 324
R1B0 PREP RHINOLOGIQUES V.GEN	19 311	28 967	35%	10 138	11%	12 277	0	12 277		1 228	1 228
		0	35%	0						0	0
R4A0 REVULSIFS ET PRDT INHAL	10 616	15 924	35%	5 573	19%	7 532	0	7 532		753	753
M6A0 ENZYMES ANTI INFLAMMAT.	7 987	11 981	35%	4 193	15%	5 352	0	5 352		535	535

V3A0 MEDICAMENTS DIVERS	761	1 142	35%	400	61%	851	0	851		85	85
R5A0 PRDT BRONCHO-PULM -ANTIB	640	960	35%	336	19%	458	0	458		46	46
R3B2 XANTHINES V.GENERALE	239	359	65%	233	67%	317	35	317		64	28
		0		0						0	0
S2C0 PRDT OTOLOG CORT+ANTIINF	46	69	35%	24	13%	30	0	30		3	3
M2A0 REVULSIFS ANTIRHUMATISM	42	63	35%	22	23%	31	0	31		3	3
S1G0 PREP.TRAT.N/ESP.CONJONCT	5	8	35%	3	19%	4	0	4		0	0
R3X2 TS.AUT.BRONCHODILAT.,SYS	0	0	65%	0	38%	0	0	0		0	0
déremb hépato gastro	1 153 473	1 730 210		826 830		1 069 074	143 946	1 069 074		236 459	92 513
A7F0 ANTIDIAR.MICROORGANISMES	179 438	269 157	35%	94 205	18%	125 106	0	125 106		12 511	12 511
A2A1 ANTIACIDES SEULS	169 731	254 597	65%	165 488	36%	197 574	48 877	197 574		63 746	14 870
A7B0 ADSORBANTS INTESTINAUX	161 932	242 898	65%	157 884	31%	184 185	50 325	184 185		63 711	13 386
A7A0 ANTIINFECT INTESTINAUX	122 186	183 279	35%	64 148	14%	80 270	0	80 270		8 027	8 027
A2A7 A-FLAT.ET/OU CARM+A-PRDT	102 944	154 416	65%	100 370	32%	117 475	31 664	117 475		40 245	8 581
A5B0 HEPATOPROTEC.LIPOTROPES	91 225	136 838	35%	47 893	49%	91 364	0	91 364		9 136	9 136
C5A2 ANTIHEMORROID.LOC.-CORT	71 471	107 207	35%	37 522	23%	53 477	0	53 477		5 348	5 348
A5A1 CHOLERETIQ.CHOLECYSTOKIN	56 417	84 626	35%	29 619	14%	37 306	0	37 306		3 731	3 731
A2A2 ANTIFLATULENTS SEULS	39 950	59 925	35%	20 974	22%	29 727	0	29 727		2 973	2 973
A2B9 AUTRES ANTIULCEREUX	29 051	43 577	65%	28 325	55%	36 700	5 895	36 700		8 975	3 081
A9A0 PROD DIGEST.ENZYMES INCL	24 188	36 282	35%	12 699	46%	23 610	0	23 610		2 361	2 361
A3C0 ASS.ANTISPASM+TRANQ.DIV	21 059	31 589	35%	11 056	19%	15 020	0	15 020		1 502	1 502
G4B9 TS AUT.PROD.UROLOGIQUES	19 500	29 250	35%	10 238	12%	12 466	0	12 466		1 247	1 247
A2A4 A-ACID.+A-FLAT.OU CARMIN	17 209	25 814	65%	16 779	35%	19 940	5 034	19 940		6 525	1 491
A6A1 LAXATIFS EMOLLIENTS	13 785	20 678	35%	7 237	30%	11 253	0	11 253		1 125	1 125
N7X0 AUT.PROD.ACTIFS SNC	10 814	16 221	65%	10 544	56%	13 711	2 152	13 711		3 307	1 156
A6A2 LAXATIFS DRASTIQUES	8 186	12 279	35%	4 298	33%	6 956	0	6 956		696	696
A2A6 ANTIACIDES+AUTRES PRDTS.	6 205	9 308	35%	3 258	31%	5 127	0	5 127		513	513
A5C0 CHOLAGOGUE+HEPATOPROTEC.	2 955	4 433	35%	1 551	14%	1 949	0	1 949		195	195
J1X2 POLYMYXINES	2 852	4 278	35%	1 497	91%	4 017	0	4 017		402	402
		0	65%	0						0	0
A6A3 LAXATIFS AUGM.BOL FOECAL	1 280	1 920	35%	672	24%	968	0	968		97	97
A7H0 INHIB TRANSIT INTESTINAL	617	926	35%	324	34%	531	0	531		53	53
		0	35%	0	100%	0	0	0		0	0
A3A0 ANTISPASM+ANTICHOL.SEULS	276	414	35%	145	20%	199	0	199		20	20
A2A3 ANTIACIDES AV.ANTISPASM.	128	192	35%	67	20%	92	0	92		9	9
A2C0 AUT.PRDT TROUBLES ESTOMA	71	107	35%	37	14%	47	0	47		5	5
K1E1 SOLUTION STANDART	3	5	35%	2	86%	4	0	4		0	0
J7C0 AUTRES VACCINS	0	0	35%	0	11%	0	0	0		0	0
35% pneumo	1 113 285	1 669 928		1 085 453		1 242 450	366 409	0		454 013	87 604
R6A0 ANTIHISTAMINIQUES	892 712	1 339 068	65%	870 394	23%	978 246	309 276			376 173	66 897
R3C2 ANTIINFL RESP N.S.V.GEN	50 599	75 899	65%	49 334	17%	53 899	18 856			22 361	3 504
R3C1 ANTIINFLAM.RESP.N.S INH	49 886	74 829	65%	48 639	28%	55 942	16 189			20 164	3 975
R3B2 XANTHINES V.GENERALE	47 913	71 870	65%	46 715	67%	63 584	7 102			12 750	5 648
R3A2 B2 STIMULANTS V GENERALE	44 464	66 696	65%	43 352	55%	56 196	9 000			13 720	4 720
R7A0 STIMULANTS RESPIRATOIRES	13 229	19 844	65%	12 898	83%	18 686	992			2 761	1 769
V1A0 ALLERGENES	11 656	17 484	65%	11 365	24%	12 803	4 012			4 891	879
R1A1 CORTIC.RHINOL.SS.ANTIINF	2 540	3 810	65%	2 477	23%	2 778	885			1 074	189
		0	65%	0	100%	0	0			0	0
S2C0 PRDT OTOLOG CORT+ANTIINF	231	347	65%	225	21%	251	82			99	17
R3X2 TS.AUT.BRONCHODILAT.,SYS	55	83	65%	54	38%	65	15			20	5
		0	65%	0	100%	0	0			0	0
R3B1 XANTHINES, INHALANTS	0	0	65%	0	55%	0	0			0	0
35 % hepato gastro	631 725	947 588		615 932		734 686	182 487	0		237 707	55 220
A3F0 GASTROPROKINETIQUES	361 248	541 872	65%	352 217	35%	418 757	105 527			136 850	31 323
A2A1 ANTIACIDES SEULS	161 092	241 638	65%	157 065	36%	187 518	46 389			60 502	14 113

A2B3 PROSTAGLANDIN. ANTIULCER	65 795	98 693	65%	64 150	39%	77 725	17 972			23 948	5 975
A4A9 AUT.ANTIEMETIQ/ANTINAUS	37 785	56 678	65%	36 840	36%	44 002	10 865			14 179	3 314
		0	65%	0	100%	0	0			0	0
		0	65%	0	100%	0	0			0	0
A3E0 ANTISPASM+AUTRES PRDTS.	5 668	8 502	65%	5 526	33%	6 513	1 705			2 185	481
A5A2 ANTILITHIASIQUES	100	150	65%	98	58%	128	19			30	11
C5A2 ANTIHEMORROID.LOC.-CORT	37	56	65%	36	36%	43	11			14	3
déremb pneumo	445 208	667 812		237 799		310 022	3 129	310 022		33 818	30 689
R5D2 AUTR.ANTITUSSIFS +ASSOC.	235 625	353 438	35%	123 703	14%	156 448	0	156 448		15 645	15 645
R3X2 TS.AUT.BRONCHODILAT.,SYS	81 423	122 135	35%	42 747	25%	62 368	0	62 368		6 237	6 237
R5D1 ANTITUSSIFS SEULS	55 493	83 240	35%	29 134	14%	36 695	0	36 695		3 669	3 669
R5F0 AUTRES ANTITUS+P BR.PULM	20 023	30 035	35%	10 512	15%	13 427	0	13 427		1 343	1 343
R5C0 EXPECTORANTS	17 128	25 692	35%	8 992	22%	12 617	0	12 617		1 262	1 262
R5A0 PRDT BRONCHO-PULM -ANTIB	11 044	16 566	35%	5 798	19%	7 898	0	7 898		790	790
R6A0 ANTIHISTAMINIQUES	9 032	13 548	65%	8 806	23%	9 897	3 129	9 897		3 806	677
R1B0 PREP RHINOLOGIQUES V.GEN	8 328	12 492	35%	4 372	11%	5 295	0	5 295		529	529
J1B0 CHLORAMPHENICOL ET ASSOC	3 601	5 402	35%	1 891	36%	3 143	0	3 143		314	314
A12C2 AUTRES SUPPLEMENTS MINER	3 224	4 836	35%	1 693	12%	2 066	0	2 066		207	207
R5B0 PRDTS PR FROID+ANTIINFEC	287	431	35%	151	6%	169	0	169		17	17
35 % psychiatrie 2ème phase	37 845	56 768		36 899		46 655	8 668	0		12 466	3 799
N5C0 TRANQUILLISANTS	25 929	38 894	65%	25 281	50%	32 129	5 798			8 431	2 633
N6A0 ANTIDEPRESSEURS	11 916	17 874	65%	11 618	46%	14 526	2 869			4 035	1 166
déremb infectiologie	29 440	44 160		20 648		24 370	3 781	24 370		5 840	2 059
A12C2 AUTRES SUPPLEMENTS MINER	17 724	26 586	35%	9 305	12%	11 357	0	11 357		1 136	1 136
J5B0 ANTIVIRAUX SAUF ANTI HIV	7 744	11 616	65%	7 550	28%	8 684	2 513	8 684		3 130	617
G4A3 AUTRES ANTISEPTIQ.URIN.	1 165	1 748	65%	1 136	45%	1 410	290	1 410		402	112
J1A0 TETRACYCLINES ET ASSOC.	1 143	1 715	65%	1 114	14%	1 197	443	1 197		519	75
J1F0 MACROLIDES ET APPARENTES	1 124	1 686	65%	1 096	20%	1 214	404	1 214		485	81
G1B0 ANTIFONGIQ.GYNECOLOGIQ.	346	519	65%	337	19%	371	127	371		151	24
A12C1 MAGNESIUM	178	267	35%	93	14%	117	0	117		12	12
J1E0 ASS AV TRIMETHOP.APPAR.	15	23	65%	15	42%	18	4	18		5	1
T2X0 AUTRES TESTS DIAGNOSTICS	1	2	65%	1	6%	1	0	1		0	0
35 % infectiologie	19 666	29 499		19 174		24 289	4 466	0		6 448	1 982
J2A0 ANTIMYCOTIQUES V GENER	14 029	21 044	65%	13 678	52%	17 485	3 050			4 494	1 443
J1C1 PENICIL.LARG.SPECT.US.OR	2 950	4 425	65%	2 876	19%	3 168	1 078			1 287	209
N4A0 ANTIPARKINSONIENS	1 728	2 592	65%	1 685	90%	2 498	81			322	242
J1G1 FLUOROQUINOLONES ORALES	443	665	65%	432	42%	529	116			157	41
J1C2 PENICIL.LARG.SPEC.INJECT	301	452	65%	293	55%	380	61			93	32
J7B1 VACCIN EN ASSOCIATION	120	180	65%	117	8%	122	50			57	7
J1X9 AUT.ANTIBIOTIQUES	83	125	65%	81	32%	95	25			32	7
J7A9 AUTRES VACCINS	12	18	65%	12	7%	12	5			6	1
Total deuxième phase	CAHT	PPTTC estimé	taux de remboursement actuel	montant théorique des remboursements	taux d'exonération TM estimé	montant réel des remboursements	économie passage à 35%	économie dérembourse ment	économie totale	économie passage à 35% et baisse des prix de 10%	économie supplémentaire liée à la baisse des prix
sans déremboursement (les dérembourse	5 332 095	7 998 143		3 866 484		4 791 899	730 132	0	730 132	1 136 309	406 177
proposition de la commission (dérembour	5 332 095	7 998 143		3 866 484		4 791 899	562 030	2 743 818	3 305 848		

DSS/FOS

Impact des propositions de la commission de la transparence - première phase de réévaluation

01/03/2000

Variable :FRS (Milliers)	CMA/8/99 FRS										
Total deux phases	CAHT	estimation CA PPTTC (CAHT *1,5)	taux de remboursement actuel	montant théorique des remboursements	taux d'exonération TM estimé	montant réel des remboursements	économie passage à 35%	économie déremboursement	économie totale	économie passage à 35% et baisse des prix de 10%	économie supplémentaire liée à la baisse des prix
TOTAL sans déremboursement	15 369 474	23 054 210		12 014 039		15 383 757	2 163 586	0	2 163 586	3 485 603	1 322 017
TOTAL proposition de la commissio	15 369 474	23 054 210		12 014 039		15 383 757	1 261 377	9 602 943	10 864 319		
Première phase de réévaluation											
déremb cardiologie	5 653 039	8 479 559		4 261 461		5 710 885	592 926	5 710 885		1 104 722	511 796
C5C0 VASOPROTECTEURS V GENER	2 678 016	4 017 024	35%	1 405 958	23%	2 013 113	0	2 013 113		201 311	201 311
DAFLON	431 384	647 076	35%	226 477	23%	324 279	0	324 279		32 428	32 428
GINKOR	380 165	570 248	35%	199 587	23%	285 777	0	285 777		28 578	28 578
VEINAMITOL	336 566	504 849	35%	176 697	23%	253 003	0	253 003		25 300	25 300
ENDOTELON	273 248	409 872	35%	143 455	23%	205 405	0	205 405		20 541	20 541
DIOVENOR	241 184	361 776	35%	126 622	23%	181 302	0	181 302		18 130	18 130
ESBERIVEN	201 911	302 867	35%	106 003	23%	151 780	0	151 780		15 178	15 178
CYCLO 3	152 174	228 261	35%	79 891	23%	114 392	0	114 392		11 439	11 439
ETIOVEN	104 135	156 203	35%	54 671	23%	78 280	0	78 280		7 828	7 828
CIRKAN	100 378	150 567	35%	52 698	23%	75 456	0	75 456		7 546	7 546
DIFRAREL	62 973	94 460	35%	33 061	23%	47 338	0	47 338		4 734	4 734
RHEOFLUX	58 611	87 917	35%	30 771	23%	44 059	0	44 059		4 406	4 406
RELVENE	57 916	86 874	35%	30 406	23%	43 537	0	43 537		4 354	4 354
VELITEN	36 223	54 335	35%	19 017	23%	27 229	0	27 229		2 723	2 723
AMPECYCLAL	24 369	36 554	35%	12 794	23%	18 319	0	18 319		1 832	1 832
VEINOTONYL 75	22 423	33 635	35%	11 772	23%	16 856	0	16 856		1 686	1 686
DIOSMIL	20 475	30 713	35%	10 749	23%	15 391	0	15 391		1 539	1 539
FLEBOSMIL	17 146	25 719	35%	9 002	23%	12 889	0	12 889		1 289	1 289
ADENYL	15 928	23 892	35%	8 362	23%	11 973	0	11 973		1 197	1 197
CAMPEL	15 657	23 486	35%	8 220	23%	11 770	0	11 770		1 177	1 177
VEINOBIASE	14 054	21 081	35%	7 378	23%	10 565	0	10 565		1 056	1 056
FLAVAN	13 934	20 901	35%	7 315	23%	10 474	0	10 474		1 047	1 047
DOXIUM	13 603	20 405	35%	7 142	23%	10 226	0	10 226		1 023	1 023
DIO GE	13 496	20 244	35%	7 085	23%	10 145	0	10 145		1 015	1 015
DICYNONE	13 190	19 785	35%	6 925	23%	9 915	0	9 915		992	992
VENIRENE GE	12 434	18 651	35%	6 528	23%	9 347	0	9 347		935	935
MEDIVEINE GE	11 136	16 704	35%	5 846	23%	8 371	0	8 371		837	837
MADECASSOL	7 142	10 713	35%	3 750	23%	5 369	0	5 369		537	537
INTERCYTON	6 876	10 314	35%	3 610	23%	5 169	0	5 169		517	517
DIAMORIL	4 846	7 269	35%	2 544	23%	3 643	0	3 643		364	364
VEINOSTASE	3 610	5 415	35%	1 895	23%	2 714	0	2 714		271	271
ENDIUM GE	2 713	4 070	35%	1 424	23%	2 039	0	2 039		204	204
VASCOCITROL	2 591	3 887	35%	1 360	23%	1 948	0	1 948		195	195
DIOSMINE RATIOPH.	2 109	3 164	35%	1 107	23%	1 585	0	1 585		159	159
DIOSMINE MERCK	1 284	1 926	35%	674	23%	965	0	965		97	97
DIOSMINE RPG	920	1 380	35%	483	23%	692	0	692		69	69
OPO VEINOGENE	759	1 139	35%	398	23%	571	0	571		57	57
VIVENE	349	524	35%	183	23%	262	0	262		26	26

NIGRANTYL	78	117	35%	41	23%	59	0	59		6	6
HAMAMELIS COMPOSE	27	41	35%	14	23%	20	0	20		2	2
FRAGIPREL	0	0	35%	0	23%	0	0	0		0	0
GINKOR PROCTO	0	0	35%	0	23%	0	0	0		0	0
REPARIL	0	0	35%	0	23%	0	0	0		0	0
VEINAMITOL PROCTO	0	0	35%	0	23%	0	0	0		0	0
C4A1 VASODIL.CEREB+PERIP-C4A2	2 415 986	3 623 979	65%	2 355 586	55%	3 050 685	491 395	3 050 685		747 324	255 929
TANAKAN	613 346	920 019	65%	598 012	55%	774 477	124 750	774 477		189 723	64 973
SERMION	334 708	502 062	65%	326 340	55%	422 638	68 077	422 638		103 533	35 456
FONZYLANE	299 663	449 495	65%	292 171	55%	378 387	60 949	378 387		92 693	31 744
PRAXILENE	270 511	405 767	65%	263 748	55%	341 576	55 020	341 576		83 676	28 656
TRIVASTAL	141 510	212 265	65%	137 972	55%	178 686	28 782	178 686		43 773	14 990
VASOBRAL	116 301	174 452	65%	113 393	55%	146 854	23 655	146 854		35 975	12 320
ISKEDYL	112 485	168 728	65%	109 673	55%	142 036	22 879	142 036		34 794	11 916
TORENTAL	111 813	167 720	65%	109 018	55%	141 187	22 742	141 187		34 587	11 845
CERVOXAN	106 796	160 194	65%	104 126	55%	134 852	21 722	134 852		33 035	11 313
DUXIL	67 841	101 762	65%	66 145	55%	85 663	13 798	85 663		20 985	7 186
VADILEX	65 670	98 505	65%	64 028	55%	82 922	13 357	82 922		20 313	6 957
NAFTILUX	32 568	48 852	65%	31 754	55%	41 124	6 624	41 124		10 074	3 450
DI ACTANE GE	30 434	45 651	65%	29 673	55%	38 429	6 190	38 429		9 414	3 224
GINKOGINK	27 914	41 871	65%	27 216	55%	35 247	5 678	35 247		8 634	2 957
HYDERGINE	23 785	35 678	65%	23 190	55%	30 034	4 838	30 034		7 357	2 520
PENTOFLUX GE	13 506	20 259	65%	13 168	55%	17 054	2 747	17 054		4 178	1 431
CARLYTENE	11 764	17 646	65%	11 470	55%	14 854	2 393	14 854		3 639	1 246
BUFLOMEDIL MERCK	9 497	14 246	65%	9 260	55%	11 992	1 932	11 992		2 938	1 006
LOFTYL	5 528	8 292	65%	5 390	55%	6 980	1 124	6 980		1 710	586
NAFTIDROFURYL MERC	5 200	7 800	65%	5 070	55%	6 566	1 058	6 566		1 608	551
GEVATRAN	3 214	4 821	65%	3 134	55%	4 058	654	4 058		994	340
HATIAL GE	2 387	3 581	65%	2 327	55%	3 014	485	3 014		738	253
VINCARUTINE	1 967	2 951	65%	1 918	55%	2 484	400	2 484		608	208
OXADILENE	1 404	2 106	65%	1 369	55%	1 773	286	1 773		434	149
RHEOBRAL	1 336	2 004	65%	1 303	55%	1 687	272	1 687		413	142
CAPERGYL	787	1 181	65%	767	55%	994	160	994		243	83
ZENIUM GE	711	1 067	65%	693	55%	898	145	898		220	75
VINCA	581	872	65%	566	55%	734	118	734		180	62
RUTOVINCINE	512	768	65%	499	55%	647	104	647		158	54
VINCAFOR	504	756	65%	491	55%	636	103	636		156	53
PENTOXIFYLLINE M/G	386	579	65%	376	55%	487	79	487		119	41
ERGODOSE	376	564	65%	367	55%	475	76	475		116	40
CERVILANE	344	516	65%	335	55%	434	70	434		106	36
OPTAMINE	296	444	65%	289	55%	374	60	374		92	31
STRATENE	128	192	65%	125	55%	162	26	162		40	14
VASOCET	88	132	65%	86	55%	111	18	111		27	9
PERENAN	83	125	65%	81	55%	105	17	105		26	9
DIHYDROERGOTOX.RPG	43	65	65%	42	55%	54	9	54		13	5
NICERGOLINE RPG	2	3	65%	2	55%	3	0	3		1	0
OXYPHAR GE	0	0	65%	0	55%	0	0	0		0	0
N6D0 NOOTROPIQUES	223 409	335 114	65%	217 824	51%	277 695	49 216	277 695		72 064	22 848
NOOTROPYL	186 673	280 010	65%	182 006	51%	232 032	41 123	232 032		60 214	19 091
GABACET	28 379	42 569	65%	27 670	51%	35 275	6 252	35 275		9 154	2 902
AXONYL	8 074	12 111	65%	7 872	51%	10 036	1 779	10 036		2 604	826
GERAM GE	253	380	65%	247	51%	314	56	314		82	26
PIRACETAM GNR	29	44	65%	28	51%	36	6	36		9	3
C6A0 AUTRES CARDIOVASCULAIRES	84 949	127 424	65%	82 825	49%	104 564	19 594	104 564		28 091	8 497
HEPTAMYL	84 949	127 424	65%	82 825	49%	104 564	19 594	104 564		28 091	8 497
C5B0 ANTIVARIQUEUX V.LOC.	65 200	97 800	35%	34 230	26%	50 517	0	50 517		5 052	5 052
HIRUCREME	23 384	35 076	35%	12 277	26%	18 118	0	18 118		1 812	1 812

C10C3	13 479	20 219	35%	7 076	26%	10 443	0	10 443		1 044	1 044
PHLEBOGEL	12 238	18 357	35%	6 425	26%	9 482	0	9 482		948	948
ESCINOGEL	7 685	11 528	35%	4 035	26%	5 954	0	5 954		595	595
REPARIL	4 889	7 334	35%	2 567	26%	3 788	0	3 788		379	379
RELVENE	3 524	5 286	35%	1 850	26%	2 730	0	2 730		273	273
C10B0 ANTI-ATHEROM.ORIG.NATUR	67 772	101 658	65%	66 078	46%	82 582	16 351	82 582		22 974	6 623
TOCO	65 829	98 744	65%	64 183	46%	80 214	15 882	80 214		22 316	6 433
TOCOPHAN	1 942	2 913	65%	1 893	46%	2 366	469	2 366		658	190
TOCOFILAN	0	0	65%	0	46%	0	0	0		0	0
C1D0 THERAPIE CORON.SF C1E+C8	50 192	75 288	65%	48 937	63%	65 608	8 297	65 608		14 028	5 731
PERSANTINE	29 334	44 001	65%	28 601	63%	38 344	4 849	38 344		8 198	3 349
CLERIDIUM	19 791	29 687	65%	19 296	63%	25 870	3 272	25 870		5 531	2 260
PERKOD GE	978	1 467	65%	954	63%	1 278	162	1 278		273	112
PROTANGIX	89	134	65%	87	63%	116	15	116		25	10
C1C1 STIMUL.CARD.SF.DOPAMIN.	23 984	35 976	65%	23 384	44%	28 871	6 090	28 871		8 368	2 278
PRAXINOR	21 579	32 369	65%	21 040	44%	25 976	5 479	25 976		7 529	2 050
EFFORTIL	2 405	3 608	65%	2 345	44%	2 895	611	2 895		839	228
G4B3 DYSFONCTION.ERECTION	10 132	15 198	35%	5 319	32%	8 476	0	8 476		848	848
YOHIMBINE HOUDE	10 132	15 198	35%	5 319	32%	8 476	0	8 476		848	848
G2X9 AUT.PROD.GYNECOLOGIQUES	10 258	15 387	35%	5 385	19%	7 310	0	7 310		731	731
CLIMAXOL	10 258	15 387	35%	5 385	19%	7 310	0	7 310		731	731
C4A2 ANTAGONIST CA VIS.CEREB	5 724	8 586	65%	5 581	39%	6 748	1 576	6 748		2 093	517
CYCLOSPASMOL	3 457	5 186	65%	3 371	39%	4 075	952	4 075		1 264	312
SUREPTIL	1 265	1 898	65%	1 233	39%	1 491	348	1 491		463	114
VASCUNORMYL	765	1 148	65%	746	39%	902	211	902		280	69
CYCLERGINE GE	135	203	65%	132	39%	159	37	159		49	12
NOVODIL	102	153	65%	99	39%	120	28	120		37	9
S1X1 AUT.PRDTS OPHT.V.GENER	4 753	7 130	35%	2 495	22%	3 517	0	3 517		352	352
OPHTADIL	3 436	5 154	35%	1 804	22%	2 543	0	2 543		254	254
CYCLOREL	1 317	1 976	35%	691	22%	975	0	975		97	97
C5A1 ANTIHEMORROID.LOC.+CORT	4 656	6 984	35%	2 444	19%	3 315	0	3 315		331	331
CIRKAN	4 656	6 984	35%	2 444	19%	3 315	0	3 315		331	331
A11H3 AUTRES VITAMINES SEULES	2 997	4 496	35%	1 573	31%	2 471	0	2 471		247	247
VIT E GNR	2 244	3 366	35%	1 178	31%	1 850	0	1 850		185	185
TOCOLION	753	1 130	35%	395	31%	621	0	621		62	62
C1B0 ANTIARYTHMIQUES	2 364	3 546	65%	2 305	65%	3 106	377	3 106		650	273
PALPIPAX	1 486	2 229	65%	1 449	65%	1 952	237	1 952		409	172
BRADYL	823	1 235	65%	802	65%	1 081	131	1 081		226	95
ALUPENT	54	81	65%	53	65%	71	9	71		15	6
B2G0 HEMOSTIPTIQUE	2 326	3 489	35%	1 221	28%	1 861	0	1 861		186	186
DICYNONE	2 326	3 489	35%	1 221	28%	1 861	0	1 861		186	186
B1C0 INHIBITEUR AGGRE PLAQUET	321	482	65%	313	79%	446	30	446		72	42
DIPHAR GE	295	443	65%	288	79%	410	28	410		66	38
CORONARINE	25	38	65%	24	79%	35	2	35		6	3
35% cardiologie	1 541 109	2 311 664		1 502 581		1 989 760	275 917	0		447 301	171 384
C1D0 THERAPIE CORON.SF C1E+C8	796 547	1 194 821	65%	776 633	63%	1 041 203	131 672			222 625	90 953
VASTAREL 20	795 724	1 193 586	65%	775 831	63%	1 040 127	131 536			222 395	90 859
TRIMETAZIDINE GNR	608	912	65%	593	63%	795	101			170	69
CENTROPHENE	215	323	65%	210	63%	281	36			60	25
C2A1 ANTIHYPERTENS.SEUL.CENTR	382 849	574 274	65%	373 278	56%	486 736	75 032			116 203	41 170
HYPERIUM	271 568	407 352	65%	264 779	56%	345 259	53 223			82 427	29 204
PHYSIOTENS	62 238	93 357	65%	60 682	56%	79 126	12 198			18 891	6 693
CATAPRESSAN	27 401	41 102	65%	26 716	56%	34 836	5 370			8 317	2 947
ALDOMET	18 883	28 325	65%	18 411	56%	24 007	3 701			5 731	2 031
ESTULIC	1 118	1 677	65%	1 090	56%	1 421	219			339	120
METHYLDOPA RPG	767	1 151	65%	748	56%	975	150			233	82
METHYLDOPA MSD	503	755	65%	490	56%	639	99			153	54

CLONIDINE RPG	371	557	65%	362	56%	472	73			113	40
C2A2 ANTIHYPERTENS.SEUL.PERIP	307 688	461 532	65%	299 996	57%	391 358	60 149			93 270	33 121
ALPRESS	124 274	186 411	65%	121 167	57%	158 068	24 294			37 671	13 377
MEDIATENSYL	93 338	140 007	65%	91 005	57%	118 720	18 246			28 294	10 047
EUPRESSYL	81 672	122 508	65%	79 630	57%	103 881	15 966			24 757	8 792
MINIPRESS	8 404	12 606	65%	8 194	57%	10 689	1 643			2 548	905
C1B0 ANTIARYTHMIQUES	49 965	74 948	65%	48 716	65%	65 650	7 969			13 737	5 768
RYTHMODAN	40 612	60 918	65%	39 597	65%	53 361	6 477			11 166	4 688
ISORYTHM LP	4 546	6 819	65%	4 432	65%	5 973	725			1 250	525
LONGACOR	2 553	3 830	65%	2 489	65%	3 354	407			702	295
MEXITIL	1 874	2 811	65%	1 827	65%	2 462	299			515	216
QUINIDURULE	192	288	65%	187	65%	252	31			53	22
CARDIOQUINE	107	161	65%	104	65%	141	17			29	12
ISORYTHM GE	83	125	65%	81	65%	109	13			23	10
C10A9 AUT.REDUCT.CHOLEST&TRIGL	4 060	6 090	65%	3 959	40%	4 812	1 095			1 467	372
FONLIPOL	4 060	6 090	65%	3 959	40%	4 812	1 095			1 467	372
35% rhumatologie hors myorelaxant	768 660	1 152 990		749 444		882 633	231 734	0		296 824	65 090
M1A1 ANTIRHUMAT NON STER SEUL	336 574	504 861	65%	328 160	27%	376 373	110 133			136 757	26 624
ART 50	289 014	433 521	65%	281 789	27%	323 189	94 570			117 432	22 862
ZONDAR	47 560	71 340	65%	46 371	27%	53 184	15 562			19 325	3 762
M5X0 AUT PRDT PR APP LOCO-MOT	175 339	263 009	65%	170 956	30%	198 705	55 118			69 476	14 359
CHONDROSULF	175 339	263 009	65%	170 956	30%	198 705	55 118			69 476	14 359
A12A0 CALCIUM	149 171	223 757	65%	145 442	43%	179 336	38 074			52 201	14 126
OROCAL	36 066	54 099	65%	35 164	43%	43 359	9 206			12 621	3 415
CACIT	26 364	39 546	65%	25 705	43%	31 695	6 729			9 226	2 497
OSSOPAN	16 731	25 097	65%	16 313	43%	20 114	4 270			5 855	1 584
CALCIUM SANDOZ	16 075	24 113	65%	15 673	43%	19 326	4 103			5 625	1 522
SANDOCAL	14 388	21 582	65%	14 028	43%	17 298	3 672			5 035	1 363
OSTRAM	13 333	20 000	65%	13 000	43%	16 029	3 403			4 666	1 263
CALTRATE	8 981	13 472	65%	8 756	43%	10 797	2 292			3 143	850
CALPEROS	5 004	7 506	65%	4 879	43%	6 016	1 277			1 751	474
CALCIPRAT	2 479	3 719	65%	2 417	43%	2 980	633			867	235
CALCIFORTE	2 287	3 431	65%	2 230	43%	2 749	584			800	217
CALCIDOSE	2 211	3 317	65%	2 156	43%	2 658	564			774	209
DENSICAL	1 945	2 918	65%	1 896	43%	2 338	496			681	184
EFICAL	1 432	2 148	65%	1 396	43%	1 722	366			501	136
PERICAL	981	1 472	65%	956	43%	1 179	250			343	93
CALPRIMUM	581	872	65%	566	43%	698	148			203	55
CALCIUM MERCK	269	404	65%	262	43%	323	69			94	25
CALNOVA	45	68	65%	44	43%	54	11			16	4
H4A0 CALCITONINES	105 348	158 022	65%	102 714	41%	125 139	28 185			37 881	9 695
CIBACALCINE	44 405	66 608	65%	43 295	41%	52 747	11 880			15 967	4 087
CALSYN	23 416	35 124	65%	22 831	41%	27 815	6 265			8 420	2 155
MIACALCIC	20 206	30 309	65%	19 701	41%	24 002	5 406			7 266	1 860
CADENS GE	9 972	14 958	65%	9 723	41%	11 845	2 668			3 586	918
CALCITONINE GNR	6 137	9 206	65%	5 984	41%	7 290	1 642			2 207	565
CALCITONINE RATIOP	1 213	1 820	65%	1 183	41%	1 441	325			436	112
STAPOROS	0	0	65%	0	41%	0	0			0	0
M1C0 ANTIRHUMAT SPECIFIQUES	2 228	3 342	65%	2 172	78%	3 080	225			510	286
RIDAURAN	2 228	3 342	65%	2 172	78%	3 080	225			510	286
déremb metabolisme	678 578	1 017 867		430 326		533 266	44 396	533 266		93 283	48 887
A12C1 MAGNESIUM	500 771	751 157	35%	262 905	14%	329 517	0	329 517		32 952	32 952
MAGNE B6	236 665	354 998	35%	124 249	14%	155 730	0	155 730		15 573	15 573
MAG 2	116 675	175 013	35%	61 254	14%	76 774	0	76 774		7 677	7 677
MEGAMAG	65 885	98 828	35%	34 590	14%	43 354	0	43 354		4 335	4 335
OROMAG	23 084	34 626	35%	12 119	14%	15 190	0	15 190		1 519	1 519
SPASMAG	20 859	31 289	35%	10 951	14%	13 726	0	13 726		1 373	1 373

UVIMAG B6	14 036	21 054	35%	7 369	14%	9 236	0	9 236		924	924
MAGNOGENE	8 221	12 332	35%	4 316	14%	5 410	0	5 410		541	541
TOP MAG	6 347	9 521	35%	3 332	14%	4 176	0	4 176		418	418
IONIMAG	5 556	8 334	35%	2 917	14%	3 656	0	3 656		366	366
SOLUMAG	1 757	2 636	35%	922	14%	1 156	0	1 156		116	116
EFIMAG	748	1 122	35%	393	14%	492	0	492		49	49
PIDOLATE MG RATIOP	727	1 091	35%	382	14%	478	0	478		48	48
PIDOLATE MG RPG	212	318	35%	111	14%	139	0	139		14	14
C10A9 AUT.REDUCT.CHOLEST&TRIGL	164 606	246 909	65%	160 491	40%	195 114	44 396	195 114		59 468	15 072
MEDIATOR	164 606	246 909	65%	160 491	40%	195 114	44 396	195 114		59 468	15 072
A12C2 AUTRES SUPPLEMENTS MINER	12 204	18 306	35%	6 407	12%	7 820	0	7 820		782	782
OLIGOSOL ZN NI CO	12 204	18 306	35%	6 407	12%	7 820	0	7 820		782	782
A15A0 OREXIGENES	997	1 496	35%	523	30%	815	0	815		82	82
FENUGRENE	997	1 496	35%	523	30%	815	0	815		82	82
déremb rhumatologie hors myorelaxant	282 189	423 284		152 430		204 212	2 228	204 212		22 427	20 198
M5X0 AUT PRDT PR APP LOCO-MOT	210 548	315 822	35%	110 538	19%	149 244	0	149 244		14 924	14 924
UTEPLEX	123 840	185 760	35%	65 016	19%	87 782	0	87 782		8 778	8 778
ATEPADENE	69 084	103 626	35%	36 269	19%	48 969	0	48 969		4 897	4 897
SPECYTON CART PTH	14 146	21 219	35%	7 427	19%	10 027	0	10 027		1 003	1 003
MYOVITON	3 478	5 217	35%	1 826	19%	2 465	0	2 465		247	247
M1A1 ANTIRHUMAT NON STER SEUL	65 737	98 606	35%	34 512	17%	45 285	0	45 285		4 529	4 529
JONCTUM	65 737	98 606	35%	34 512	17%	45 285	0	45 285		4 529	4 529
M2A0 REVULSIFS ANTIRHUMATISM	25 890	38 835	35%	13 592	23%	19 390	0	19 390		1 939	1 939
NEURIPLEGE	10 012	15 018	35%	5 256	23%	7 498	0	7 498		750	750
AROMA BAUME	7 479	11 219	35%	3 926	23%	5 601	0	5 601		560	560
INONGAN	2 700	4 050	35%	1 418	23%	2 022	0	2 022		202	202
DOLAL	2 206	3 309	35%	1 158	23%	1 652	0	1 652		165	165
ALGESAL SURACTIVE	1 924	2 886	35%	1 010	23%	1 441	0	1 441		144	144
ANTIPHLOGISTINE	1 087	1 631	35%	571	23%	814	0	814		81	81
REFLEX SPRAY	198	297	35%	104	23%	148	0	148		15	15
DISALGYL BAUME	173	260	35%	91	23%	130	0	130		13	13
ALGESAL	111	167	35%	58	23%	83	0	83		8	8
M6A0 ENZYMES ANTI INFLAMMAT.	23 528	35 292	35%	12 352	15%	15 764	0	15 764		1 576	1 576
RIBATRAN	21 365	32 048	35%	11 217	15%	14 315	0	14 315		1 432	1 432
ALPHACHYMO CHOAY	1 011	1 517	35%	531	15%	677	0	677		68	68
ALPHACUTANEE	968	1 452	35%	508	15%	649	0	649		65	65
ALPHINTERN	184	276	35%	97	15%	123	0	123		12	12
A12C2 AUTRES SUPPLEMENTS MINER	12 711	19 067	35%	6 673	12%	8 145	0	8 145		815	815
GRANIONS SELENIUM	11 891	17 837	35%	6 243	12%	7 620	0	7 620		762	762
OSTEOFLUOR	821	1 232	65%	800	20%	887	295	887		355	59
RUMAFLUOR	0	0	65%	0	20%	0	0	0		0	0
M4A0 ANTI GOUTTEUX	6 132	9 198	65%	5 979	51%	7 605	1 365	7 605		1 989	624
DISSOLVUROL	6 132	9 198	65%	5 979	51%	7 605	1 365	7 605		1 989	624
A12A0 CALCIUM	3 380	5 070	65%	3 296	43%	4 064	863	4 064		1 183	320
FLUOCALCIC	3 109	4 664	65%	3 031	43%	3 738	794	3 738		1 088	294
ARCHITEX	271	407	65%	264	43%	326	69	326		95	26
N5A9 ANTIPSYCHOTIQUES CONVNTL	0	0	65%	0	79%	0	0	0		0	0
NEURIPLEGE	0	0	65%	0	79%	0	0	0		0	0
déremb psychiatrie	361 663	542 495		317 977		377 484	85 173	377 484		114 404	29 231
N5B2 HYPNOT ASS DE NON BARBIT	143 329	214 994	65%	139 746	35%	166 216	41 810	166 216		54 250	12 441
EUPHYTOSE	97 453	146 180	65%	95 017	35%	113 014	28 427	113 014		36 886	8 459
VAGOSTABYL	32 650	48 975	65%	31 834	35%	37 864	9 524	37 864		12 358	2 834
TRANQUITAL	8 903	13 355	65%	8 680	35%	10 325	2 597	10 325		3 370	773
PASSIFLORINE	2 175	3 263	65%	2 121	35%	2 522	634	2 522		823	189
GALIRENE	1 200	1 800	65%	1 170	35%	1 392	350	1 392		454	104
LESOURD ANTINERV	604	906	65%	589	35%	700	176	700		229	52
SPASMINE	202	303	65%	197	35%	234	59	234		76	18

NEUROCALCIUM	143	215	65%	139	35%	166	42	166		54	12
C1X0 AUT PRODUITS CARDIOLOG.	88 853	133 280	65%	86 632	24%	98 022	30 221	98 022		37 001	6 780
SPASMINE	84 768	127 152	65%	82 649	24%	93 515	28 831	93 515		35 300	6 468
CARDIOCALM	2 901	4 352	65%	2 828	24%	3 200	987	3 200		1 208	221
BIOCARDE	1 061	1 592	65%	1 034	24%	1 170	361	1 170		442	81
SPASMOSEDINE	123	185	65%	120	24%	136	42	136		51	9
A12C2 AUTRES SUPPLEMENTS MINER	47 596	71 394	35%	24 988	12%	30 499	0	30 499		3 050	3 050
OLIGOSOL LI	47 596	71 394	35%	24 988	12%	30 499	0	30 499		3 050	3 050
A12C1 MAGNESIUM	29 392	44 088	35%	15 431	14%	19 340	0	19 340		1 934	1 934
OLIGOSOL MG	20 221	30 332	35%	10 616	14%	13 306	0	13 306		1 331	1 331
GRANIONS MAGNESIUM	9 171	13 757	35%	4 815	14%	6 035	0	6 035		603	603
N5B1 HYPNOT NON BARBIT SEULS	20 454	30 681	65%	19 943	52%	25 538	4 408	25 538		6 521	2 113
CALCIBRONAT	14 168	21 252	65%	13 814	52%	17 690	3 053	17 690		4 517	1 464
NOPRON	6 133	9 200	65%	5 980	52%	7 657	1 322	7 657		1 955	634
CRATAEGOL	153	230	65%	149	52%	191	33	191		49	16
N5B4 HYPNOT.+BARBITURIQUES	23 148	34 722	65%	22 569	31%	26 286	7 231	26 286		9 136	1 906
SYMPAVAGOL	18 151	27 227	65%	17 697	31%	20 612	5 670	20 612		7 164	1 494
SYMPATHYL	2 430	3 645	65%	2 369	31%	2 759	759	2 759		959	200
SYMPANEUROL	1 015	1 523	65%	990	31%	1 153	317	1 153		401	84
SEDATONYL	569	854	65%	555	31%	646	178	646		225	47
NEUROCALCIUM	496	744	35%	260	19%	353	0	353		35	35
SPASMIDENAL	487	731	35%	256	19%	347	0	347		35	35
C1B0 ANTIARYTHMIQUES	7 267	10 901	65%	7 085	65%	9 548	1 159	9 548		1 998	839
NATISEDINE	6 586	9 879	65%	6 421	65%	8 654	1 050	8 654		1 811	760
VERICARDINE	369	554	65%	360	65%	485	59	485		101	43
ANXORAL	312	468	65%	304	65%	410	50	410		86	36
N5C0 TRANQUILLISANTS	1 341	2 012	65%	1 307	50%	1 662	300	1 662		436	136
COVATINE	1 341	2 012	65%	1 307	50%	1 662	300	1 662		436	136
N5B3 HYPNOT.BARBITUR. SEULS	283	425	65%	276	65%	373	45	373		77	33
BUTOBARBITAL DIPH.	283	425	65%	276	65%	373	45	373		77	33
déremb myorelaxants	29 484	44 225		28 746		33 277	9 384	33 277		11 773	2 389
M3B0 MYORELAXANTS ACT.CENTRAL	29 484	44 225	65%	28 746	29%	33 277	9 384	33 277		11 773	2 389
COLTRAMYL	23 128	34 692	65%	22 550	29%	26 104	7 361	26 104		9 236	1 874
MIOREL GE	6 098	9 146	65%	5 945	29%	6 882	1 941	6 882		2 435	494
THIOCOLCHIC. NOVAL	258	387	65%	251	29%	291	82	291		103	21
35% métabolisme	139 120	208 680		135 642		189 868	16 124	0		33 499	17 374
V3A0 MEDICAMENTS DIVERS	139 120	208 680	65%	135 642	74%	189 868	16 124			33 499	17 374
CETORNAN	139 120	208 680	65%	135 642	74%	189 868	16 124			33 499	17 374
35% psychiatrie	144 247	216 371		140 641		174 459	35 924	0		49 778	13 853
N5C0 TRANQUILLISANTS	60 115	90 173	65%	58 612	50%	74 490	13 443			19 547	6 105
EQUANIL	34 743	52 115	65%	33 874	50%	43 051	7 769			11 297	3 528
STRESAM	25 259	37 889	65%	24 628	50%	31 299	5 648			8 213	2 565
MEPROBAMATE RICHA.	63	95	65%	61	50%	78	14			20	6
NOVALM	50	75	65%	49	50%	62	11			16	5
N5B2 HYPNOT ASS DE NON BARBIT	48 043	72 065	65%	46 842	35%	55 714	14 014			18 184	4 170
MEPRONIZINE	25 558	38 337	65%	24 919	35%	29 639	7 455			9 674	2 218
NOCTRAN	22 484	33 726	65%	21 922	35%	26 074	6 559			8 510	1 952
N6A0 ANTIDEPRESSEURS	27 735	41 603	65%	27 042	46%	33 810	6 679			9 392	2 713
VIVALAN	21 440	32 160	65%	20 904	46%	26 137	5 163			7 260	2 097
HUMORYL	6 295	9 443	65%	6 138	46%	7 674	1 516			2 132	616
N5B1 HYPNOT NON BARBIT SEULS	8 354	12 531	65%	8 145	52%	10 445	1 788			2 654	866
MOGADON	4 786	7 179	65%	4 666	52%	5 984	1 025			1 520	496
NUCTALON	2 635	3 953	65%	2 569	52%	3 294	564			837	273
HALCION	934	1 401	65%	911	52%	1 168	200			297	97
35% myorelaxants	439 290	658 935		428 308		496 014	139 647	0		175 284	35 637
M3B0 MYORELAXANTS ACT.CENTRAL	439 290	658 935	65%	428 308	29%	496 014	139 647			175 284	35 637

Total première phase	CAHT	PPTTC estimé	taux de remboursement actuel	montant théorique des remboursements	taux d'exonération TM estimé	montant réel des remboursements	économie passage à 35%	économie dérembourse ment	économie totale	économie passage à 35% et baisse des prix de 10%	économie supplémentaire liée à la baisse des prix
sans déremboursement (les dérembourse	10 037 379	15 056 068		8 147 555		10 591 859	1 433 454	0	1 433 454	2 349 294	915 841
proposition de la commission (dérembou	10 037 379	15 056 068		8 147 555		10 591 859	699 347	6 859 124	7 558 471		
Deuxième phase de réévaluation											
déremb ORL	1 901 453	2 852 180		1 023 749		1 340 353	17 247	1 340 353		149 557	132 311
R5C0 EXPECTORANTS	808 931	1 213 397	35%	424 689	22%	595 887	0	595 887		59 589	59 589
MUCOMYST	135 333	203 000	35%	71 050	22%	99 691	0	99 691		9 969	9 969
SURBRONC	106 384	159 576	35%	55 852	22%	78 366	0	78 366		7 837	7 837
BRONCHOKOD GE	97 374	146 061	35%	51 121	22%	71 729	0	71 729		7 173	7 173
EXOMUC	96 104	144 156	35%	50 455	22%	70 794	0	70 794		7 079	7 079
MAXILASE	73 430	110 145	35%	38 551	22%	54 091	0	54 091		5 409	5 409
MUCICLAR GE	53 691	80 537	35%	28 188	22%	39 551	0	39 551		3 955	3 955
FLUIMUCIL	39 872	59 808	35%	20 933	22%	29 371	0	29 371		2 937	2 937
MUCOLATOR	34 050	51 075	35%	17 876	22%	25 082	0	25 082		2 508	2 508
MUXOL	25 549	38 324	35%	13 413	22%	18 820	0	18 820		1 882	1 882
SOLACY	24 244	36 366	35%	12 728	22%	17 859	0	17 859		1 786	1 786
SOLMUCOL	21 702	32 553	35%	11 394	22%	15 986	0	15 986		1 599	1 599
VECTRINE	12 577	18 866	35%	6 603	22%	9 265	0	9 265		926	926
TIXAIR	8 035	12 053	35%	4 218	22%	5 919	0	5 919		592	592
BISOLVON	7 152	10 728	35%	3 755	22%	5 268	0	5 268		527	527
MUCOTHIOL	6 812	10 218	35%	3 576	22%	5 018	0	5 018		502	502
BRONKIREX GE	6 273	9 410	35%	3 293	22%	4 621	0	4 621		462	462
FLUISEDAL SS PROME	5 705	8 558	35%	2 995	22%	4 203	0	4 203		420	420
CARBOCISTEINE GNR	4 978	7 467	35%	2 613	22%	3 667	0	3 667		367	367
AMBROXOL BAYER	4 732	7 098	35%	2 484	22%	3 486	0	3 486		349	349
ACETYLCYST BIOGAR.	3 588	5 382	35%	1 884	22%	2 643	0	2 643		264	264
OZOTHINE	3 534	5 301	35%	1 855	22%	2 603	0	2 603		260	260
ACETYLCYST GNR	3 373	5 060	35%	1 771	22%	2 485	0	2 485		248	248
EDIREL	3 371	5 057	35%	1 770	22%	2 483	0	2 483		248	248
CARBOCISTEINE BYI	3 155	4 733	35%	1 656	22%	2 324	0	2 324		232	232
CAMPHOPNEUMINE	2 849	4 274	35%	1 496	22%	2 099	0	2 099		210	210
GUETHURAL	2 829	4 244	35%	1 485	22%	2 084	0	2 084		208	208
CARBOCISTEINE MERC	2 797	4 196	35%	1 468	22%	2 060	0	2 060		206	206
CARBOCISTEINE RPG	2 623	3 935	35%	1 377	22%	1 932	0	1 932		193	193
CARBOCISTEINE LRP	2 608	3 912	35%	1 369	22%	1 921	0	1 921		192	192
BRONCHORECTINE	2 284	3 426	35%	1 199	22%	1 682	0	1 682		168	168
CARBOCISTEINE BIOG	1 991	2 987	35%	1 045	22%	1 467	0	1 467		147	147
VISCOTIOL	1 804	2 706	35%	947	22%	1 329	0	1 329		133	133
TERPONE	1 771	2 657	35%	930	22%	1 305	0	1 305		130	130
OZOTHINE DIPROPHYL	1 311	1 967	35%	688	22%	966	0	966		97	97
TUSSILENE GE	1 260	1 890	35%	662	22%	928	0	928		93	93
BRONCHODERMINE	952	1 428	35%	500	22%	701	0	701		70	70
AMBROXOL MERCK	843	1 265	35%	443	22%	621	0	621		62	62
AMBROXOL BIOGARAN	787	1 151	35%	403	22%	565	0	565		56	56
AMBROXOL RATIOPH.	499	749	35%	262	22%	368	0	368		37	37
ACETYLCYST MERCK	436	654	35%	229	22%	321	0	321		32	32
MUCOSPIRE	215	323	35%	113	22%	158	0	158		16	16
DIMOTAPP	51	77	35%	27	22%	38	0	38		4	4
ACETYLCYST G GAM	24	36	35%	13	22%	18	0	18		2	2

THIOPREOL	0	0	35%	0	22%	0	0	0		0	0
R2A0 ANTIINF.DECONGES.PHARYNX	263 131	394 697	35%	138 144	17%	182 200	0	182 200		18 220	18 220
LYSOPAINE	89 855	134 783	35%	47 174	17%	62 218	0	62 218		6 222	6 222
OROPIVALONE BACITR	78 813	118 220	35%	41 377	17%	54 572	0	54 572		5 457	5 457
HEXASPRAY	38 814	58 221	35%	20 377	17%	26 876	0	26 876		2 688	2 688
THIOVALONE	13 792	20 688	35%	7 241	17%	9 550	0	9 550		955	955
COLLU HEXTRIL	11 919	17 879	35%	6 257	17%	8 253	0	8 253		825	825
ALPHA AMYLASE BYI	5 937	8 906	35%	3 117	17%	4 111	0	4 111		411	411
ELUDRIL	5 466	8 199	35%	2 870	17%	3 785	0	3 785		378	378
COLLUNOVAR	5 390	8 085	35%	2 830	17%	3 732	0	3 732		373	373
GLOSSITHIASE	4 249	6 374	35%	2 231	17%	2 942	0	2 942		294	294
HEXOMEDINE	4 244	6 366	35%	2 228	17%	2 939	0	2 939		294	294
HEXALYSE	2 646	3 969	35%	1 389	17%	1 832	0	1 832		183	183
MAXILASE BACITRAC.	1 767	2 651	35%	928	17%	1 224	0	1 224		122	122
MEGAMYLASE ALPHA	228	342	35%	120	17%	158	0	158		16	16
NANBACINE	10	15	35%	5	17%	7	0	7		1	1
J7C0 AUTRES VACCINS	262 380	393 570	35%	137 750	11%	166 414	0	166 414		16 641	16 641
BIOSTIM	168 968	253 452	35%	88 708	11%	107 168	0	107 168		10 717	10 717
RIBOMUNYL	49 536	74 304	35%	26 006	11%	31 418	0	31 418		3 142	3 142
IMOCUR	26 845	40 268	35%	14 094	11%	17 026	0	17 026		1 703	1 703
I R S 19	16 509	24 764	35%	8 667	11%	10 471	0	10 471		1 047	1 047
RHINOPTEN	522	783	35%	274	11%	331	0	331		33	33
R1A4 ANTIINF.RHINOL.SS.CORTIC	194 572	291 858	35%	102 150	13%	126 997	0	126 997		12 700	12 700
LOCABIOTAL	149 293	223 940	35%	78 379	13%	97 444	0	97 444		9 744	9 744
ISOFRA	29 140	43 710	35%	15 299	13%	19 020	0	19 020		1 902	1 902
RHINOTROPHYL	14 284	21 426	35%	7 499	13%	9 323	0	9 323		932	932
FRAZOLINE	1 838	2 757	35%	965	13%	1 200	0	1 200		120	120
RHINO SULFORGAN	16	24	35%	8	13%	10	0	10		1	1
R1A3 CORTIC.RHINOL.AV.ANTIINF	157 845	236 768	35%	82 869	10%	97 884	0	97 884		9 788	9 788
PIVALONE NEOMYCINE	137 617	206 426	35%	72 249	10%	85 340	0	85 340		8 534	8 534
FRAMYXONE	15 134	22 701	35%	7 945	10%	9 385	0	9 385		939	939
POLYDEXA PHENYLEPH	4 643	6 965	35%	2 438	10%	2 879	0	2 879		288	288
CORTIFRA	260	390	35%	137	10%	161	0	161		16	16
CHIBRO CADRON	191	287	35%	100	10%	118	0	118		12	12
J1X9 AUT.ANTIBIOTIQUES	56 398	84 597	65%	54 988	32%	64 517	17 211	64 517		21 942	4 731
OCTOFENE	45 886	68 829	65%	44 739	32%	52 492	14 003	52 492		17 852	3 849
NANBACINE	10 512	15 768	65%	10 249	32%	12 025	3 208	12 025		4 090	882
R1A7 DECONGESTIONNANTS NASAUX	51 914	77 871	35%	27 255	14%	34 133	0	34 133		3 413	3 413
RHINOFLUIMUCIL	49 831	74 747	35%	26 161	14%	32 763	0	32 763		3 276	3 276
HUILE GOMENOLEE	2 083	3 125	35%	1 094	14%	1 370	0	1 370		137	137
THIOPON BALSAMIQUE	0	0	35%	0	14%	0	0	0		0	0
		0	35%	0						0	0
		0	35%	0	100%	0	0	0		0	0
R5F0 AUTRES ANTITUS+P BR.PULM	25 804	38 706	35%	13 547	15%	17 304	0	17 304		1 730	1 730
ACTISOUFRE	10 514	15 771	35%	5 520	15%	7 051	0	7 051		705	705
SOLACY	9 108	13 662	35%	4 782	15%	6 108	0	6 108		611	611
COQUELUSEDAL PARAC	3 654	5 481	35%	1 918	15%	2 450	0	2 450		245	245
GOMENOL	2 528	3 792	35%	1 327	15%	1 695	0	1 695		170	170
EUCALYBROL	0	0	35%	0	15%	0	0	0		0	0
R1A9 AUT.PREP.RHINOL.TOPIQUES	20 897	31 346	35%	10 971	19%	14 930	0	14 930		1 493	1 493
NECYRANE	20 266	30 399	35%	10 640	19%	14 480	0	14 480		1 448	1 448
VASELINE GOMENOLEE	629	944	35%	330	19%	449	0	449		45	45
STILLARGOL	1	2	35%	1	19%	1	0	1		0	0
R5D2 AUTR.ANTITUSSIFS +ASSOC.	19 934	29 901	35%	10 465	14%	13 236	0	13 236		1 324	1 324
COQUELUSEDAL	19 492	29 238	35%	10 233	14%	12 942	0	12 942		1 294	1 294
OZOTHINE	232	348	35%	122	14%	154	0	154		15	15
TERPINE MONT DORE	210	315	35%	110	14%	139	0	139		14	14

R1B0 PREP RHINOLOGIQUES V.GEN	19 311	28 967	35%	10 138	11%	12 277	0	12 277		1 228	1 228
RINUTAN	17 061	25 592	35%	8 957	11%	10 846	0	10 846		1 085	1 085
RINUREL	1 925	2 888	35%	1 011	11%	1 224	0	1 224		122	122
FUMIGALENE	325	488	35%	171	11%	207	0	207		21	21
		0	35%	0						0	0
		0	35%	0	100%	0	0	0		0	0
R4A0 REVULSIFS ET PRDT INHAL	10 616	15 924	35%	5 573	19%	7 532	0	7 532		753	753
CALYPTOL	6 063	9 095	35%	3 183	19%	4 301	0	4 301		430	430
BRONCHODERMINE	4 541	6 812	35%	2 384	19%	3 222	0	3 222		322	322
BRONCHOSPRAY	8	12	35%	4	19%	6	0	6		1	1
GOMENOL	5	8	35%	3	19%	4	0	4		0	0
M6A0 ENZYMES ANTI INFLAMMAT.	7 987	11 981	35%	4 193	15%	5 352	0	5 352		535	535
DAZEN	7 987	11 981	35%	4 193	15%	5 352	0	5 352		535	535
V3A0 MEDICAMENTS DIVERS	761	1 142	35%	400	61%	851	0	851		85	85
DESINTEX	563	845	35%	296	61%	629	0	629		63	63
GOMENOLEO	181	272	65%	176	74%	247	21	247		44	23
THIOPON PANTOTHEN	17	26	35%	9	61%	19	0	19		2	2
THIOPHEOL	0	0	35%	0	61%	0	0	0		0	0
THIOPON	0	0	35%	0	61%	0	0	0		0	0
R5A0 PRDT BRONCHO-PULM -ANTIB	640	960	35%	336	19%	458	0	458		46	46
CARBOCISTEINE RPG	640	960	35%	336	19%	458	0	458		46	46
R3B2 XANTHINES V.GENERALE	239	359	65%	233	67%	317	35	317		64	28
HYPNASMINE	239	359	65%	233	67%	317	35	317		64	28
		0		0						0	0
		0		0	#DIV/0!	#DIV/0!	0	#DIV/0!		#DIV/0!	#DIV/0!
S2C0 PRDT OTOLOG CORT+ANTIINF	46	69	35%	24	13%	30	0	30		3	3
FRAMYXONE	46	69	35%	24	13%	30	0	30		3	3
CORTIFRA	0	0	35%	0	13%	0	0	0		0	0
M2A0 REVULSIFS ANTIRHUMATISM	42	63	35%	22	23%	31	0	31		3	3
PNEUMOPLASME HIST	42	63	35%	22	23%	31	0	31		3	3
S1G0 PREP.TRAT.N/ESP.CONJONCT	5	8	35%	3	19%	4	0	4		0	0
STILLARGOL	5	8	35%	3	19%	4	0	4		0	0
R3X2 TS.AUT.BRONCHODILAT.,SYS	0	0	65%	0	38%	0	0	0		0	0
EPHEIODINE	0	0	65%	0	38%	0	0	0		0	0
déremb hépato gastro	1 153 473	1 730 210		826 830		1 069 074	143 946	1 069 074		236 459	92 513
A7F0 ANTIDIAR.MICROORGANISMES	179 438	269 157	35%	94 205	18%	125 106	0	125 106		12 511	12 511
ULTRA LEVURE	140 529	210 794	35%	73 778	18%	97 978	0	97 978		9 798	9 798
LACTEOL	28 983	43 475	35%	15 216	18%	20 207	0	20 207		2 021	2 021
BACILOR	6 037	9 056	35%	3 169	18%	4 209	0	4 209		421	421
LYOBIFIDUS	3 186	4 779	35%	1 673	18%	2 221	0	2 221		222	222
BACTISUBTIL	702	1 053	35%	369	18%	489	0	489		49	49
KINESERYL	0	0	35%	0	18%	0	0	0		0	0
A2A1 ANTIACIDES SEULS	169 731	254 597	65%	165 488	36%	197 574	48 877	197 574		63 746	14 870
SMECTA	127 666	191 499	65%	124 474	36%	148 608	36 763	148 608		47 948	11 184
PHOSPHALUGEL	18 685	28 028	65%	18 218	36%	21 750	5 381	21 750		7 018	1 637
ROCGEL	16 502	24 753	65%	16 089	36%	19 209	4 752	19 209		6 198	1 446
MOXYDAR	2 211	3 317	65%	2 156	36%	2 574	637	2 574		830	194
ISUDRINE	1 805	2 708	65%	1 760	36%	2 101	520	2 101		678	158
SUPRALOX	1 726	2 589	65%	1 683	36%	2 009	497	2 009		648	151
ANTI H	657	986	65%	641	36%	765	189	765		247	58
GASTROPULGITE	313	470	65%	305	36%	364	90	364		118	27
GASTRALUGEL	110	165	65%	107	36%	128	32	128		41	10
MUCAL	56	84	65%	55	36%	65	16	65		21	5
ULFON	1	2	65%	1	36%	1	0	1		0	0
ALUMINIUM HYDR RPG	0	0	65%	0	36%	0	0	0		0	0
A7B0 ADSORBANTS INTESTINAUX	161 932	242 898	65%	157 884	31%	184 185	50 325	184 185		63 711	13 386
BEDELIX	65 366	98 049	65%	63 732	31%	74 349	20 314	74 349		25 718	5 403

ACTAPULGITE	31 497	47 246	65%	30 710	31%	35 825	9 789	35 825		12 392	2 604
CARBOLEVURE	28 135	42 203	35%	14 771	19%	20 102	0	20 102		2 010	2 010
KAOLOGEAIS	13 428	20 142	65%	13 092	31%	15 273	4 173	15 273		5 283	1 110
BOLINAN	9 256	13 884	65%	9 025	31%	10 528	2 877	10 528		3 642	765
KARAYAL	6 906	10 359	65%	6 733	31%	7 855	2 146	7 855		2 717	571
MUCIPULGITE	2 638	3 957	65%	2 572	31%	3 001	820	3 001		1 038	218
ACTICARBINE	2 481	3 722	35%	1 303	19%	1 773	0	1 773		177	177
MULKINE	1 674	2 511	65%	1 632	31%	1 904	520	1 904		659	138
NORGAGIL	458	687	65%	447	31%	521	142	521		180	38
SALICAIRINE	92	138	65%	90	31%	105	29	105		36	8
A7A0 ANTIINFECT INTESTINAUX	122 186	183 279	35%	64 148	14%	80 270	0	80 270		8 027	8 027
ERCEFURYL	85 146	127 719	35%	44 702	14%	55 936	0	55 936		5 594	5 594
PANFUREX GE	20 490	30 735	35%	10 757	14%	13 461	0	13 461		1 346	1 346
RICRIDENE	9 740	14 610	35%	5 114	14%	6 399	0	6 399		640	640
NIFUROXAZIDE RATIO	1 833	2 750	35%	962	14%	1 204	0	1 204		120	120
LUMIFUREX GE	1 554	2 331	35%	816	14%	1 021	0	1 021		102	102
COLIMYCINE	1 073	1 610	35%	563	14%	705	0	705		70	70
NIFUROXAZIDE RPG	722	1 083	35%	379	14%	474	0	474		47	47
NIFUROXAZIDE BAYER	504	756	35%	265	14%	331	0	331		33	33
NEOMYCINE DIAMANT	485	728	35%	255	14%	319	0	319		32	32
NIFUROXAZIDE IREX	288	432	35%	151	14%	189	0	189		19	19
GANIDAN	222	333	35%	117	14%	146	0	146		15	15
NIFUROXAZIDE GNR	99	149	35%	52	14%	65	0	65		7	7
NIFUROXAZIDE DAKOT	23	35	35%	12	14%	15	0	15		2	2
NIFUROXAZIDE MERCK	7	11	35%	4	14%	5	0	5		0	0
MANDOCARBINE	0	0	35%	0	14%	0	0	0		0	0
A2A7 A-FLAT.ET/OU CARM+A-PRDT	102 944	154 416	65%	100 370	32%	117 475	31 664	117 475		40 245	8 581
POLYKARAYA	82 723	124 085	65%	80 655	32%	94 399	25 444	94 399		32 340	6 896
PEPSANE	20 221	30 332	65%	19 715	32%	23 075	6 220	23 075		7 905	1 686
A5B0 HEPATOPROTEC.LIPOTROPES	91 225	136 838	35%	47 893	49%	91 364	0	91 364		9 136	9 136
CITR BETAINE UPSA	40 365	60 548	35%	21 192	49%	40 427	0	40 427		4 043	4 043
LEGALON	26 259	39 389	35%	13 786	49%	26 299	0	26 299		2 630	2 630
ARGININE	16 051	24 077	35%	8 427	49%	16 075	0	16 075		1 608	1 608
CITR BETAINE BEAUF	6 538	9 807	35%	3 432	49%	6 548	0	6 548		655	655
EPURAM	1 896	2 844	35%	995	49%	1 899	0	1 899		190	190
TIADILON	116	174	35%	61	49%	116	0	116		12	12
C5A2 ANTIHEMORROID.LOC.-CORT	71 471	107 207	35%	37 522	23%	53 477	0	53 477		5 348	5 348
PROCTOLOG	36 466	54 699	35%	19 145	23%	27 285	0	27 285		2 729	2 729
TITANOREINE	33 886	50 829	35%	17 790	23%	25 355	0	25 355		2 535	2 535
ANOREINE	1 119	1 679	35%	587	23%	837	0	837		84	84
A5A1 CHOLERETIQ.CHOLECYSTOKIN	56 417	84 626	35%	29 619	14%	37 306	0	37 306		3 731	3 731
CANOL	25 881	38 822	65%	25 234	23%	28 383	8 947	28 383		10 891	1 944
FLUBILAR	8 426	12 639	35%	4 424	14%	5 572	0	5 572		557	557
CHOPHYTOL	5 673	8 510	35%	2 978	14%	3 751	0	3 751		375	375
VIBTIL	5 551	8 327	35%	2 914	14%	3 671	0	3 671		367	367
CANTABILINE	5 017	7 526	35%	2 634	14%	3 317	0	3 317		332	332
HEPARGITOL	2 691	4 037	35%	1 413	14%	1 779	0	1 779		178	178
HEPADIAL	902	1 353	35%	474	14%	596	0	596		60	60
CEBERA	754	1 131	35%	396	14%	499	0	499		50	50
SULFARLEM	666	999	35%	350	14%	440	0	440		44	44
TRANSODDI	558	837	35%	293	14%	369	0	369		37	37
RELAXODDI	167	251	35%	88	14%	110	0	110		11	11
HEBUCOL	131	197	35%	69	14%	87	0	87		9	9
VANILONE	0	0	35%	0	14%	0	0	0		0	0
A2A2 ANTIFLATULENTS SEULS	39 950	59 925	35%	20 974	22%	29 727	0	29 727		2 973	2 973
CARBOSYLANE	37 419	56 129	35%	19 645	22%	27 843	0	27 843		2 784	2 784
POLYSILANE JOULLIE	2 531	3 797	65%	2 468	35%	2 933	740	2 933		960	219

POLYSILANE MIDY	0	0	65%	0	35%	0	0	0		0	0
A2B9 AUTRES ANTIULCEREUX	29 051	43 577	65%	28 325	55%	36 700	5 895	36 700		8 975	3 081
ULCAR	23 740	35 610	65%	23 147	55%	29 990	4 817	29 990		7 334	2 517
KEAL	4 980	7 470	65%	4 856	55%	6 291	1 010	6 291		1 539	528
SUCRALFATE RPG	314	471	65%	306	55%	397	64	397		97	33
SUCRALFATE GNR	17	26	65%	17	55%	21	3	21		5	2
A9A0 PROD DIGEST.ENZYMES INCL	24 188	36 282	35%	12 699	46%	23 610	0	23 610		2 361	2 361
ZYMOPLEX	19 824	29 736	35%	10 408	46%	19 350	0	19 350		1 935	1 935
PANCREAL	1 463	2 195	35%	768	46%	1 428	0	1 428		143	143
AMYLODIASTASE	1 341	2 012	35%	704	46%	1 309	0	1 309		131	131
ENTECET	740	1 110	35%	389	46%	722	0	722		72	72
AEROCID	408	612	35%	214	46%	398	0	398		40	40
FLAVIASTASE	395	593	35%	207	46%	386	0	386		39	39
PANCRELASE	18	27	35%	9	46%	18	0	18		2	2
A3C0 ASS.ANTISPASM+TRANQ.DIV	21 059	31 589	35%	11 056	19%	15 020	0	15 020		1 502	1 502
LIBRAX	16 657	24 986	35%	8 745	19%	11 880	0	11 880		1 188	1 188
VESADOL	4 403	6 605	35%	2 312	19%	3 140	0	3 140		314	314
G4B9 TS AUT.PROD.UROLOGIQUES	19 500	29 250	35%	10 238	12%	12 466	0	12 466		1 247	1 247
HEPANEPHROL	19 500	29 250	35%	10 238	12%	12 466	0	12 466		1 247	1 247
A2A4 A-ACID.+A-FLAT.OU CARMIN	17 209	25 814	65%	16 779	35%	19 940	5 034	19 940		6 525	1 491
GELOX	11 386	17 079	65%	11 101	35%	13 193	3 331	13 193		4 317	986
GASTRALGINE	4 939	7 409	65%	4 816	35%	5 723	1 445	5 723		1 873	428
CONTRACIDE	884	1 326	65%	862	35%	1 024	259	1 024		335	77
POLYSILANE REG MID	0	0	65%	0	35%	0	0	0		0	0
POLYSILANE REG UPS	0	0	65%	0	35%	0	0	0		0	0
A6A1 LAXATIFS EMOLLIENTS	13 785	20 678	35%	7 237	30%	11 253	0	11 253		1 125	1 125
LUBENTYL MAGNESIE	13 785	20 678	35%	7 237	30%	11 253	0	11 253		1 125	1 125
N7X0 AUT.PROD.ACTIFS SNC	10 814	16 221	65%	10 544	56%	13 711	2 152	13 711		3 307	1 156
GENESERINE 3	8 260	12 390	65%	8 054	56%	10 473	1 643	10 473		2 526	883
MESTINON	2 466	3 699	65%	2 404	56%	3 127	491	3 127		754	264
NEOSTIGMINE LAPHAL	88	132	65%	86	56%	112	18	112		27	9
A6A2 LAXATIFS DRASTIQUES	8 186	12 279	35%	4 298	33%	6 956	0	6 956		696	696
MODANE	6 874	10 311	35%	3 609	33%	5 841	0	5 841		584	584
REX DRG VEGETALES	1 312	1 968	35%	689	33%	1 115	0	1 115		111	111
A2A6 ANTIACIDES+AUTRES PRDTS.	6 205	9 308	35%	3 258	31%	5 127	0	5 127		513	513
ACIDRINE	4 203	6 305	35%	2 207	31%	3 473	0	3 473		347	347
MUTESA	2 002	3 003	65%	1 952	45%	2 429	492	2 429		686	194
LYCAON	0	0	65%	0	45%	0	0	0		0	0
A5C0 CHOLAGOGUE+HEPATOPROTEC.	2 955	4 433	35%	1 551	14%	1 949	0	1 949		195	195
NIVABETOL	1 220	1 830	35%	641	14%	805	0	805		80	80
ROMARINEX CHOLINE	1 138	1 707	35%	597	14%	751	0	751		75	75
ORNITAINE	474	711	35%	249	14%	313	0	313		31	31
DESINTEX-CHOLINE	123	185	35%	65	14%	81	0	81		8	8
J1X2 POLYMYXINES	2 852	4 278	35%	1 497	91%	4 017	0	4 017		402	402
COLIMYCINE	2 852	4 278	65%	2 781	95%	4 199	68	4 199		481	413
		0	65%	0						0	0
		0	65%	0	100%	0	0	0		0	0
A6A3 LAXATIFS AUGM.BOL FOECAL	1 280	1 920	35%	672	24%	968	0	968		97	97
NORMACOL BOURDAINE	1 280	1 920	35%	672	24%	968	0	968		97	97
A7H0 INHIB TRANSIT INTESTINAL	617	926	35%	324	34%	531	0	531		53	53
DIARSED	617	926	35%	324	34%	531	0	531		53	53
		0	35%	0	100%	0	0	0		0	0
		0	35%	0	100%	0	0	0		0	0
A3A0 ANTISPASM+ANTICHOL.SEULS	276	414	35%	145	20%	199	0	199		20	20
GENATROPINE	236	354	35%	124	20%	170	0	170		17	17
SPASMODEX	39	59	35%	20	20%	28	0	28		3	3
A2A3 ANTIACIDES AV.ANTISPASM.	128	192	35%	67	20%	92	0	92		9	9

GASTROPAX	128	192	35%	67	20%	92	0	92		9	9
A2C0 AUT.PRDT TROUBLES ESTOMA	71	107	35%	37	14%	47	0	47		5	5
MAGNESIE COMP LEHN	37	56	35%	19	14%	25	0	25		2	2
GASTROSEDYL	34	51	35%	18	14%	23	0	23		2	2
K1E1 SOLUTION STANDART	3	5	35%	2	86%	4	0	4		0	0
ARGININE GLUC V.F	3	5	35%	2	86%	4	0	4		0	0
J7C0 AUTRES VACCINS	0	0	35%	0	11%	0	0	0		0	0
AMPHO VACCINS	0	0	35%	0	11%	0	0	0		0	0
35% pneumo	1 113 285	1 669 928		1 085 453		1 242 450	366 409	0		454 013	87 604
R6A0 ANTIHISTAMINIQUES	892 712	1 339 068	65%	870 394	23%	978 246	309 276			376 173	66 897
ZYRTEC	367 723	551 585	65%	358 530	23%	402 956	127 396			154 952	27 556
CLARITYNE	282 513	423 770	65%	275 450	23%	309 582	97 875			119 046	21 171
VIRLIX	111 477	167 216	65%	108 690	23%	122 158	38 621			46 974	8 354
TELFAST	35 259	52 889	65%	34 378	23%	38 637	12 215			14 858	2 642
PRIMALAN	47 146	70 719	65%	45 967	23%	51 663	16 334			19 866	3 533
MIZOLLEN	40 107	60 161	65%	39 104	23%	43 950	13 895			16 900	3 005
POLARAMINE	7 693	11 540	65%	7 501	23%	8 430	2 665			3 242	576
DIMEGAN	773	1 160	65%	754	23%	847	268			326	58
ALLERGEFON	21	32	65%	20	23%	23	7			9	2
R3C2 ANTIINFL RESP N.S.V.GEN	50 599	75 899	65%	49 334	17%	53 899	18 856			22 361	3 504
ZADITEN	50 599	75 899	65%	49 334	17%	53 899	18 856			22 361	3 504
R3C1 ANTIINFLAM.RESP.N.S INH	49 886	74 829	65%	48 639	28%	55 942	16 189			20 164	3 975
TILADE	36 617	54 926	65%	35 702	28%	41 062	11 883			14 801	2 918
LOMUDAL	13 269	19 904	65%	12 937	28%	14 880	4 306			5 363	1 057
R3B2 XANTHINES V.GENERALE	47 913	71 870	65%	46 715	67%	63 584	7 102			12 750	5 648
EUPHYLLINE L.A.	22 443	33 665	65%	21 882	67%	29 783	3 327			5 972	2 646
TRENTADIL	9 503	14 255	65%	9 265	67%	12 611	1 409			2 529	1 120
THEOSTAT	8 546	12 819	65%	8 332	67%	11 341	1 267			2 274	1 007
DILATRANE	3 143	4 715	65%	3 064	67%	4 171	466			836	371
THEOLAIR LP	1 678	2 517	65%	1 636	67%	2 227	249			447	198
TEDRALAN	1 463	2 195	65%	1 426	67%	1 942	217			389	172
XANTHIUM LP	866	1 299	65%	844	67%	1 149	128			230	102
PLANPHYLLINE	191	287	65%	186	67%	253	28			51	23
THEOLAIR	80	120	65%	78	67%	106	12			21	9
THEOPEXINE	0	0	65%	0	67%	0	0			0	0
THEOPHYLLINE	0	0	65%	0	67%	0	0			0	0
R3A2 B2 STIMULANTS V GENERALE	44 464	66 696	65%	43 352	55%	56 196	9 000			13 720	4 720
OXEOL	29 344	44 016	65%	28 610	55%	37 087	5 940			9 054	3 115
BRICANYL LP	15 120	22 680	65%	14 742	55%	19 109	3 060			4 665	1 605
R7A0 STIMULANTS RESPIRATOIRES	13 229	19 844	65%	12 898	83%	18 686	992			2 761	1 769
VECTARION	13 229	19 844	65%	12 898	83%	18 686	992			2 761	1 769
V1A0 ALLERGENES	11 656	17 484	65%	11 365	24%	12 803	4 012			4 891	879
HYPOSTAMINE	11 181	16 772	65%	10 901	24%	12 281	3 849			4 692	843
ALLPYRAL	361	542	65%	352	24%	397	124			151	27
ASAD	114	171	65%	111	24%	125	39			48	9
R1A1 CORTIC.RHINOL.SS.ANTIINF	2 540	3 810	65%	2 477	23%	2 778	885			1 074	189
SOLUCORT	2 540	3 810	65%	2 477	23%	2 778	885			1 074	189
		0	65%	0	100%	0	0			0	0
		0	65%	0	100%	0	0			0	0
S2C0 PRDT OTOLOG CORT+ANTIINF	231	347	65%	225	21%	251	82			99	17
DESOCORT	231	347	65%	225	21%	251	82			99	17
R3X2 TS.AUT.BRONCHODILAT.,SYS	55	83	65%	54	38%	65	15			20	5
EPHEDROIDES	55	83	65%	54	38%	65	15			20	5
		0	65%	0	100%	0	0			0	0
		0	65%	0	100%	0	0			0	0
R3B1 XANTHINES, INHALANTS	0	0	65%	0	55%	0	0			0	0
THEOPHYLLINE	0	0	65%	0	55%	0	0			0	0

35 % hepato gastro	631 725	947 588		615 932		734 686	182 487	0		237 707	55 228
A3F0 GASTROPROKINETIQUES	361 248	541 872	65%	352 217	35%	418 757	105 527			136 850	31 323
PREPULSID	304 871	457 307	65%	297 249	35%	353 405	89 058			115 493	26 435
PRIMPERAN	53 379	80 069	65%	52 045	35%	61 877	15 593			20 221	4 628
PROKINYL	1 588	2 382	65%	1 548	35%	1 841	464			602	138
ANAUSIN	1 410	2 115	65%	1 375	35%	1 634	412			534	122
A2A1 ANTIACIDES SEULS	161 092	241 638	65%	157 065	36%	187 518	46 389			60 502	14 113
GAVISCON	143 276	214 914	65%	139 694	36%	166 779	41 259			53 811	12 552
TOPAAL	17 816	26 724	65%	17 371	36%	20 739	5 130			6 691	1 561
A2B3 PROSTAGLANDIN. ANTIULCER	65 795	98 693	65%	64 150	39%	77 725	17 972			23 948	5 975
CYTOTEC	65 795	98 693	65%	64 150	39%	77 725	17 972			23 948	5 975
A4A9 AUT.ANTIEMETIQ/ANTINAUS	37 785	56 678	65%	36 840	36%	44 002	10 865			14 179	3 314
VOGALENE	37 785	56 678	65%	36 840	36%	44 002	10 865			14 179	3 314
		0	65%	0	100%	0	0			0	0
		0	65%	0	100%	0	0			0	0
		0	65%	0	100%	0	0			0	0
		0	65%	0	100%	0	0			0	0
A3E0 ANTISPASM+AUTRES PRDTS.	5 668	8 502	65%	5 526	33%	6 513	1 705			2 185	481
METEOXANE	5 668	8 502	65%	5 526	33%	6 513	1 705			2 185	481
A5A2 ANTILITHIASIQUES	100	150	65%	98	58%	128	19			30	11
ARSACOL	87	131	65%	85	58%	111	17			26	9
DESTOLIT	12	18	65%	12	58%	15	2			4	1
C5A2 ANTIHEMORROID.LOC.-CORT	37	56	65%	36	36%	43	11			14	3
KINUREA	37	56	65%	36	36%	43	11			14	3
déremb pneumo	445 208	667 812		237 799		310 022	3 129	310 022		33 818	30 689
R5D2 AUTR.ANTITUSSIFS +ASSOC.	235 625	353 438	35%	123 703	14%	156 448	0	156 448		15 645	15 645
TOPLEXIL	82 285	123 428	35%	43 200	14%	54 635	0	54 635		5 463	5 463
NEO CODION	43 086	64 629	35%	22 620	14%	28 608	0	28 608		2 861	2 861
DIMETANE EXPECT	31 856	47 784	35%	16 724	14%	21 151	0	21 151		2 115	2 115
DENORAL	23 673	35 510	35%	12 428	14%	15 718	0	15 718		1 572	1 572
BIOCALYPTOL PHOLCO	23 041	34 562	35%	12 097	14%	15 299	0	15 299		1 530	1 530
TUSSISEDAL	9 494	14 241	35%	4 984	14%	6 304	0	6 304		630	630
NETUX	8 020	12 030	35%	4 211	14%	5 325	0	5 325		533	533
PULMOSERUM	4 868	7 302	35%	2 556	14%	3 232	0	3 232		323	323
NORTUSSINE	2 521	3 782	35%	1 324	14%	1 674	0	1 674		167	167
HEXAPNEUMINE	2 518	3 777	35%	1 322	14%	1 672	0	1 672		167	167
RECTOPLEXIL	2 417	3 626	35%	1 269	14%	1 605	0	1 605		160	160
PULMOSODYL	683	1 025	35%	359	14%	453	0	453		45	45
EPHYDION	521	782	35%	274	14%	346	0	346		35	35
PAXELADINE NOCTEE	435	653	35%	228	14%	289	0	289		29	29
CAMPHODIONYL	102	153	35%	54	14%	68	0	68		7	7
THERALENE	78	117	35%	41	14%	52	0	52		5	5
EPHEDROMEL	26	39	35%	14	14%	17	0	17		2	2
R3X2 TS.AUT.BRONCHODILAT.,SYS	81 423	122 135	35%	42 747	25%	62 368	0	62 368		6 237	6 237
PNEUMOREL	74 993	112 490	35%	39 371	25%	57 443	0	57 443		5 744	5 744
CALMIXENE	6 431	9 647	65%	6 270	38%	7 549	1 798	7 549		2 373	575
ASTHMASEDINE	0	0	65%	0	38%	0	0	0		0	0
R5D1 ANTITUSSIFS SEULS	55 493	83 240	35%	29 134	14%	36 695	0	36 695		3 669	3 669
HELICIDINE	51 658	77 487	35%	27 120	14%	34 159	0	34 159		3 416	3 416
PAXELADINE	3 835	5 753	35%	2 013	14%	2 536	0	2 536		254	254
R5F0 AUTRES ANTITUS+P BR.PULM	20 023	30 035	35%	10 512	15%	13 427	0	13 427		1 343	1 343
HEXAPNEUMINE	20 023	30 035	35%	10 512	15%	13 427	0	13 427		1 343	1 343
R5C0 EXPECTORANTS	17 128	25 692	35%	8 992	22%	12 617	0	12 617		1 262	1 262
FLUISEDAL	17 128	25 692	35%	8 992	22%	12 617	0	12 617		1 262	1 262
GAIARSOL	0	0	35%	0	22%	0	0	0		0	0
R5A0 PRDT BRONCHO-PULM -ANTIB	11 044	16 566	35%	5 798	19%	7 898	0	7 898		790	790
DENORAL	11 044	16 566	35%	5 798	19%	7 898	0	7 898		790	790

DEBAR SIROP	0	0	35%	0	19%	0	0	0		0	0
R6A0 ANTIHISTAMINIQUES	9 032	13 548	65%	8 806	23%	9 897	3 129	9 897		3 806	677
THERALENE	9 032	13 548	65%	8 806	23%	9 897	3 129	9 897		3 806	677
R1B0 PREP RHINOLOGIQUES V.GEN	8 328	12 492	35%	4 372	11%	5 295	0	5 295		529	529
HEXAPNEUMINE	8 328	12 492	35%	4 372	11%	5 295	0	5 295		529	529
J1B0 CHLORAMPHENICOL ET ASSOC	3 601	5 402	35%	1 891	36%	3 143	0	3 143		314	314
FLUIMUCIL ANTIBIOT	3 601	5 402	35%	1 891	36%	3 143	0	3 143		314	314
A12C2 AUTRES SUPPLEMENTS MINER	3 224	4 836	35%	1 693	12%	2 066	0	2 066		207	207
OLIGOSOL MN	3 224	4 836	35%	1 693	12%	2 066	0	2 066		207	207
R5B0 PRDTS PR FROID+ANTIINFEC	287	431	35%	151	6%	169	0	169		17	17
ISOMYRTINE	287	431	35%	151	6%	169	0	169		17	17
35 % psychiatrie 2ème phase	37 845	56 768		36 899		46 655	8 668	0		12 466	3 799
N5C0 TRANQUILLISANTS	25 929	38 894	65%	25 281	50%	32 129	5 798			8 431	2 633
ATRIUM	25 929	38 894	65%	25 281	50%	32 129	5 798			8 431	2 633
N6A0 ANTIDEPRESSEURS	11 916	17 874	65%	11 618	46%	14 526	2 869			4 035	1 166
PRAZINIL	11 916	17 874	65%	11 618	46%	14 526	2 869			4 035	1 166
déremb infectiologie	29 440	44 160		20 648		24 370	3 781	24 370		5 840	2 059
A12C2 AUTRES SUPPLEMENTS MINER	17 724	26 586	35%	9 305	12%	11 357	0	11 357		1 136	1 136
GRANIONS CUIVRE	17 724	26 586	35%	9 305	12%	11 357	0	11 357		1 136	1 136
J5B0 ANTIVIRAUX SAUF ANTI HIV	7 744	11 616	65%	7 550	28%	8 684	2 513	8 684		3 130	617
ISOPRINOSINE	7 744	11 616	65%	7 550	28%	8 684	2 513	8 684		3 130	617
G4A3 AUTRES ANTISEPTIQ.URIN.	1 165	1 748	65%	1 136	45%	1 410	290	1 410		402	112
NIBIOL	1 165	1 748	65%	1 136	45%	1 410	290	1 410		402	112
J1A0 TETRACYCLINES ET ASSOC.	1 143	1 715	65%	1 114	14%	1 197	443	1 197		519	75
AMPHOCYCLINE	1 106	1 659	65%	1 078	14%	1 159	429	1 159		502	73
TERRAMYC SOLU RET	37	56	65%	36	14%	39	14	39		17	2
J1F0 MACROLIDES ET APPARENTES	1 124	1 686	65%	1 096	20%	1 214	404	1 214		485	81
SPIRAM COQUELUSED	1 124	1 686	65%	1 096	20%	1 214	404	1 214		485	81
G1B0 ANTIFONGIQ.GYNECOLOGIQ.	346	519	65%	337	19%	371	127	371		151	24
AMPHOCYCLINE	346	519	65%	337	19%	371	127	371		151	24
A12C1 MAGNESIUM	178	267	35%	93	14%	117	0	117		12	12
IONARTHROL	178	267	35%	93	14%	117	0	117		12	12
J1E0 ASS AV TRIMETHOP.APPAR.	15	23	65%	15	42%	18	4	18		5	1
TRIMADIAZ ANTRIMA	15	23	65%	15	42%	18	4	18		5	1
T2X0 AUTRES TESTS DIAGNOSTICS	1	2	65%	1	6%	1	0	1		0	0
MULTITEST IMC	1	2	65%	1	6%	1	0	1		0	0
35 % infectiologie	19 666	29 499		19 174		24 289	4 466	0		6 448	1 982
J2A0 ANTIMYCOTIQUES V GENER	14 029	21 044	65%	13 678	52%	17 485	3 050			4 494	1 443
NIZORAL	13 428	20 142	65%	13 092	52%	16 736	2 920			4 301	1 382
ANCOTIL	601	902	100%	902	62%	902	0			289	289
J1C1 PENICIL.LARG.SPECT.US.OR	2 950	4 425	65%	2 876	19%	3 168	1 078			1 287	209
TOTAPEN	2 876	4 314	65%	2 804	19%	3 088	1 051			1 254	204
AMPICILLINE GNR	74	111	65%	72	19%	79	27			32	5
N4A0 ANTIPARKINSONIENS	1 728	2 592	65%	1 685	90%	2 498	81			322	242
MANTADIX	1 728	2 592	65%	1 685	90%	2 498	81			322	242
J1G1 FLUOROQUINOLONES ORALES	443	665	65%	432	42%	529	116			157	41
ZAGAM	443	665	65%	432	42%	529	116			157	41
J1C2 PENICIL.LARG.SPEC.INJECT	301	452	65%	293	55%	380	61			93	32
TOTAPEN	301	452	65%	293	55%	380	61			93	32
J7B1 VACCIN EN ASSOCIATION	120	180	65%	117	8%	122	50			57	7
VAC DT COQ MERIEUX	120	180	65%	117	8%	122	50			57	7
J1X9 AUT.ANTIBIOTIQUES	83	125	65%	81	32%	95	25			32	7
TROBICINE	83	125	65%	81	32%	95	25			32	7
J7A9 AUTRES VACCINS	12	18	65%	12	7%	12	5			6	1

Total deuxième phase	CAHT	PPTTC estimé	taux de remboursement actuel	montant théorique des remboursements	taux d'exonération TM estimé	montant réel des remboursements	économie passage à 35%	économie déremboursement	économie totale	économie passage à 35% et baisse des prix de 10%	économie supplémentaire liée à la baisse des prix
sans déremboursement (les déremboursé	5 332 095	7 998 143		3 866 484		4 791 899	730 132	0	730 132	1 136 309	406 177
proposition de la commission (déremboú	5 332 095	7 998 143		3 866 484		4 791 899	562 030	2 743 818	3 305 848		

ANNEXE III

A l'attention de Hervé Le Louët (4 pages)

En ce qui concerne la première vague, un SMR **insuffisant** a été attribué pour les classes suivantes :

1- les veinotoniques
2- les vasodilatateurs
3- les magnésiums
4- les sédatifs à base de plantes

1- Concernant les veinotoniques, ces prescriptions représentent 3,8% des ventes des spécialités remboursables ce qui représente un coût d'environ 1,6 milliard de francs pour les régimes d'assurance maladie.
L'estimation du nombre d'utilisateurs de ces produits est de 6 millions de personnes pour 18 millions de prescriptions par an.
Deux tiers des utilisateurs sont âgés de plus de 50 ans dont 80% sont des femmes.

2- Concernant les vasodilatateurs, ces prescriptions représentent 2,6% des ventes des spécialités remboursables ce qui représente un coût d'environ 2,7 milliards de francs pour les régimes d'assurance maladie.
L'estimation du nombre d'utilisateurs de ces produits est de 1,3 million de personnes pour 14 millions de prescriptions par an.
Plus de 90% des utilisateurs sont âgés de plus de 60 ans dont 55% sont des femmes.

3- Concernant les magnésiums, ces prescriptions représentent 0,7 % des ventes des spécialités remboursables ce qui représente un coût d'environ 0,3 milliard de francs pour les régimes d'assurance maladie.
Le nombre de prescriptions de ces produits est de 5,5 millions par an.
La plupart des utilisateurs ont entre 20 et 55 ans , dont 70% sont des femmes.

4- Concernant les sédatifs, ces prescriptions représentent 0,3 % des ventes des spécialités remboursables ce qui représente un coût d'environ 0,2 milliard de francs pour les régimes d'assurance maladie.
Le nombre de prescriptions de ces produits est de 2,6 millions par an.
La moitié des utilisateurs ont entre 20 et 55 ans , dont 76% sont des femmes.

NB : Il ne peut être procédé à une addition du nombre de personnes consommant les médicaments des deux premières classes pour laquelle cette information est disponible puisqu'une même personne peut consommer plusieurs de ces médicaments à la fois.

Pour les autres classes, le nombre d'utilisateurs des produits concernés n'a pu être estimé fautes de données sur les durées effectives de traitements et sur les renouvellements de prescription. De plus, l'ensemble des informations concernent en général des classes thérapeutiques pour lesquelles les posologies et conditionnements de chaque produit doivent être considérés pour ces estimations.

Les seules informations rapidement disponibles sont le nombre de prescriptions par an et les données de vente.

ANNEXE IV

Annexe 4-17

annexe IV

ELEMENTS POUR UNE LETTRE DE LA MINISTRE AUX MEDECINS ET AUX PHARMACIENS

Pour les informer des résultats de la réévaluation des médicaments et leur expliquer les conséquences qui vont en être tirées.

Une orientation essentielle de la politique du médicament conduite par le Gouvernement consiste, comme vous le savez, à s'assurer que la prise en charge collective des spécialités et son montant sont, pour chacune d'elles, justifiés par le service médical qu'elle rend au regard de son efficacité, de ses effets indésirables, de sa place dans les stratégies thérapeutiques et de la gravité des maladies soignées ou prévenues. C'est en effet l'une des conditions pour que, par ailleurs, les médicaments innovants puissent continuer à être rapidement remboursés par la sécurité sociale et ainsi mis à la disposition de tous les malades.

A cette fin, j'ai demandé à la commission de la transparence de procéder à une évaluation de l'ensemble des médicaments actuellement remboursables par l'assurance maladie afin d'en déterminer le niveau de service médical rendu. Ce travail sera achevé avant la fin de cette année, mais la commission m'a d'ores et déjà transmis l'avis qu'elle a rendu à l'issue de la première phase de ses travaux, qui ont porté sur les classes de médicaments suivantes : système cardiovasculaire, rhumatologie, métabolisme-nutrition et, pour partie, psychiatrie.

J'ai décidé de diffuser cet avis et il m'a paru naturel que les premiers destinataires de cette diffusion soient les médecins et les pharmaciens, comme étant à la fois les mieux qualifiés pour recevoir cette information et susceptibles de la prendre en compte, s'ils l'estiment justifié, dans leurs pratiques de prescription, de délivrance ou de conseil, étant bien entendu qu'il ne s'agit encore que d'un avis, mais que cet avis émane d'une commission impartiale, composée d'experts reconnus, et dont les travaux ont été conduits en toute indépendance de jugement.

Vous constaterez dans le document ci-joint que la commission de la transparence a classé les médicaments évalués selon cinq niveaux de service médical rendu : majeur, important, modéré, faible et insuffisant. Les quatre premiers niveaux n'appellent pas de commentaire particulier, et il est probable que ce classement recoupe, pour l'essentiel, votre propre jugement sur les médicaments concernés si l'on se réfère aux critères du service médical rendu tels que je les rappelais au début de cette lettre. Ce classement fondera désormais le niveau de prise en charge des médicaments remboursables par l'assurance maladie obligatoire.

En revanche, l'attribution à certains médicaments d'un niveau de service médical rendu insuffisant nécessite des explications. Il faut rappeler avant tout que ce classement ne signifie pas, contrairement à ce qui a pu être dit ici ou là, que les médicaments en question sont inutiles. Il s'agit de médicaments au plein sens du terme, qui ont reçu à ce titre une

autorisation de mise sur le marché, et pour lesquels il a donc été établi qu'ils exerçaient une action sur l'organisme et que leur rapport bénéfice-risque était favorable. Il peut certes se faire que, pour tel ou tel d'entre eux, le progrès des connaissances et celui des techniques d'évaluation amène aujourd'hui à considérer que sa mise à la disposition des malades ne se justifie plus, ou seulement pour des indications plus restreintes. Mais ce n'était pas la question posée à la commission de la transparence, et ce n'est donc pas le sens qu'il faut donner à son avis.

La question posée à la commission de la transparence était celle du niveau de service médical rendu au dessous duquel la prise en charge collective, par l'assurance maladie obligatoire, d'un médicament pourrait n'être pas justifiée. L'avis qu'elle a rendu répond à cette question dans le registre scientifique et technique qui est le sien.

Il appartient désormais à l'Etat de prendre les décisions, sur la base de cet avis, mais en intégrant également d'autres considérations d'ordre sanitaire, économique ou social. J'ai donc procédé à une large concertation, en particulier avec vos représentants des ordres ou des syndicats ainsi qu'avec les industriels du médicament et leurs représentants.

Il apparaît clairement, au terme de cette concertation, qu'un déremboursement immédiat et donc sans préparation de l'ensemble des médicaments concernés aurait des conséquences très préjudiciables à un grand nombre de malades. C'est vrai en particulier dans les cas où ces produits, bien que leur efficacité démontrée soit faible ou très faible, constituent aujourd'hui la moins mauvaise des réponses médicamenteuses possibles à des souffrances qui, elles, sont bien réelles.

Il demeure cependant indispensable de traduire dans les faits le processus de réévaluation engagé, dont les objectifs conservent toute leur pertinence. J'ai donc décidé de donner suite aux avis rendus par la commission de la transparence, mais de façon progressive, éventuellement sélective et en tenant le plus grand compte des opinions et des suggestions formulées par les représentants de vos professions.

De manière générale, les déremboursements proposés par la commission de la transparence seront différés pour ne prendre effet qu'au 31 décembre 2003. Je souhaite que ce temps soit mis à profit – et ce ne peut être que par votre concours et dans l'exercice de votre responsabilité- pour que la prescription de ces médicaments, au vu de l'information nouvelle qui résulte de l'avis, soit progressivement réduite pour se limiter aux indications les mieux établies.

De leur côté, les laboratoires pharmaceutiques qui le souhaiteront et qui l'estimeront possible pourront utiliser ce délai pour obtenir, sur la base de preuves nouvelles, une nouvelle évaluation de la commission de la transparence et justifier ainsi, au terme du délai fixé, le maintien de la prise en charge de certains de ces médicaments.

Afin cependant qu'il soit sans attendre tiré les premières conséquences de l'avis de la commission, sans préjudice pour les malades, au plan de la répartition des ressources collectives consacrées au médicament, il sera demandé aux entreprises de baisser les prix de ceux de leurs produits dont le service médical rendu a été considéré comme insuffisant.

Enfin, l'opportunité de dérembourser plus rapidement telle ou telle catégorie de médicaments sera examinée au cas par cas, en tenant compte notamment des considérations

médicales, économiques ou sociales qui peuvent justifier le passage de ces médicaments sur le marché dit de la médecine familiale ou de « l'automédication ».

ANNEXE IV

Annexe 4-17

MINISTERE DE L'EMPLOI
ET DE LA SOLIDARITE

REPUBLIQUE FRANCAISE

PARIS, le mercredi 8 mars 2000

DIRECTION GENERALE DE LA SANTE

LE DIRECTEUR GÉNÉRAL

LA/DC

00. 255

NOTE

Pour

Madame la ministre de l'emploi et de la solidarité

A l'attention de Monsieur Hervé LE LOUET

OBJET : Réévaluation des spécialités pharmaceutiques

Après l'avis de la Commission de transparence sur les spécialités jugées comme ayant un "SMR" insuffisant, il me semble important que des décisions soient prises assez rapidement car : l'absence de décision pourrait entraîner une perte de crédibilité importante pour tout le processus de réévaluation, avec des conséquences potentiellement sérieuses dans un contexte où la "menace" de déremboursement est souvent brandie vis à vis des firmes qui ne respecteraient pas leurs engagements pour de nouveaux produits.

1- Remarque sur les éléments d'évaluation

Trois remarques doivent être faites en préalable.

La Commission de transparence a attribué le même SMR, jugé "insuffisant", à toutes ces spécialités ; elle s'est basée pour cela, à juste titre, sur la qualité des dossiers scientifiques fournis par les firmes. Ceci ne peut être remis en question.

Mais derrière cette même « côte », se retrouvent des réalités parfois assez différentes,qui font qu'une mesure unique pour toutes les spécialités me semble difficilement envisageable. Des différences importantes existent à plusieurs niveaux :

1) la pathologie-cible des traitements alors que certaines de ces molécules s'adressent à des entités cliniques mal définies (ex : perte cognitive) ou très bénignes (problèmes cutanés), voire indéfinies (« fatigue ») d'autres sont censées apporter une contribution à la prise en charge des pathologies graves (artérites des membres inférieurs).

2) pour certains produits il n' existe pas d'alternative thérapeutiques bien documentées (certains troubles des artérites) ; dans certains cas, les alternatives sont plus dangereuses (benzodiazépines à la place de sédatifs mineurs), ou beaucoup plus chères, avec une efficacité discutable (traitement de l'Alzheimer pour les pertes cognitives). Se pose alors la question du report de prescriptions.

3) Niveau de preuve : un SMR peut avoir été jugé insuffisant soit parce que, malgré des études adéquates, la molécule n'a pas d'effet notable sur la santé, soit parce qu'aucune étude n'a été réalisée qui aurait permis de mettre en évidence de façon incontestable l'existence d'un effet. Ceci est souvent une question de moyens.

Ces trois éléments (pathologie-cible, alternatives thérapeutiques et niveau de preuve) peuvent orienter une politique modulée vis à vis de l'ensemble de ces molécules. En effet, une politique drastique, uniforme et brutale pourrait avoir des conséquences délétères en termes de service médical rendu, de coût, pouvant aboutir ainsi à l'inverse de l'effet recherché.

2 – Mesures envisageables :

Trois mesures peuvent être envisagées :

- la réduction du taux de remboursement
- la baisse de prix
- le déremboursement (immédiat ou à terme)

La réduction du taux de remboursement des spécialités qui bénéficient encore d'un taux élevé, ne peut s'envisager qu'accompagnée d'au moins une baisse des prix ou une prévision de déremboursement à moyen terme, afin de ne pas faire supporter le fardeau de cette mesure entièrement par les assurances complémentaires (mutuelles). Si ceci était acquis, aucun produit ne devrait avoir un remboursement supérieur à 35 % par l'assurance maladie, afin de bien marquer l'insuffisance de "SMR" notée par la Commission de transparence pour ces spécialités.

Une baisse de prix de l'ordre de 25 à 30 % (7 à 8 % par an en moyenne) est sans doute acceptable pour une large gamme de produits. Cette baisse aboutirait sans doute au retrait (du remboursement) de molécules à faible marché, mais celles largement utilisées – et donc couvrant une vaste population – devraient la supporter.

Le déremboursement devrait être annoncé immédiatement et de façon claire, avec une application soit à court terme (1 an) soit dans un délai de 3 ans, selon les spécialités, en fonction des critères définis plus haut. Les molécules bénéficiant d'un délai, auraient ainsi une possibilité de recours en cas d'élément nouveau justifiant une réévaluation du SMR (au moins une nouvelle étude incontestable pour pouvoir prétendre à une réévaluation dans 3 ans). Ceci donnerait le temps aux molécules à SMR jugées insuffisantes par manque de preuve de faire appel de cette décision par la mise en place d'études appropriées. Le délai de 3 ans ne devrait s'adresser qu'aux molécules répondant à l'un des critères suivants : i) pathologie sérieuse ; ii) pas d'alternative ou report de prescription probable plus coûteux ou plus dangereux.

3 - **Mise en place**

La fixation du remboursement à 35 % devrait se faire après information des principales mutuelles, en montrant que la baisse de prix et le déremboursement à terme se traduit par un gain probable pour elles. Cela ne concerne que peu de molécules, la plupart des spécialités réévaluées étant déjà à ce niveau de remboursement.

La baisse de prix doit s'accompagner de la définition de critères simples :

- baisse modérée pour les produits les moins chers de la classe
- alignement des autres prix sur ceux des produits les moins chers de la classe
- volume

Le déremboursement à court terme (1 an) ou à moyen terme (3 ans) peut être décidé classe par classe ou par grande catégorie de produits, en appliquant les critères proposés plus haut. La DGS peut rapidement (1 mois) procéder à une proposition à cette classification avec quelques experts.

Il faut noter la nécessité de prévoir des mesures d'accompagnement pour le déremboursement éventuel :

- information des médecins et des patients (DGS/AFSSAPS/CFES)
- "toilettage" de certaines AMM pour permettre l'automédication dans certains cas
- éventuellement vérification de certains textes
- guides de bonnes pratiques (AFSSAPS/ANAES/DGS)

Le directeur général de la santé

Professeur Lucien ABENHAIM

Ministère de l'Emploi
et de la Solidarité

Le Conseiller

Annexe 4-17

RÉPUBLIQUE FRANÇAISE

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NOTE

A l'attention de Madame la Ministre
S/C de Monsieur Pierre-Louis BRAS
Directeur-adjoint du Cabinet

OBJET : Politique du médicament. Préparation de la réunion des Ministres et préparation de la réunion avec le SNIP.

Compte tenu du dépassement des dépenses consacrées au médicament par rapport à l'objectif fixé, des propositions ont été discutées en réunion interministérielle avec le Ministère de l'Economie, des Finances et de l'Industrie sur la base du document joint (annexe I).

I – CONSEQUENCES A TIRER DE LA REEVALUATION DE L'ENSEMBLE DES CLASSES THERAPEUTIQUES

Vous avez proposé que deux types de mesures soient prises :

➢ *des mesures à terme :*

- déremboursement à terme de 2 ou 3 ans des médicaments dont le SMR est insuffisant. Cette mesure aurait un impact sur environ 10 % du chiffre d'affaires de l'industrie pharmaceutique (9,16 MdF) ;

- passage de 65 % à 35 % des médicaments à SMR modéré ou faible (sauf les vasodilatateurs). Cette mesure pénalisante pour la mutualité et les assurés génèrera un gain de 2 MF.

➢ *des mesures immédiates :*

- baisse d'environ 7 % par an sur 3 ans (soit 20 % au total) pour les médicaments à SMR insuffisant. Le gain généré peut être estimé à 500 MF en année pleine. Une baisse de 10% par an est très largement négociable avec le SNIP ;

- passage de 65 % à 35 % de la classe des vasodilatateurs : gain généré 600 MF.

Le MEFI émet un avis favorable sur ces mesures, estimant que le coût industriel est tolérable. En effet, celui-ci considère que ces mesures ne feront qu'accélérer la recomposition nécessaire du tissu industriel dans le domaine pharmaceutique. Il évoque toutefois la possibilité de fermeture de quelques usines, dont les plus significatives sont celles de Beaufour à Dreux, et de Negma à Quimper (800 emplois au total). A cet égard vous trouverez, en annexe II, l'impact des déremboursements et des baisses de taux sur les principaux laboratoires ainsi que les sites d'implantations.

C'est en raison de ce risque que nous avions décidé de ne procéder à des déremboursements qu'au terme de 2 à 3 ans, et ce, afin de laisser aux entreprises concernées la possibilité de se reconvertir ou de préparer le passage à l'automédication.

Néanmoins, ceci n'exclut pas des situations difficiles, voire des fermetures de sites.

II – LE DURCISSEMENT DE LA CLAUSE DE SAUVEGARDE (annexe III)

Nous avons proposé une augmentation de barème de la clause de sauvegarde afin d'en augmenter le rendement. Du fait de l'effet seuil, la sécurité sociale récupère aujourd'hui, de manière aléatoire, entre 60 et 30 % du dépassement.

Le MEFI semble favorable au principe d'un tel durcissement.

Cette démarche comporte un risque réel vis-à-vis de la politique conventionnelle.

Si nous durcissons le barème de la clause de sauvegarde, nous pourrions donner instruction au président de CEM d'établir un système de remise, certes plus élevé que celui en vigueur, mais plus avantageux que la clause de sauvegarde. En effet, actuellement, les instructions données au président du CEM consistent à récupérer en remises conventionnelles au moins ce qu'aurait rapporté l'application de la cause de sauvegarde. Ainsi, si nous décidons d'établir un barème allant jusqu'à un taux de récupération de 80 % du dépassement, l'objectif à atteindre dans le cadre des remises conventionnelles pourrait s'établir à 70 %. Il y aurait donc intérêt pour les industriels à passer une convention.

Pour M. RENAUDIN, un tel objectif de 80 % est trop élevé (risque de rejet de toute politique conventionnelle, forte contestation des laboratoires

étrangers...). Il pense que le maximum que nous puissions imposer pour la clause de sauvegarde est 70 %, avec un écart de 20 % pour le dispositif conventionnel, soit 50 %.

Les diverses hypothèses sont décrites en annexe III

Il semble que dans un premier temps, nous pouvons maintenir une position dure vis-à-vis de l'industrie pharmaceutique pour donner des garanties à l'assurance maladie. Les Finances devraient jouer leur rôle d'avocat des laboratoires.

Pour apprécier la rigueur du mécanisme, si un taux de récupération de 80 % est élevé, il faut tenir compte du fait que les objectifs pour l'année n+1 sont rebasés, et que l'industrie pharmaceutique engrange en potentiel de chiffre d'affaires les dépassement de l'année n.

L'hypothèse de M.RENAUDIN est toutefois un point d'arrivée acceptable, le rendement pour la sécurité sociale est plus sûr (on obtient dans toutes les hypothèses 50 % de récupération). Les pertes par rapport au dispositif actuel sont limitées à quelques situations (cf. annexe III).

III – LA MAITRISE DES ACTIONS PROMOTIONNELLES ET LA MISE EN PLACE D'UN SYSTEME D'INFORMATION DESTINE AUX MEDECINS

Considérant que la politique du Gouvernement en matière de médicament est trop centrée sur l'offre et que nous atteignons les limites du faisable, le MEFI s'est prononcé positivement sur un renforcement de la maîtrise de la demande.

Ainsi, une modification de la loi anti-cadeau a été insérée dans le projet de loi de modernisation du système de santé. La nouveauté consiste à ne plus uniquement sanctionner les praticiens, comme cela est le cas actuellement mais de sanctionner également les industriels.

De plus, le principe d'une augmentation de la taxe promotionnelle a également fait l'objet d'un accord. Nous avons évoqué une augmentation de 30 % de la taxe actuelle, qui rapporte 1,2 MdF, soit 400 MF.

Enfin nous travaillons actuellement à définir une structure visant à informer les médecins sur le bon usage des soins et à concurrencer la promotion des laboratoires. Cette mission serait confiée à l'AFSSAPS. D'ores et déjà, et selon les premières concertations, un budget de 100 MF est à prévoir. Cette structure pourrait être financée par les recettes générées par l'augmentation de la taxe promotionnelle.

IV - DIVERS

Enfin, le MEFI a plaidé pour deux types de mesures supplémentaires :

- le conditionnement de l'évolution du revenu des praticiens au respect d'une enveloppe de prescription. Ceci reviendrait à remettre en cause les principes adoptés lors de la LFSS 2000 ;

- l'adoption d'un remboursement forfaitaire par classe thérapeutique. Sur ce dernier point, les exemples étrangers (allemand et hollandais) ne sont guère concluants, et en tout cas difficilement applicables en France. Nous avons reçu l'aval du cabinet du premier ministre sur le refus d'une telle démarche.

CONCLUSION

Les mesures qui vous sont proposées sont évidemment maximales. Ceci vous laisse ainsi toute marge de manœuvre dans la pondération que vous voudrez leur apporter lors de leur négociation avec le SNIP.

Hervé LE LOUËT

ANNEXE I

MEDICAMENT

I - Evolution des dépenses depuis 1997

	REGIME GENERAL (%)	TOUS REGIMES (%)
1997	5,1	4,7
1998	8,1	7,7
1999	6,3	5,9
1er trimestre 2000 *	11,5	11,1
Prévisions 2000	6 – 6,5	5,6 – 6,1

* Les résultats élevés du premier trimestre sont essentiellement liés à l'épidémie de grippe et de gastro-entérite ainsi qu'au 31 décembre 1999.

La croissance française des ventes de médicaments de prescription en officine, en 1999, reste la plus faible des grands pays industrialisés : 5 %. Elle est de 6 % en Allemagne, 9 % en Italie, 10 % au Royaume-Uni, 11 % en Espagne et 16 % en Amérique du Nord.

Une progression de 6 % des dépenses de médicaments par rapport à un objectif fixé à 2 % entraîne un dépassement d'environ 3 MdF. La clause de sauvegarde ou les remises conventionnelles permettent de récupérer environ 1 MdF de ce dépassement (1,2 MdF en 1999, 0,9 MdF en 2000). Mais les nouveaux objectifs étant fixés par rapport au réalisé, le dépassement est acquis pour l'industrie pharmaceutique les années ultérieures.

Cette croissance des dépenses correspond à une tendance de fond (innovation thérapeutique, produits plus coûteux), comme le démontre l'évolution des autres pays. Est-elle justifiée ? Mais il est vrai que nous consommons en France plus que nos voisins (antidépresseurs, antibiotiques...). Les veinotoniques, par exemple, sont une spécificité française puisque nous consommons 70 % du marché mondial. La part du médicament dans les dépenses de santé est élevée en France : 18 % contre 10 % aux Etats-Unis et 14 % en Allemagne.

Ainsi, un certain nombre de mesures correctrices doivent être adoptées.

II - Réévaluation

L'accès au remboursement des médicaments a été réformé par le décret du 27 octobre 1999. Les critères d'accès au remboursement ne sont plus fondés sur la seule gravité de la pathologie, mais sur le service médical rendu. Ce dernier prend en compte les effets indésirables du médicament, sa place dans la stratégie thérapeutique, notamment au regard des autres thérapies disponibles, la gravité de l'affection à laquelle le médicament est destiné, ainsi que le caractère préventif, curatif ou symptomatique du traitement médicamenteux et son intérêt pour la santé publique.

V - Réforme de la loi anti-cadeaux

Actuellement, la loi anti-cadeaux (article L.365.1 du code de la santé publique), qui limite la possibilité pour une firme d'agir directement et financièrement sur le prescripteur, s'applique essentiellement à l'encontre du professionnel de santé, l'entreprise pharmaceutique ne pouvant être poursuivie qu'indirectement à titre de complicité. Cet article ne permet pas de poursuivre directement l'entreprise et donc de regrouper l'ensemble des plaintes relatives à une même opération de promotion. Ainsi, un article visant à poursuivre directement le laboratoire en cause sera proposé dans le cadre de la loi sur la modernisation du système de santé.

VI - Dispositif d'information sur les prescriptions

Le développement d'une politique d'information publique est d'autant plus indispensable que l'on sait que tout contrôle de la promotion ne pourra jamais être que partiel. Il faut, dès lors, qu'une information objective puisse se substituer à l'information commerciale diffusée par les entreprises. Actuellement, deux outils sont en vigueur : la diffusion des fiches de transparence et le guide des équivalents thérapeutiques de la CNAMTS. Bien évidemment, la CNAMTS se doit de prendre ses responsabilités dans le domaine de l'information des prescripteurs. Toutefois, la possibilité de mettre en place un dispositif pour informer les prescripteurs d'une façon indépendante de toute promotion pharmaceutique est à l'étude.

Annexe 4-17

AB-VB-EN- 8/6/00

Mesures relatives au médicament

Propositions du MEFI en vue de la réunion interministérielle du 9 juin 2000

Le médicament figure régulièrement parmi les postes en plus forte croissance au sein des dépenses d'assurance maladie (+8,1 % en 1998 et +6,3 % en 1999 pour le régime général). Avec près de 90 MdsF, il représente 30 % des dépenses de soins de ville.

Certes, la croissance des dépenses de médicament est également forte dans les autres pays développés, du fait notamment de la mise sur le marché de médicaments innovants. Cependant, au-delà de l'effet des mesures prises depuis 1997 pour maîtriser la dépense de médicaments, l'augmentation récente moins forte en France que dans les pays comparables s'explique principalement par les facteurs intrinsèques suivants :

- importance du poste en volume absolu, ce qui limite la croissance relative, mais sans remettre en cause pour l'instant la position peu enviable de la France, deuxième derrière les Etats Unis pour ce qui est de la dépense de médicament par habitant ;
- diminution tendancielle des ventes de certains produits anciens (veinotoniques, vasodilatateurs), qui représentent en France des dépenses importantes, à la différence des autres pays, ce qui permet de peser sur l'évolution d'ensemble ;
- lenteur relative à l'entrée sur le marché de produits nouveaux, comparativement à nos partenaires.

Le poste médicament est caractérisé par un encadrement complet de l'offre par les pouvoirs publics : prix fixés administrativement, clauses de révision prix-volume par produits, clause de sauvegarde en cas de dépassement, encadrement et taxation spécifique de la promotion. Il demeure cependant en rapide évolution, ce qui appelle des mesures portant également sur la prescription.

La présente note passe en revue les principaux axes d'action envisageables, et en premier lieu la responsabilisation des prescripteurs (infra I). Elle examine ensuite les propositions du MES dans sa note du 29 mai 2000 (infra II et III), centrées pour l'essentiel sur un renforcement de l'encadrement de l'offre. Elle propose enfin d'agir sur la maîtrise des coûts de distribution (infra IV).

Par ailleurs, le MEFI considère toujours que la mise en œuvre de prix de référence (remboursement forfaitaire par classe thérapeutique) est une mesure structurante susceptible de générer des économies importantes grâce à une amélioration de la concurrence entre

laboratoires. Elle permettrait de limiter l'intervention critiquée des pouvoirs publics dans la fixation systématique des prix. A court terme, il est possible d'expérimenter la mise en œuvre de prix de référence sur certaines classes spécifiques (cf. fiche jointe). Dans un deuxième temps, une extension aux classes où existent des génériques est souhaitable. Cette extension devra intervenir une fois engrangés les effets de la substitution. Une troisième phase consistera à généraliser à l'ensemble des classes adaptées à ce mode de régulation.

I. Responsabilisation des prescripteurs

1 - Une maîtrise structurelle des dépenses de médicament ne peut se passer d'une action sur les prescripteurs

a) Une action portant uniquement sur l'industrie pharmaceutique ne permet pas d'agir efficacement sur le volume de la consommation, dont le niveau élevé caractérise la France

Le marché français se caractérise d'abord par le niveau élevé et la progression de la consommation *en volume*. Ainsi, si la France est le deuxième pays en matière de dépense par habitant, elle a connu une stagnation du niveau des prix relatifs des médicaments compensée par une forte progression de la dépense en volume (cf. annexe 1).

Or, si les laboratoires pharmaceutiques sont en mesure d'influencer le comportement des prescripteurs grâce aux actions de promotion, les politiques de régulation qui leur sont appliquées demeurent d'un effet limité sur le volume de la consommation. Elles se traduisent essentiellement par une réduction ou une limitation des prix, et par le versement de contributions qui compensent en recettes les dépassements observés mais sont sans impact sur le niveau des dépenses publiques.

b) Les exemples de nos partenaires étrangers tendent à montrer que la maîtrise des dépenses de médicament repose sur la combinaison de la régulation de l'offre et d'une responsabilisation des prescripteurs et des patients.

Ainsi, au Royaume-Uni comme en Allemagne, la responsabilisation des prescripteurs (médecins) a été recherchée par la fixation de cibles d'évolution des dépenses combinée à des outils de maîtrise médicalisée incitant à réduire le coût des prescriptions (lignes directrices, information des médecins…). La responsabilisation des patients a quant à elle pris la forme du remboursement forfaitaire en Allemagne et, dans ces deux pays, d'un relèvement significatif des franchises de remboursement (cf. annexe 2).

c) La révision de la liste des médicaments remboursables, réforme la plus porteuse d'économies à terme, doit être accompagnée d'actions de sensibilisation des prescripteurs et des patients afin d'éviter des reports de prescriptions vers des médicaments maintenus au remboursement et plus coûteux sans être nécessairement plus efficaces pour l'indication considérée.

2 – De nouvelles modalités de responsabilisation et de sensibilisation des médecins doivent donc être mises en place

a) La responsabilité première des médecins en matière de prescriptions devrait être réaffirmée par la mise en place d'enveloppes-cibles de prescriptions

La définition d'enveloppes opposables aux médecins en matière de prescriptions répond à la nécessité de réaffirmer que la responsabilité des médecins, mais également de la CNAMTS, ne se limite pas au respect des objectifs fixés en matière d'honoraires (qui ne représentent que 30% des dépenses générées par les médecins) mais porte également sur l'ensemble des prescriptions.

Elle vise ainsi à inciter les partenaires conventionnels à mettre en œuvre tous les moyens disponibles afin de limiter les prescriptions inutiles et de réduire le coût des prescriptions. Elle constitue en particulier un moyen puissant de favoriser, en même temps que d'encadrer, la conclusion des accords de « bon usage des soins », introduits par la loi de financement de la sécurité sociale pour 2000 et qui peuvent fixer des objectifs quantifiés d'évolution de certaines dépenses et prévoir les modalités selon lesquelles les médecins peuvent percevoir une partie du montant des dépenses évitées par la mise en œuvre de l'accord. Les dépenses de médicament constituent à l'évidence un champ d'action privilégié pour la mise en place de tels accords.

Concrètement, il pourrait s'agir soit d'établir un objectif de dépenses médicales englobant honoraires et prescriptions et se substituant à l'objectif de dépenses d'honoraires déjà prévu par la LFSS, soit d'un objectif portant uniquement sur les prescriptions et s'ajoutant à l'enveloppe d'honoraires. Cette seconde solution s'inscrit mieux dans la continuité du dispositif mis en place par la LFSS 2000.

L'objectif de dépenses de prescriptions serait déterminé annuellement dans les annexes aux conventions médicales ou à défaut dans les « mesures » des caisses, dans le respect de l'objectif prévisionnel des dépenses de soins de ville. Le suivi de ces dépenses serait effectué, comme pour l'objectif d'honoraires, tous les quatre mois et donnerait lieu, le cas échéant, à la mise en œuvre d'actions destinées à en assurer le respect (définition de RMO, de recommandations, actions d'évaluation, et conclusion d'accords de bon usage des soins).

Sans revenir à un dispositif de reversement en cas de dépassement, qui pénalise les médecins sur des dépenses qui ne constituent pas pour eux un revenu, les médecins seraient financièrement incités au respect de cet objectif par la conditionnalité des revalorisations d'honoraires au respect de cet objectif de prescriptions. Il s'agirait en quelque sorte d'une sanction positive. Une proposition en ce sens figure en annexe 3.

Le caractère collectif de cette « sanction », conforme à la logique qui sous-tend de manière générale le dispositif de régulation mis en place par la LFSS 2000, ne doit pas faire oublier qu'elle constitue d'abord une incitation à recourir à d'autres outils, qui peuvent être davantage ciblés sur certains types de dépenses ou certaines régions (accords de bon usage de soins notamment), voire sur certains individus (contrats de bonne pratique, sanctions en cas de non respect des références médicales opposables,...).

b) Le respect de ces objectifs devrait être facilité par le renforcement des outils de maîtrise médicalisée à la disposition des caisses et des médecins

Le développement de l'information sur les prescriptions à destination des médecins vise à les sensibiliser au rapport coût / efficacité de leurs prescriptions. La mise en place d'un dispositif d'information objective et indépendante sur les médicaments, envisagée par le ministère de l'emploi et de la solidarité, est souhaitable mais ne constitue qu'un des axes à envisager. Elle devrait être complétée par la transmission aux médecins, selon une périodicité régulière, d'informations individualisées sur leurs prescriptions de médicaments et de comparaisons de ces données individuelles avec un profil de prescription théorique en fonction de l'aire géographique ou des caractéristiques de leur clientèle. De ce point de vue, les informations aujourd'hui transmises aux médecins grâce aux RIAP (relevés individuels d'activité des praticiens) sont encore très incomplètes : elles restent très agrégées (médicaments non décomposés par classes, pas d'information sur les génériques...) et ne permettent la comparaison qu'avec une moyenne départementale. La mise en œuvre aujourd'hui effective du codage devrait permettre d'enrichir considérablement leur qualité.

La possibilité donnée aux médecins de prescrire en Dénomination Commune Internationale (DCI) favoriserait un développement plus rapide du marché des génériques. Elle pourrait être associée, pour les pharmaciens, à l'obligation de délivrer un générique en cas de prescription en DCI. La formation des médecins devrait être aménagée en ce sens.

Ultime recours à la disposition des caisses, les moyens de contrôle et de sanctions doivent être simplifiés et renforcés. En priorité, les sanctions en cas de non-respect des références médicales opposables (RMO), dont le dispositif a été annulé par le Conseil d'Etat en 1999, doivent être rétablies sur des bases juridiques plus solides. Au-delà, une réforme d'ensemble des procédures relatives aux contrôles et aux sanctions des professionnels devra être envisagée pour remédier aux blocages (comités médicaux régionaux) constatés aujourd'hui.

II. Réévaluation des spécialités

L'avis rendu par la Commission de la transparence sur les spécialités réévaluées a mis en lumière un service médical rendu (SMR) insuffisant pour justifier le remboursement, pour environ le quart des produits examinés. Ces avis ont été rendus publics et largement médiatisés. Le Gouvernement est donc en situation de prendre des mesures pour donner suite à ces avis.

La proposition du MES consiste à atteindre graduellement une situation où toutes les spécialités de SMR insuffisant seraient déremboursées, et les taux de remboursement portés à 35 % pour les spécialités de SMR faible ou moyen.

Il paraît souhaitable d'organiser cette évolution en deux temps, comme le propose le MES.

A. Une première étape consisterait à baisser en deux temps (été 2000 et été 2001) les prix des spécialités de SMR insuffisant et à porter les taux de remboursement à 35 % sur les seuls vaso-dilatateurs.

Cette disposition est rentable pour l'assurance-maladie et équilibrée pour les patients ou les organismes complémentaires, les baisses de prix compensant la baisse du niveau de remboursement. Cette dernière est d'autre part rendue moins délicate par la CMU pour les ménages les plus modestes.

L'impact de ce premier train de mesures sera concentré sur les laboratoires à capitaux français, de toute taille, dont il affectera la rentabilité. Affaiblissant principalement les laboratoires petits et moyens, il accélérera la concentration du secteur, où plusieurs rachats de laboratoires ont déjà eu lieu - Logeais, Théramex, Doms Adrian, Bouchara. Cette évolution du tissu industriel est naturelle, du fait du niveau très élevé des tickets d'entrée et de maintien sur le marché pharmaceutique.

Cette première étape serait donc politiquement peu sensible envers les patients et acceptable pour les laboratoires.

B. Une deuxième étape consisterait à dérembourser l'ensemble des spécialités de SMR insuffisant. Cette mesure pourrait être annoncée dès l'été 2000, pour prendre effet trois ans plus tard.

Il est souhaitable de s'engager dans cette voie afin d'initier une gestion plus dynamique que par le passé du panier de soins remboursables (sortie des produits inefficaces d'un point de vue thérapeutique, meilleur remboursement des soins dentaires ou des lunettes,...). Cependant, compte tenu de l'impact sur les patients (nombre important de consommateurs des produits appelés à être déremboursés) et de l'effet sur certains laboratoires français, cette deuxième étape est plus sensible que la précédente.

S'agissant de l'industrie pharmaceutique, il est souhaitable que la démarche soit annoncée au départ, donnant aux laboratoires la visibilité nécessaire pour gérer une transition difficile. En effet, ce deuxième train de mesures touchera fortement les laboratoires familiaux, mais certains d'entre eux peuvent y résister et ont un certain potentiel pour demeurer des acteurs significatifs de l'industrie pharmaceutique. Il conviendra donc, pendant la période qui précédera et suivra le déremboursement, de veiller à limiter les autres mesures susceptibles de toucher ces laboratoires, afin que leur affaiblissement ne soit que passager. Le déremboursement devrait conduire par ailleurs à la disparition de nombreux laboratoires français petits et moyens, qui n'auraient pas été auparavant rachetés par des laboratoires plus importants. Le déremboursement des produits issus de ces laboratoires n'incitera pas au maintien de leurs capacités de production par leurs éventuels acheteurs. Plusieurs fermetures d'usines sont donc à prévoir, les plus significatives étant celles de Beaufour à Dreux et de Negma à Quimper (environ 400 emplois chacune).

Afin de lisser quelque peu ces effets, il serait possible d'instaurer des forfaits de remboursement par classe pour certains de ces produits, à des niveaux relativement bas, en repoussant à une troisième étape le déremboursement définitif.

Le Gouvernement continuerait ainsi à prendre en charge ces pathologies, tout en affichant pour elles un budget limité de l'assurance maladie. Le marché se réorganiserait rapidement au profit des laboratoires capables de fournir les produits les moins chers. Il convient de noter que cette alternative devrait faire l'objet de dispositions législatives.

III. Les autres mesures ciblées sur l'industrie pharmaceutique

1 - Durcissement de la clause de sauvegarde

Le niveau de la clause de sauvegarde a un impact direct sur le conventionnement des laboratoires, le niveau de retour qu'elle fixe étant considéré comme le rendement à atteindre

par l'ensemble des conventions. En 1999, l'exercice conventionnel a pu être bouclé pour assurer un retour de 900 MF environ. La signature de conventions, outre sa cohérence avec l'orientation prise par le Gouvernement en 1998, simplifie les relations avec les laboratoires et permet des négociations assez libres, sans grand risque de harcèlement juridique de la part des laboratoires. Elle implique aussi l'adhésion des laboratoires au mécanisme de régulation par classes thérapeutiques, qui permet de répartir les retours selon les familles de produits et leur progression respective.

Le durcissement du barème de la clause de sauvegarde conduirait le Comité Economique à négocier des remises plus importantes avec les laboratoires pour respecter l'objectif de rendement égal qui lui a été donné. Les laboratoires pourraient alors s'interroger sur le bien fondé de signer une convention. Dans l'hypothèse où les quelques laboratoires en forte croissance qui assurent l'essentiel de la progression du marché signeraient des conventions, il s'avérerait beaucoup plus économique pour les autres entreprises d'être soumis au régime de la clause de sauvegarde. En effet, les ventes des autres laboratoires progressant peu, ce sont les taux les plus bas de la clause qui s'appliqueraient à cette population.

Outre qu'elle romprait l'équilibre souhaité par le Gouvernement en 1998, cette configuration conduirait à une perte financière importante pour l'assurance maladie. Comme en témoigne l'exemple de l'année 1999, ces comportements stratégiques n'apparaissent pas pour des remises de l'ordre de 20 à 30 millions de francs mais pourraient se produire si elles atteignaient 50 MF.

Dans l'hypothèse où les opérateurs anticiperaient des niveaux très élevés de remises et un échec du jeu conventionnel, il est à craindre que cela ne conduise les entreprises à stimuler leur effort de vente pour anticiper cette taxation, ce qui n'est souhaitable ni pour les patients, ni pour l'assurance maladie.

2 - Maîtrise des actions promotionnelles

L'impact effectif d'une augmentation de la taxe sur la promotion réalisée par les laboratoires n'est pas prouvé, notamment dès lors que certaines dépenses peuvent être transférées à l'étranger par les laboratoires internationaux.

Il s'agit d'une mesure peu structurante, qui ne peut être soutenue qu'en raison de son impact financier immédiat positif pour l'assurance maladie.

Par ailleurs, il est envisagé de modifier l'article L. 365-1 CSP pour permettre de poursuivre directement les laboratoires auteurs de pratiques répréhensibles au titre de cette disposition. Cette disposition peut modifier le comportement des parquets, qui hésitent actuellement à poursuivre les professionnels de santé à ce titre. On peut donc en attendre une modification des comportements. Une expertise complémentaire de la mesure serait toutefois souhaitable, afin d'anticiper de possibles contournements par les professionnels et les laboratoires.

IV. Maîtrise des coûts de distribution

Le circuit de distribution pharmaceutique intervient pour environ le tiers du poste médicament de l'assurance maladie. L'accord de stabilisation de la marge signé en 1999 avec les officinaux n'a pas été respecté, la marge des officines ayant cru de 900 MF. Le caractère structurellement dynamique de la marge des officines conduit à envisager des mesures de maîtrise des coûts de distribution.

En effet, la réforme de la marge des pharmaciens, décidée en 1999, était encadrée par un engagement ferme de stabilité en valeur absolue de la marge 1999 à son niveau constaté en 1998 : cet engagement, acté par le cabinet du Premier ministre, figure explicitement dans le protocole d'accord signé par les pharmaciens.

En réalité, en raison de l'accélération des dépenses de médicaments, et du caractère beaucoup plus dynamique de la nouvelle marge des pharmaciens, cette dernière a atteint 29,1 MdF en 1999, soit une augmentation de 900MF (dont 250 MF dus à la seule réforme de la marge, sur 4 mois).

Pour l'assurance-maladie, le surcoût de la dérive de la marge peut être évalué, pour 1999, à 780MF, avec un acquis sur 2000 de 810MF, compte tenu des effets de la déformation de la structure de remboursement des médicaments. Si l'on déduit l'impact lié au développement des génériques et à la réduction de la marge des grossistes, le surcoût net pour la sécurité sociale reste de 760 MF au titre de 1999 et 2000.

Par ailleurs, les enquêtes menées par la DGCCRF en 1999 ont permis de constater que les grossistes répartiteurs faisaient systématiquement bénéficier leurs clients pharmaciens de remises au moins égales au plafond légal de 2,5% du prix facturé aux pharmaciens, sans compter les remises supérieures pour les génériques (10,74% du prix fabricant) et les escomptes pour paiement comptant.

Compte tenu de ces éléments et de l'accord passé avec les pharmaciens, un montant de 900 MF pourrait être récupéré par l'une des mesures ci-après :

1. Réduction du forfait par unité de conditionnement de 30 centimes (2,7 Md d'unités remboursables vendues).

2. Diminution de la marge des grossistes de 1,1 point (soit l'équivalent de 900MF), qui devraient, au moins partiellement, être répercutés sur les remises que les grossistes accordent aux pharmaciens.

Le contexte (annonce d'un dispositif de maîtrise du poste médicament de l'assurance maladie) semble propice pour engager une telle mesure. En l'absence d'un bilan suffisant à ce jour de la substitution par les pharmaciens au profit des génériques, il est sans doute prématuré d'engager une action directe sur la marge des officinaux. C'est pourquoi une action immédiate doit de préférence porter sur une diminution de la marge des grossistes répartiteurs (proposition 2). Cette diminution, à hauteur de 1,1 point, représenterait moins de la moitié du niveau actuel des remises qu'ils accordent.

Le poids de cette réduction pèsera soit sur les seuls grossistes s'ils sont en mesure d'accroître leur productivité ou d'altérer leur rentabilité, soit sur les pharmaciens si les grossistes répercutent en tout ou partie la diminution de leur marge sur le niveau des remises qu'ils accordent. Ne visant pas directement les officines, cette mesure rendra plus difficile une réaction publique des pharmaciens.

Annexe 4-17

FICHE

SIMULATION DE REMBOURSEMENT FORFAITAIRE

Les exemples de remboursement forfaitaire présentés ici ont été établis à partir du coût de traitement journalier moyen des produits les moins chers inscrits dans la classe concernée et représentant une part significative des ventes en jours de traitement.

Les prix de vente fabricant sont libres, à la hausse ou à la baisse. En revanche, pour que les efforts consentis par les laboratoires pour rapprocher le prix de leur produit du forfait de remboursement ne soient pas compensés par une hausse corrélative des coûts de distribution, il n'est pas envisagé de libérer les marges des grossistes et des pharmaciens.

Sur chaque unité de conditionnement devra figurer le prix de vente au public ainsi que le forfait de remboursement, qui serait égal au coût de traitement journalier de la classe multipliée par le nombre de jours de traitement qui est fonction du dosage et du nombre d'unités contenus dans la présentation de la spécialité.

Sur les classes les plus anciennes, on peut escompter une limitation progressive du nombre de produits en concurrence, au bénéfice des moins chers. La baisse des prix de vente moyens ainsi que le nombre réduit de concurrents conduira à une diminution de la pression promotionnelle et à de là une baisse des prescription, facteur supplémentaire d'économie pour l'assurance maladie.

LES VEINOTONIQUES CO5C

Le coût de traitement journalier moyen des veinotoniques est actuellement de 2,11 F en prix PFHT avec des écarts maximum de 3,40 F (1,5 % des jours de traitement) à 1,15 (7,20 % des jours de traitement).

Sur la base d'un forfait de remboursement de 1,90 F par jour de traitement (les ventes en volume de produits dont le CTJ est égal ou inférieur à 1,90 F représentent 16,4 % des jours de traitement dans la classe) l'économie pour la sécurité sociale est de 160 MF.

Sur la base d'un forfait de remboursement de 1,60 F par jour de traitement (les ventes en volume des produits dont le CTJ est égal ou inférieur à 1,60 F représentent 15 % des jours de traitement dans la classe) l'économie pour la sécurité sociale est de 390 MF.

Sur la base de 1,30 F (11 % des jours de traitement) l'économie sécurité sociale est de 620 MF.

LES VASODILATATEURS

Le coût de traitement journalier moyen des VASODILATATEURS est actuellement de 2.40 F en prix PFHT avec des écarts maximum de 5.42 F (0.7 % des jours de traitement) à 0.3F (0.4 % des jours de traitement).

Sur la base d'un forfait de remboursement de 1,50 F par jour de traitement (les ventes en volume de produits dont le CTJ est égal ou inférieur à 1,50 F représentent 12% des jours de traitement dans la classe) l'économie pour la sécurité sociale est de 515 MF.

CONTRACEPTIFS ORAUX

1/ SITUATION ACTUELLE

Seules les pilules de 1ère et 2ème génération sont actuellement prises en charge par l'assurance maladie. Le coût de traitement journalier (CTJ) de ces dispositifs est de 0,44 F en moyenne, en prix fabricant hors taxes (PFHT).

Les ventes des contraceptifs oraux, dont le CTJ est égal ou inférieur à 0,26 F, représentent, en jours de traitement, près de 17 % du marché des pilules remboursables.

Avant la hausse demandée aux pouvoirs publics par Wyeth Lederlé pour ADEPAL et MINIDRIL en 1998 et 1999, le CTJ moyen de la classe était de 0,33 F. Les ventes de spécialités à un CTJ égal ou inférieur à 0,26 F représentaient alors 60 % des jours de traitement.

2/ REMBOURSEMENT FORFAITAIRE

a) Hypothèse sans extension du champ de remboursement

En instaurant, dans cette classe, le remboursement forfaitaire sur la base d'un CTJ de 0,26 F, le coût pour l'assurance maladie des pilules de 1ère et 2ème génération passerait de 335 MF à 197 MF (soit une économie de près de 140 MF) (voir hypothèse H1 ci-joint).

b/ Hypothèse avec extension du remboursement aux pilules de 3ème génération

La mise en place du remboursement forfaitaire dans la classe des contraceptifs oraux pourrait être l'occasion d'ouvrir au remboursement les pilules de 3ème génération dont le CTJ moyen (prix PFHT) est actuellement de 1,27 F.

Le forfait de remboursement de l'ensemble des contraceptifs oraux pourrait, dans cette hypothèse, être fixé à 0,50 F : les ventes en volume de produits dont le CTJ est égal ou inférieur à 0,50 F représentent 92 % des ventes de spécialités remboursables et 58 % de l'ensemble des contraceptifs remboursables et contraceptifs de 3ème génération.

Le surcoût pour l'assurance maladie de cette opération serait limité à 270 MF alors que, dans les chiffrages actuels les plus optimistes, les propositions des différents laboratoires conduisent à un surcoût de plus de 500 MF pour la prise en charge complète de cette classe.

Même à prix fabricant hors taxe inchangés, les spécialités de 3ème génération bénéficieraient du plafonnement de la marge des intermédiaires, ainsi que d'un taux de TVA ramené de 5,5 % à 2,1%. La prise en charge de la pilule de 3ème génération induirait donc d'emblée une économie pour les consommatrices de plus de 40 %, à laquelle viendrait s'ajouter le remboursement du forfait.

ANNEXE 2

LA REGULATION DES DEPENSES PHARMACEUTIQUES

Allemagne, Royaume-Uni et France

	Allemagne	Royaume-Uni	France
Régulation de l'industrie pharmaceutique	- prix libres mais remboursement sur la base de prix de référence, couvrent 60% du marché	- contrôle des profits : taux de bénéfice autorisé négocié entre l'administration et l'industrie pour chaque entreprise ; remises ou baisse de prix en cas de dépassement. - fixation administrative du prix des génériques	- fixation des prix par voie conventionnelle (industrie, comité économique du médicament) ou à défaut administrative - clause de régulation : objectif annuel de chiffre d'affaires dont le dépassement déclenche l'application d'une taxation collective, ou la mise en œuvre de remises et de baisses de prix individualisées pour les laboratoires conventionnés
Responsabilisation des prescripteurs	- information des médecins sur leurs écarts de prescription par rapport à la moyenne. - lignes directrices encadrant la pratique, élaborées conjointement avec les médecins. - politique d'enveloppe : enveloppe médicaments dont le non-respect est sanctionné par des retenues sur honoraires de 93 à 97 (difficilement appliquée) ; réforme 2000 : enveloppes maintenues mais ajustements non automatiques.	- mécanisme de transmission d'informations sur les prescriptions mis en place en 1976 : relevé périodique adressé aux médecins comparant leurs prescriptions à celles d'un cabinet théorique ayant une clientèle comparable. - enveloppes-cibles de dépenses de médicaments (pas de sanction en cas de dépassement).	*- références médicales opposables (RMO) introduites en 1994 :* ***sanctions annulées*** *par le Conseil d'Etat* *- 1997-1998 : enveloppes opposables de prescriptions, dont le dépassement devait donner lieu à reversement ;* ***suppression en LFSS 2000.***
Responsabilisation des patients	- remboursement sur la base des prix de référence pour 60 % des médicaments. - franchise par boîte (relevée au cours des années 90 : de 4 à 8 DM par boîte selon le conditionnement) pour tous les médicaments. Exonération des populations en difficulté.	- franchise par boîte (£ 5,6 par boîte) ; 50% de la population exonérée (80% des médicaments prescrits)	*- ticket modérateur différencié (0%, 35%, 65%) selon les médicaments,* ***mais pris en charge par les mutuelles ou la CMU.***

Annexe 3

REGULATION DES DEPENSES DE SOINS DE VILLE

INTRODUCTION D'UN OBJECTIF DE PRESCRIPTIONS

1) Retrait du dispositif général des dispositions relatives aux médecins

A l'article L.162-15-2, supprimer au premier alinéa du I les mots « L.162-5 ».

Au 1° du I, supprimer les mots « un objectif étant fixé pour les médecins généralistes d'une part et pour les médecins spécialistes d'autre part »

Au 2°, supprimer les mots « les médecins et ».

2) Dispositif propre aux médecins : proposition de rédaction d'un article L.162-5-3 nouveau :

I – Chaque année, dans le respect de l'objectif prévisionnel des dépenses de soins de ville et de l'objectif de dépenses déléguées mentionnés au II de l'article L.227-1, une annexe à la ou aux conventions prévues à l'article L.162-5 fixe, pour les médecins généralistes d'une part et pour les médecins spécialistes d'autre part :

1° L'objectif de dépenses d'honoraires, incluant les dépenses d'honoraires, rémunérations et frais accessoires. Cet objectif s'applique à compter du 1er janvier de l'année civile concernée et porte sur les dépenses remboursables par les régimes d'assurance maladie, maternité, invalidité et accidents du travail ;

2° L'objectif de dépenses de prescriptions. Cet objectif s'applique à compter du 1er janvier de l'année civile concernée et porte sur les dépenses remboursables par les régimes d'assurance maladie, maternité, invalidité et accidents du travail ;

3° Les tarifs des honoraires, rémunérations et frais accessoires dus aux médecins par les assurés sociaux, en dehors des cas de dépassement autorisés par la convention.

4° Le cas échéant, les mesures de toute nature propres à garantir le respect des objectifs fixés et notamment :

a) Toute action visant à réduire le volume des actes **et prescriptions** non justifiés au plan médical et notamment les actions d'information, de promotion des références professionnelles opposables et des recommandations de bonne pratique ou d'évaluation des pratiques ;

b) Les modifications, dans la limite de 20% de la cotation des actes inscrits à la nomenclature établie pour les actes pris en charge par l'assurance maladie auxquelles les parties à la convention peuvent procéder.

A défaut de convention, et après consultation des syndicats représentatifs, ou à défaut d'annexe pour l'une des conventions, la Caisse nationale de l'assurance maladie des travailleurs salariés et au moins une autre caisse nationale signataire de la convention déterminent les éléments de l'annexe visés au 1°, 2°, 3° et 4°.

II – Les parties à la ou aux conventions effectuent le suivi des dépenses lors de la fixation des objectifs mentionnés au 1° et au 2° du I, et au moins deux fois dans l'année, une première fois au vu des résultats des quatre premiers mois de l'année, et une seconde fois au vu des résultats des huit premiers mois de l'année.

A défaut de convention, la Caisse nationale de l'assurance maladie des travailleurs salariés et au moins une autre caisse nationale d'assurance maladie assurent ce suivi et consultent les syndicats représentatifs.

1) Lorsqu'elles constatent que l'évolution des dépenses d'honoraires n'est pas compatible avec le respect de l'objectif fixé en application du 1° du I, les parties à la ou aux conventions déterminent, par une annexe modificative, les mesures de toute nature propres à garantir son respect et notamment celles prévues au 4° ainsi que, le cas échéant, les ajustements des tarifs prévus au 3°du I.

A défaut de mesures proposées par les parties conventionnelles ou en l'absence de convention, après consultation des syndicats représentatifs et lorsque le montant des dépenses réalisées n'est manifestement pas de nature à permettre le respect de l'objectif fixé, la Caisse nationale de l'assurance maladie des travailleurs salariés et au moins une autre caisse nationale signataire de la convention concernée déterminent les mesures prévues à l'alinéa précédent.

En cas de carence des caisses nationales ou lorsqu'il apparaît que les mesures proposées au titre des quatre alinéas précédents ne sont manifestement pas de nature à permettre le respect de l'objectif des dépenses, un arrêté interministériel fixe les tarifs et mesures mentionnés au 3° et 4°(b) du I.

2) Lorsqu'elles constatent que l'évolution des dépenses de prescriptions n'est pas compatible avec le respect de l'objectif fixé en application du 2° du I, les parties à la ou aux conventions déterminent les mesures de toute nature propres à favoriser son respect, et notamment celles prévues au a) du 4° du I et la conclusion d'accords de « bon usage des soins » prévus à l'article L.162-12-17.

Une revalorisation d'honoraires ne peut être accordée que si l'objectif d'évolution des dépenses de prescriptions de l'année précédente a été respecté.

3) Prise en compte de ces modifications dans l'article relatif à l'approbation des annexes annuelles

A l'article L.162-15-3, les références à l'article L.162-15-2 doivent être remplacées par des références aux articles L.162-5-3 et L.162-15-2.

4) Prise en compte de l'objectif de dépenses médicales pour la conclusion des ABUS

A la fin de la première phrase de l'article L. 162-12-17 (« un ou des accords de « bon usage de soins » peuvent être conclus… »), ajouter les mots **« dans le respect de l'objectif de dépenses de prescriptions mentionné au I de l'article L. 162-5-3 »**.

ANNEXE 2

Annexe 4-17

LA REGULATION DES DEPENSES PHARMACEUTIQUES

Allemagne, Royaume-Uni et France

	Allemagne	Royaume-Uni	France
Régulation de l'industrie pharmaceutique	- prix libres mais remboursement sur la base de prix de référence, couvrent 60% du marché	- contrôle des profits : taux de bénéfice autorisé négocié entre l'administration et l'industrie pour chaque entreprise ; remises ou baisse de prix en cas de dépassement. - fixation administrative du prix des génériques	- fixation des prix par voie conventionnelle (industrie, comité économique du médicament) ou à défaut administrative - clause de régulation : objectif annuel de chiffre d'affaires dont le dépassement déclenche l'application d'une taxation collective, ou la mise en œuvre de remises et de baisses de prix individualisées pour les laboratoires conventionnés
Responsabilisation des prescripteurs	- information des médecins sur leurs écarts de prescription par rapport à la moyenne. - lignes directrices encadrant la pratique, élaborées conjointement avec les médecins. - politique d'enveloppe : enveloppe médicaments dont le non-respect est sanctionné par des retenues sur honoraires de 93 à 97 (difficilement appliquée) ; réforme 2000 : enveloppes maintenues mais ajustements non automatiques.	- mécanisme de transmission d'informations sur les prescriptions mis en place en 1976 : relevé périodique adressé aux médecins comparant leurs prescriptions à celles d'un cabinet théorique ayant une clientèle comparable. - enveloppes-cibles de dépenses de médicaments (pas de sanction en cas de dépassement).	*- références médicales opposables (RMO) introduites en 1994 :* ***sanctions annulées*** *par le Conseil d'Etat* *- 1997-1998 : enveloppes opposables de prescriptions, dont le dépassement devait donner lieu à reversement ;* ***suppression en LFSS 2000.***
Responsabilisation des patients	- remboursement sur la base des prix de référence pour 60 % des médicaments. - franchise par boîte (relevée au cours des années 90 : de 4 à 8 DM par boîte selon le conditionnement) pour tous les médicaments. Exonération des populations en difficulté.	- franchise par boîte (£ 5,6 par boîte) ; 50% de la population exonérée (80% des médicaments prescrits)	*- ticket modérateur différencié (0%, 35%, 65%) selon les médicaments,* ***mais pris en charge par les mutuelles ou la CMU.***

Sur la base d'un forfait de remboursement de 1,50 F par jour de traitement (les ventes en volume de produits dont le CTJ est égal ou inférieur à 1,50 F représentent 12% des jours de traitement dans la classe) l'économie pour la sécurité sociale est de 515 MF.

CONTRACEPTIFS ORAUX

1/ SITUATION ACTUELLE

Seules les pilules de 1ère et 2ème génération sont actuellement prises en charge par l'assurance maladie. Le coût de traitement journalier (CTJ) de ces dispositifs est de 0,44 F en moyenne, en prix fabricant hors taxes (PFHT).

Les ventes des contraceptifs oraux, dont le CTJ est égal ou inférieur à 0,26 F, représentent, en jours de traitement, près de 17 % du marché des pilules remboursables.

Avant la hausse demandée aux pouvoirs publics par Wyeth Lederlé pour ADEPAL et MINIDRIL en 1998 et 1999, le CTJ moyen de la classe était de 0,33 F. Les ventes de spécialités à un CTJ égal ou inférieur à 0,26 F représentaient alors 60 % des jours de traitement.

2/ REMBOURSEMENT FORFAITAIRE

a) Hypothèse sans extension du champ de remboursement

En instaurant, dans cette classe, le remboursement forfaitaire sur la base d'un CTJ de 0,26 F, le coût pour l'assurance maladie des pilules de 1ère et 2ème génération passerait de 335 MF à 197 MF (soit une économie de près de 140 MF) (voir hypothèse H1 ci-joint).

b/ Hypothèse avec extension du remboursement aux pilules de 3ème génération

La mise en place du remboursement forfaitaire dans la classe des contraceptifs oraux pourrait être l'occasion d'ouvrir au remboursement les pilules de 3ème génération dont le CTJ moyen (prix PFHT) est actuellement de 1,27 F.

Le forfait de remboursement de l'ensemble des contraceptifs oraux pourrait, dans cette hypothèse, être fixé à 0,50 F : les ventes en volume de produits dont le CTJ est égal ou inférieur à 0,50 F représentent 92 % des ventes de spécialités remboursables et 58 % de l'ensemble des contraceptifs remboursables et contraceptifs de 3ème génération.

Le surcoût pour l'assurance maladie de cette opération serait limité à 270 MF alors que, dans les chiffrages actuels les plus optimistes, les propositions des différents laboratoires conduisent à un surcoût de plus de 500 MF pour la prise en charge complète de cette classe.

Même à prix fabricant hors taxe inchangés, les spécialités de 3ème génération bénéficieraient du plafonnement de la marge des intermédiaires, ainsi que d'un taux de TVA ramené de 5,5 % à 2,1%. La prise en charge de la pilule de 3ème génération induirait donc d'emblée une économie pour les consommatrices de plus de 40 %, à laquelle viendrait s'ajouter le remboursement du forfait.

Annexe 4-17

FICHE

SIMULATION DE REMBOURSEMENT FORFAITAIRE

Les exemples de remboursement forfaitaire présentés ici ont été établis à partir du coût de traitement journalier moyen des produits les moins chers inscrits dans la classe concernée et représentant une part significative des ventes en jours de traitement.

Les prix de vente fabricant sont libres, à la hausse ou à la baisse. En revanche, pour que les efforts consentis par les laboratoires pour rapprocher le prix de leur produit du forfait de remboursement ne soient pas compensés par une hausse corrélative des coûts de distribution, il n'est pas envisagé de libérer les marges des grossistes et des pharmaciens.

Sur chaque unité de conditionnement devra figurer le prix de vente au public ainsi que le forfait de remboursement, qui serait égal au coût de traitement journalier de la classe multipliée par le nombre de jours de traitement qui est fonction du dosage et du nombre d'unités contenus dans la présentation de la spécialité.

Sur les classes les plus anciennes, on peut escompter une limitation progressive du nombre de produits en concurrence, au bénéfice des moins chers. La baisse des prix de vente moyens ainsi que le nombre réduit de concurrents conduira à une diminution de la pression promotionnelle et à de là une baisse des prescription, facteur supplémentaire d'économie pour l'assurance maladie.

LES VEINOTONIQUES CO5C

Le coût de traitement journalier moyen des veinotoniques est actuellement de 2,11 F en prix PFHT avec des écarts maximum de 3,40 F (1,5 % des jours de traitement) à 1,15 (7,20 % des jours de traitement).

Sur la base d'un forfait de remboursement de 1,90 F par jour de traitement (les ventes en volume de produits dont le CTJ est égal ou inférieur à 1,90 F représentent 16,4 % des jours de traitement dans la classe) l'économie pour la sécurité sociale est de 160 MF.

Sur la base d'un forfait de remboursement de 1,60 F par jour de traitement (les ventes en volume des produits dont le CTJ est égal ou inférieur à 1,60 F représentent 15 % des jours de traitement dans la classe) l'économie pour la sécurité sociale est de 390 MF.

Sur la base de 1,30 F (11 % des jours de traitement) l'économie sécurité sociale est de 620 MF.

LES VASODILATATEURS

Le coût de traitement journalier moyen des VASODILATATEURS est actuellement de 2.40 F en prix PFHT avec des écarts maximum de 5.42 F (0.7 % des jours de traitement) à 0.3F (0.4 % des jours de traitement).

En effet, la réforme de la marge des pharmaciens, décidée en 1999, était encadrée par un engagement ferme de stabilité en valeur absolue de la marge 1999 à son niveau constaté en 1998 : cet engagement, acté par le cabinet du Premier ministre, figure explicitement dans le protocole d'accord signé par les pharmaciens.

En réalité, en raison de l'accélération des dépenses de médicaments, et du caractère beaucoup plus dynamique de la nouvelle marge des pharmaciens, cette dernière a atteint 29,1 MdF en 1999, soit une augmentation de 900MF (dont 250 MF dus à la seule réforme de la marge, sur 4 mois).

Pour l'assurance-maladie, le surcoût de la dérive de la marge peut être évalué, pour 1999, à 780MF, avec un acquis sur 2000 de 810MF, compte tenu des effets de la déformation de la structure de remboursement des médicaments. Si l'on déduit l'impact lié au développement des génériques et à la réduction de la marge des grossistes, le surcoût net pour la sécurité sociale reste de 760 MF au titre de 1999 et 2000.

Par ailleurs, les enquêtes menées par la DGCCRF en 1999 ont permis de constater que les grossistes répartiteurs faisaient systématiquement bénéficier leurs clients pharmaciens de remises au moins égales au plafond légal de 2,5% du prix facturé aux pharmaciens, sans compter les remises supérieures pour les génériques (10,74% du prix fabricant) et les escomptes pour paiement comptant.

Compte tenu de ces éléments et de l'accord passé avec les pharmaciens, un montant de 900 MF pourrait être récupéré par l'une des mesures ci-après :

1. Réduction du forfait par unité de conditionnement de 30 centimes (2,7 Md d'unités remboursables vendues).

2. Diminution de la marge des grossistes de 1,1 point (soit l'équivalent de 900MF), qui devraient, au moins partiellement, être répercutés sur les remises que les grossistes accordent aux pharmaciens.

Le contexte (annonce d'un dispositif de maîtrise du poste médicament de l'assurance maladie) semble propice pour engager une telle mesure. En l'absence d'un bilan suffisant à ce jour de la substitution par les pharmaciens au profit des génériques, il est sans doute prématuré d'engager une action directe sur la marge des officinaux. C'est pourquoi une action immédiate doit de préférence porter sur une diminution de la marge des grossistes répartiteurs (proposition 2). Cette diminution, à hauteur de 1,1 point, représenterait moins de la moitié du niveau actuel des remises qu'ils accordent.

Le poids de cette réduction pèsera soit sur les seuls grossistes s'ils sont en mesure d'accroître leur productivité ou d'altérer leur rentabilité, soit sur les pharmaciens si les grossistes répercutent en tout ou partie la diminution de leur marge sur le niveau des remises qu'ils accordent. Ne visant pas directement les officines, cette mesure rendra plus difficile une réaction publique des pharmaciens.

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Le Monde

Le gouvernement renonce à supprimer le remboursement des médicaments « inutiles »

LES DIFFÉRENTS MINISTÈRES chargés de la politique du médicament procédaient, dans la matinée de jeudi 7 juin, aux derniers ajustements concernant le « plan médicament » qu'Elisabeth Guigou, ministre de l'emploi et de la solidarité, et Bernard Kouchner, ministre délégué à la santé, devaient rendre public le même jour en fin d'après-midi, à l'issue de la réunion de la commission des comptes de la Sécurité sociale. Les mesures présentées devraient permettre d'obtenir, d'emblée, des économies annuelles comprises entre 2,2 et 2,5 milliards de francs pour un secteur correspondant à des remboursements de 95 milliards par les régimes d'assurance-maladie. Au vu des arbitrages rendus ces derniers jours, et dont les milieux pharmaceutiques ont pu prendre connaissance, il apparaît que le gouvernement a, en définitive, renoncé à prendre une mesure drastique et spectaculaire concernant les médicaments dont les experts estiment qu'ils ne fournissent pas la preuve d'une efficacité – un « *service médical rendu* » (SMR) – suffisante pour pouvoir être pris en charge par la collectivité.

Travaillant depuis plus de deux ans, à la demande du gouvernement, les experts de la commission de transparence de l'Agence de sécurité sanitaire des produits de santé avaient établi une liste de 835 spécialités pharmaceutiques pour lesquelles le SMR était, à leurs yeux, notoirement insuffisant (*Le Monde* du 2 juin). Ces médicaments, souvent qualifiés d'« *inutiles* », remboursés à hauteur de 65 % ou de 35 % par les caisses génèrent un chiffre d'affaires de l'ordre de 10 milliards de francs. Ils ne devraient faire l'objet que de mesures de baisses de prix qui devraient conduire à une économie globale, en année pleine, entre 800 millions et 1 milliard de francs. Contrairement à la volonté affichée par Martine Aubry lorsqu'elle était à la tête du ministère de la solidarité, le gouvernement n'a pas choisi de mettre en œuvre une réelle et profonde réforme du système de remboursement des spécialités pharmaceutiques.

L'objectif de cette réforme visait en effet à obtenir que les taux de remboursement des médicaments ne soient, à l'avenir, explicitement fondés que sur la qualité du SMR, ce qui, en toute logique sanitaire, conduisait à ne pas faire supporter à la collectivité le coût des médicaments dont les fabricants ne pouvaient apporter aux experts la démonstration scientifique de leur efficacité. Le chantage à l'emploi exercé auprès du gouvernement par les laboratoires directement concernés – souvent de petites tailles et indépendants des multinationales pharmaceutiques –, ainsi que l'impact négatif présumé qu'aurait eu une mesure radicale de déremboursement des 835 spécialités visées, expliquent la décision prudente du gouvernement.

Pour autant, sans remettre en question la politique conventionnelle, le plan annoncé par Mme Guigou et M. Kouchner comporte un certain nombre d'innovations qui devraient permettre d'obtenir un encadrement des dépenses caractérisées par une rapide progression (+ 10,7 % en 2000 et + 9 % pour les quatre premiers mois de 2001). Des mesures devraient être prises visant à faciliter la prescription et la délivrance de médicaments génériques, spécialités pharmaceutiques correspondant en tout point aux molécules d'origine n'étant plus protégées par brevet. Elles visent à une économie de l'ordre de 500 millions de francs. Une autre source d'économie devrait être obtenue par une réduction des prix des spécialités les plus innovantes, mais dont les volumes de consommation, comme c'est fréquemment le cas, dépassent les prévisions initiales. Une quinzaine de spécialités seraient concernées et la baisse de leur prix devrait être négociée avec les fabricants dans le cadre du comité économique des spécialités pharmaceutiques. L'objectif est une économie de l'ordre du milliard de francs.

Défendues M. Kouchner, diverses initiatives devraient être prises concernant l'incitation à la bonne prescription et à un bon usage du médicament. En liaison avec l'Agence française de sécurité sanitaire des produits de santé et l'Agence nationale d'accréditation et d'évaluation en santé, une structure serait créée pour permettre aux pouvoirs publics de mieux suivre l'évolution et les tendances des consommations médicamenteuses. La Caisse nationale d'assurance-maladie pourrait, de son côté, être mise à contribution pour, en liaison avec les syndicats de médecins, établir une charte du bon usage du médicament. Cet ensemble devrait être complété par une série de dispositifs comptables concernant les marges des pharmaciens d'officine et des grossistes répartiteurs, le gouvernement espérant parvenir à terme à des économies globales à hauteur d'environ 4 milliards de francs par an.

Jean-Yves Nau

AGENCE
FRANÇAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

LISTE EXPERTS
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Monsieur le Professeur Pierre CHATELAIN
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Annexe 4-19

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Monsieur le Professeur Jean Louis SELAM
Service de Diabètologie
Hôtel Dieu
PARIS

Annexe 4-20

COMMISSION DE LA TRANSPARENCE

Direction des Etudes et de
l'Information Pharmaco-Economiques

Service médical rendu par la spécialité

Avis de la Commission

21 juillet 1999

MEDIATOR, comprimé enrobé,
Boîte de 30

benfluorex

LES LABORATOIRES SERVIER (BIOPHARMA)

Indication (s) :
- Adjuvant du régime adapté dans les hypertriglycéridémies.
La poursuite du régime est toujours indispensable.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.
- Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Après avoir étudié l'ensemble des indications, la Commission a retenu pour cette spécialité, les indications ci-dessous.

INDICATION : Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale. Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Caractère habituel de gravité de l'affeetion traitée :

L'affection concernée par cette spécialité engage le pronostic vital du patient immédiatement ou par suite de complications.

Efficacité/Sécurité d'emploi de la spécialité :

Cette spécialité entre dans le cadre d'un traitement curatif.

L'efficacité de cette spécialité dans cette indication est faible

Place dans la stratégie thérapeutique :

Cette spécialité est un médicament d'appoint.

Il existe des alternatives thérapeutiques médicamenteuses ou non médicamenteuses à cette spécialité.

Intérêt en termes de santé publique :

Sans objet.

Annexe 4-20

INDICATION :
- Adjuvant du régime adapté dans les hypertriglycéridémies.
La poursuite du régime est toujours indispensable.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Caractère habituel de gravité de l'affection traitée :

L'affection concernée par cette spécialité n'engage pas le pronostic vital du patient, n'entraîne pas de complications graves , ni de handicap, ni de dégradation marquée de la qualité de vie.

Efficacité/Sécurité d'emploi de la spécialité :

Cette spécialité entre dans le cadre d'un traitement préventif.

L'efficacité de cette spécialité dans cette indication est moyenne.

Place dans la stratégie thérapeutique :

Cette spécialité est un médicament d'appoint.

Il existe des alternatives thérapeutiques médicamenteuses ou non médicamenteuses à cette spécialité.

Intérêt en termes de santé publique :

Sans objet.

Annexe 4-20

Conclusion de la Commission de la Transparence

La Commission constate, compte tenu des données dont elle dispose, qu'aucun niveau de SMR ne peut être attribué pour cette spécialité.

annexe 4-21

MEDIATOR® 150 mg

Boîte de 30 comprimés enrobés
dosés à 150 mg de Benfluorex

Dossier NL 10008
N° CIP : 317 557-9

DOSSIER D'AUDITION DE RECOURS AUPRÈS DE LA COMMISSION DE LA TRANSPARENCE

ARGUMENTAIRE

LES LABORATOIRES SERVIER
22, rue Garnier - 92200 NEUILLY-SUR-SEINE

- 19 Novembre 1999 -

annexe 4-21

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

AUDITION DE RECOURS AUPRES DE LA COMMISSION DE LA TRANSPARENCE
- 19 NOVEMBRE 1999 -

Nom de la spécialité : **MEDIATOR® 150 mg**

Dénomination commune internationale : **Benfluorex**

Nom du Laboratoire Titulaire de l'AMM : **LES LABORATOIRES SERVIER**

Indication : **Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.**

Le niveau de SMR de MEDIATOR® est *IMPORTANT*, car :

1) **Le diabète engage le pronostic vital du patient.**
2) **L'efficacité antidiabétique de MEDIATOR® est démontrée versus placebo. Cette efficacité est comparable à celle d'autres antidiabétiques, notamment la metformine, classée par la Commission en niveau de SMR *important*. Sa sécurité d'emploi est bien documentée.**
3) **MEDIATOR® est un antidiabétique de la classe des insulino-sensibilisateurs indiqué en 1ère intention quand le régime diététique ne suffit plus à lui seul pour rétablir l'équilibre glycémique.**
4) **MEDIATOR® présente un intérêt en termes de santé publique compte tenu de son efficacité dans le traitement du diabète, de la fréquence, de la gravité et du coût de cette pathologie.**

Nous contestons les points sur lesquels la Commission de la Transparence s'est appuyée pour proposer pour MEDIATOR® un niveau de SMR *insuffisant*, à savoir :

1) L'efficacité qualifiée de faible
2) Le qualificatif de médicament d'appoint
3) Le terme «sans objet» concernant l'intérêt en termes de santé publique.

Société anonyme au capital de 80 451 875 F - RCS Nanterre B 085 480 796 - Siège social: 22, rue Garnier - 92200 Neuilly-sur-Seine
Tél.: 01 55 72 60 00 - Télécopie: 01 47 38 27 39

SERVIER

annexe 4-21

I **<u>L'efficacité antidiabétique et la sécurité d'emploi de MEDIATOR® sont démontrées</u> :**

1. ***L'efficacité de MEDIATOR® est démontrée en comparaison au placebo*** à tous les stades du diabète de type 2 : en monothérapie dans les stades initiaux de la maladie, et en association chez les patients présentant un diabète plus sévère, déjà traités par d'autres antidiabétiques.

Populations	N	Durée de traitement	HbA_{1c} (%) initiale		Δ HbA_{1c} finale vs placebo
			Med.	Pl	
Régime seul *(Velussi)*	32	3 mois	6.7	6.8	0.9 (p=0.024)
Régime seul *(Leutenegger)*	435	6 mois	7.6*	7.4*	0.9 (p<0.001)
Insuline *(Erkelens)*	19	3 mois	7.1	8.7	0.9 (p<0.001)
Sulfonylurées *(Tomasi)*	58	3 mois	8.7	8.1	0.8 (p=0.007)
Sulfonylurées *(Louvet)*	24	3 mois	8.5	8.0	1.7 (p=0.023)

*après deux mois de régime strict

La différence d'évolution de l'hémoglobine glyquée (en valeur absolue) entre MEDIATOR® et placebo varie entre 0,8% et 1,7 %, ce qui est cliniquement et statistiquement significatif et concordant dans toutes les études. Dans les deux études en monothérapie, une différence proche de 1% est observée, alors même que l'état diabétique avait été préalablement amélioré par un régime diététique bien conduit abaissant l'hémoglobine glyquée d'inclusion à une valeur proche de 7%. Enfin, comme pour d'autres antidiabétiques oraux, l'efficacité de MEDIATOR® est d'autant plus importante que le diabète est sévère.

MEDIATOR® est listé parmi les antidiabétiques dans la classification ACP 1998 :Métabolisme Nutrition - Diabète sucré -P1-4.

annexe 4-21

2. ***L'efficacité de MEDIATOR® est comparable à celle d'autres antidiabétiques oraux :***

- **La metformine,** qui est l'antidiabétique insulino-sensibilisateur de référence. Dans une étude ayant inclus 722 patients diabétiques de type 2 insuffisamment équilibrés après 2 mois de régime intensif, MEDIATOR® est significativement non-inférieur à la metformine (traitement pendant 29 semaines) : différence d'évolution de l'HbA1c dans la population en intention de traiter 0,28 ± 0,12 % (IC 90% [-0,07 ; 0,48]) et dans la population per protocole, comme recommandé par ICH 9 pour les analyses de non-infériorité, 0,08 ± 0,17 %, (IC 90% [-0,12 ; 0,29]).
  La metformine a été classée par la Commission en niveau **SMR *important***.

- D'après les données de la littérature, l'efficacité antidiabétique de MEDIATOR® en monothérapie peut être comparée à celle **d'autres antidiabétiques** testés dans les mêmes conditions (HbA1c autour de 7% après régime).

  Elle est comparable à celle de la Rosiglitazone (*BARMAN-BALFOUR*, Drug 1999; *CHARBONNEL* et al., Poster ADA meeting 1999).

  Elle est supérieure à celle de l'Acarbose qui conduit à une différence finale d'HbA1c d'environ 0,6 % versus placebo (*CONIFF* et al., AJM 1995 ; *CONIFF* et al., Arch Intern Med 1994).
  L'acarbose a été classée initialement par la Commission en niveau **SMR *modéré.***

3. ***La sécurité d'emploi est confirmée et bien documentée :***

- MEDIATOR® n'entraîne ni acidose lactique ni prise de poids.

- Les événements indésirables sont peu nombreux et mineurs. Ils touchent essentiellement la sphère digestive. Les troubles gastrointestinaux sont moins fréquents sous MEDIATOR® que sous metformine (13% vs 25% dans l'étude 6 mois).

- Il n'existe aucune contre-indication ni précaution d'emploi particulière (cf RCP) notamment chez le sujet âgé.

Après 25 ans d'utilisation correspondant à un volume de prescriptions de plus de 25 millions de mois de traitement, les rapports annuels de pharmacovigilance regroupant toutes les notifications reçues par le laboratoire de la part des prescripteurs et des Autorités de santé, n'ont décelé aucun événement remarquable.

Le dernier en date a été transmis à l'AFSSAPS le 22 juin 1999.

annexe 4-21

II La place de MEDIATOR® dans la stratégie thérapeutique du diabète de type 2 est celle d'un traitement de 1ère intention :

MEDIATOR® est un insulino-sensibilisateur, tel que démontré par des études de clamp hyperinsulinémique euglycémique (*DE FEO* et al. Diabetes/Metabolism Review 1993 ; *BIANCHI* et al. Diabetes Care 1993).

Le mécanisme d'action est décrit dans le RCP.

Comme tous les antidiabétiques oraux insulino-sensibilisateurs, MEDIATOR® est indiqué en traitement de 1ère intention quand le traitement diététique ne suffit plus. En effet, l'efficacité de MEDIATOR® en monothérapie a bien été démontrée en comparaison au placebo et à la metformine chez des diabétiques de type 2 qui n'étaient pas suffisamment contrôlés par un régime intensif.

III MEDIATOR® présente un intérêt indéniable en termes de santé publique :

MEDIATOR® présente un intérêt en termes de santé publique compte tenu d'une part de son efficacité dans le traitement du diabète, d'autre part de la fréquence, de la gravité et du coût du diabète.

La diversité des alternatives thérapeutiques est une des clés pour combattre avec succès le diabète de type 2.

En conclusion, MEDIATOR® a une efficacité comparable à celle des insulino-sensibilisateurs. Le niveau de SMR pour MEDIATOR® doit donc être équivalent à celui de la metformine.

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

COMMISSION DE LA TRANSPARENCE

19 NOVEMBRE 1999

Compte rendu de l'avis

Etaient présents

M. DUPUIS, Président
M. BERGMANN, Vice-Président
M. FLEURETTE, représentant le Directeur de l'Agence Française de Sécurité Sanitaire des Produits de Santé
Mme SIMONI-THOMAS, représentant le Directeur de la Sécurité Sociale
Mme BARON représentant le Directeur Général de la Santé
M. AMEDEE-MANESME
M. BLAESI
Mme BLUM-BOISGARD
M. CASTAIGNE
M. CROCHET
Mme KOEGER
Mme LEGRAND-SIBENALER
Mme LEJEUNNE
Mme RICATTE
M.SINGLAS
M. ZARIFIAN

Etaient également présents

Mme CASTANO
Mme DENIS
Mlle DIARTE
Mlle LECLERC
M. MAUGENDRE
Mlle MOATTI
Mlle ROZET
M. SEMENZATO
Mme STAMENKOVIC

Etaient excusés

M.ALLEMAND
M. BEUCLER
M. CHANU
M. CHOUTET
M. FAIVRE
M. PARROT
M. PAINTAUD
M. TOULOUSE
M.WONG

143/147, Boulevard Anatole France - 93285 Saint-Denis Cedex - Tél. : 01.55.87.30.00

Annexe 4-22

L'ordre du jour de la Commission de la Transparence du 19 novembre 1999 est l'audition des Laboratoires dans le cadre de la réévaluation du service médical rendu (SMR) des spécialités remboursables en ville. Ces auditions constituent la deuxième et dernière étape de la phase contradictoire prévue par la procédure de réévaluation.

Les auditions reçues ce jour portent sur trois des quatre disciplines constituant la première vague de la réévaluation soit Métabolisme-Nutrition, Psychiatrie et Rhumatologie.

Au total, 20 laboratoires ont été auditionnés pour un total de 33 spécialités soit en Métabolisme-Nutrition = 10, Psychiatrie = 15 Rhumatologie = 8 (un Laboratoire s'est désisté). La liste de ces spécialités est jointe en annexe 1.

Au cours de cette Commission, 11 votes ont eu lieu sur 33 spécialités ayant effectué une demande d'audition :

1. ART 50 , gélule, boîte de 30 et ZONDAR 50 mg, gélule, boîte 30
2. CHONDROSULF, gélule, boîte de 8,
CHONDROSULF, granulé pour suspension buvable, sachets, boîte de 84
3. EUPHYTOSE comprimé enrobé, tubes de 40 et 20,
EUPHYTOSE solution buvable, flacon de 82ml
4. JONCTUM 200 mg gélule, boîte de 45
5. KETUM gel à 2,5 %, tube de 60 g (2 dossiers)
6. LITHIUM OLIGOSOL sol buv amp de 2ml, boîte de 14,
MAGNESIUM OLIGOSOL sol buv amp 2ml, boîte de 14
7. MEDIATOR 150mg comprimé enrobé, boîte de 30.
8. MODIODAL 100mg comprimé, boîte de 30.
9. PASSIFLORINE solution buvable, flacon de 125 ml
SPASMINE comprimé Boîte de 30.
SPASMINE suppositoire enfant Boîte de 10.
10. SPASMAG comprimé pour sol buvable, boîte de 42
SPASMAG, gélules, boîte de 60
SPASMAG, sol buvable ampoule de 5 ml, boîte de 30
11. SYMPATHYL comprimé pelliculé, boîte de 40.

Les résultats de ces votes sont les suivants :

ART 50 et ZONDAR 10 votants		EUPHYTOSE 11 votants	
Niveau de SMR proposé	Nombre de voix	Niveau de SMR proposé	Nombre de voix
Modéré	2	Faible	1
Faible	8	Insuffisant	9
		Abstention	1

CHONDROSULF 10 votants		JONCTUM 10 votants	
Niveau de SMR proposé	Nombre de voix	Niveau de SMR proposé	Nombre de voix
Modéré	1	Faible	2
Faible	9	Insuffisant	8

Annexe 4-22

KETUM 10 votants	
Niveau de SMR proposé	Nombre de voix
Important	1
Modéré	9

LITHIUM OLIGOSOL MAGNESIUM OLIGOSOL 12 votants	
Niveau de SMR proposé	Nombre de voix
Faible	1
Insuffisant	11

MEDIATOR 10 votants	
Niveau de SMR proposé	Nombre de voix
Faible	2
Insuffisant	7
Abstention	1

MODIODAL 12 votants	
Niveau de SMR proposé	Nombre de voix
Majeur	1
Important	11

PASSIFLORINE SPASMINE 12 votants	
Niveau de SMR proposé	Nombre de voix
Faible	1
Insuffisant	10
Abstention	1

SPASMAG Formes orales 10 votants	
Niveau de SMR proposé	Nombre de voix
Faible	1
Insuffisant	9

SYMPATHYL 12 votants	
Niveau de SMR proposé	Nombre de voix
Faible	1
Insuffisant	10
Abstention	1

Pour toutes les autres spécialités concernées par les auditions, un consensus ayant été obtenu, le niveau de SMR de ces spécialités n'a pas été modifié. Les éléments repris lors des délibérations sont les suivants :

- Les affections ou symptômes visés par les médicaments classés comme « sédatifs divers » n'ont pas de caractère habituel de gravité (états neurotoniques, irritabilité, nervosisme, manifestations mineures de l'anxiété, troubles légers du sommeil). Dans les dossiers de demande de réexamen déposés, l'efficacité n'a pas été jugée cliniquement significative. La prise en charge de ce type de trouble repose sur la qualité de la relation médecin-patient (dialogue avec le patient, rappel des règles d'hygiène de vie). Une prise en charge psychologique peut être proposée au patient selon des modalités dépendantes de chaque cas. Le risque d'un transfert de prescription vers des médicaments psychotropes (anxiolytiques, voire antidépresseurs) n'est pas documenté actuellement. De plus, les psychotropes ne sont pas indiqués dans le traitement de ces affections bénignes et leur prescription dans ces situations cliniques serait selon les experts contraire à leur bon usage. Si néanmoins, le médecin souhaite prescrire un médicament à visée sédative en raison du profil psychologique de son patient ou de l'impact attendu d'une prescription de courte durée, la prescription peut se faire indépendamment du statut de prise en charge.

- Les affections ou symptômes visés par les médicaments à base de magnésium et destinés à la voie orale n'ont pas de caractère habituel de gravité (spasmophilie). L'efficacité n'a pas été jugée cliniquement significative. La prise en charge de ce type de trouble repose sur la qualité de la relation médecin-patient (dialogue avec le patient, rappel des règles d'hygiène de vie). Le risque d'un transfert de prescription vers des médicaments psychotropes (anxiolytiques, voire antidépresseurs) n'est pas documenté actuellement. De plus les psychotropes ne sont pas indiqués dans le traitement de ces affections bénignes et leur prescription dans ces situations cliniques serait selon les experts contraire à leur bon usage. Si néanmoins, le médecin souhaite prescrire un médicament à base de magnésium (administration par voie orale) en raison du profil psychologique de son patient ou de l'impact attendu d'une prescription de courte durée, la prescription peut se faire indépendamment du statut de prise en charge.

- Le rapport efficacité/sécurité de COVATINE comprimé (captodiame), utilisé dans le traitement de l'anxiété et de ses manifestations psychosomatiques, est faible. En particulier le captodiame se distingue des benzodiazépines ou des spécialités apparentées par une efficacité nettement moins bien établie. De ce fait, il ne possède pas de place dans la stratégie thérapeutique. Si un traitement médicamenteux de courte durée s'avère nécessaire, il fera appel de préférence à une benzodiazépine, à la buspirone ou à l'hydroxyzine. Une prise en charge psychologique peut être aussi proposée.

- MEDIATOR comprimé est indiqué comme adjuvant du régime dans le « diabète asymptomatique » avec surcharge pondérale. L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée (comme indiqué dans le R.C.P.). L'étude UKPDS a montré l'intérêt d'un contrôle strict de la glycémie en cas de diabète de type II par la metformine (réduction de la mortalité chez les sujets obèses) et des complications microangiopathiques (sulfamide hypoglycémiant). MEDIATOR ne figure pas dans les recommandations de bonne pratique de l'AFSSAPS de février 1999 intitulées : « traitement médicamenteux du diabète de type 2 ».

- MODIODAL 100 mg comprimé est indiqué dans le traitement de la narcolepsie avec ou sans cataplexie. Le rapport efficacité/sécurité est important dans cette indication et cette spécialité peut être utilisée en 1ère intention.

- L'efficacité de OLIGOSOL ZINC NICKEL COBALT solution buvable prescrit en cas de régime amaigrissant (utilisé comme « modificateur du terrain » en particulier en cas de régime amaigrissant) n'a pas été jugée cliniquement significative. Il s'agit d'un traitement symptomatique dans une affection sans caractère habituel de gravité. La prise en charge d'un surpoids repose notamment sur le suivi d'un régime alimentaire adapté au patient, le respect de règles d'hygiène de vie, voire un soutien psychologique. Si néanmoins, le médecin souhaite prescrire ce médicament en raison du profil psychologique de son patient ou de l'impact attendu d'une prescription de courte durée, la prescription peut se faire indépendamment du statut de prise en charge.

- Les spécialités indiquées dans le traitement des dorsalgies « essentielles » ainsi que les topiques utilisés dans le traitement local des douleurs d'origine musculaire et tendino-ligamentaire ont une efficacité faible. Il s'agit de traitement d'appoint visant des affections dont le caractère habituel de gravité est mineur et pour lesquelles il existe des alternatives non médicamenteuses ou médicamenteuses si

nécessaire (kinésithérapie, hygiène de vie, traitement par des antalgiques voire des anti-inflammatoires non stéroïdiens).

- Pour les spécialités indiquées dans le traitement symptomatique des manifestations fonctionnelles de l'arthrose, un SMR faible est attribué aux spécialités pour lesquelles des essais (de méthodologie parfois discutable) ont montré une diminution de la consommation d'antalgiques et d'anti-inflammatoires non stéroïdiens qui sont les traitements utilisés dans cette indication. Les résultats ont établi que cette diminution était légère. Un SMR insuffisant est attribué aux spécialités n'ayant pu apporter la même démonstration (parmi lesquelles le JONCTUM, spécialité ayant fait l'objet d'une audition).

En annexe 2 de ce document sont repris les spécialités, leur niveau de service médical rendu et la date d'attribution de ce niveau.

Sont également listées les spécialités n'ayant pas eu de SMR le 21 juillet 1999 :

- pour lesquelles aucun dossier de demande de réexamen n'a été déposé,
- Et dont aucune autre spécialité ayant des indications similaires n'a déposé de dossier de demande de réexamen.

ANNEXE 1

LISTE DES SPECIALITES POUR LESQUELLES UNE AUDITION A ETE DEMANDEE

PSYCHIATRIE
(hors neuroleptiques, normothymiques et médicaments des états de dépendance)

CARDIOCALM comprimé enrobé, boîte de 40
COVATINE 50mg comprimé enrobé, boîte de 45.
EUPHYTOSE comprimé enrobé, tubes de 40 et 20.
EUPHYTOSE solution buvable, flacon de 82ml
GALIRENE solution buvable, ampoules de 10ml, boîte de 20. (DESISTEMENT)
LITHIUM OLIGOSOL sol buv amp de 2ml, boîte de 14.
MAGNESIUM OLIGOSOL sol buv amp 2ml, boîte de 14
MODIODAL 100mg comprimé, boîte de 30.
PASSIFLORINE solution buvable, flacon de 125 ml
SPASMINE comprimé Boîte de 30.
SPASMINE suppositoire enfant Boîte de 10.
SYMPATHYL comprimé pelliculé, boîte de 40.
SYMPAVAGOL comprimé enrobé, tube de 40
SYMPAVAGOL solution buvable flacon de 90ml
TRANQUITAL comprimés, boîte de 30 et de 100
VAGOSTABYL comprimé enrobé, tube de 40.

METABOLISME-NUTRITION

MAG 2 100mg comprimé, boîte de 60
MAG 2 122 mg/10 ml, solution buvable, ampoules autocassables de 10 ml, boîte de 30
MAG 2 184 mg, poudre pour solution buvable, sachets boîte de 30
MAGNE-B6, comprimé enrobé, boîte de 50
MAGNE-B6, solution buvable, ampoules de 10 ml, boîte de 30
MEDIATOR 150mg comprimé enrobé, boîte de 30.
OLIGOSOL Zinc-Nickel-Cobalt solution buvable, ampoule de 2 ml, boîte de 14
SPASMAG, sol buvable ampoule de 5 ml, boîte de 30
SPASMAG comprimé pour sol buvable, boîte de 42
SPASMAG, gélules, boîte de 60

RHUMATOLOGIE

ALGESAL SURACTIVE, crème, tube 40 g
ART 50 , gélule, boîte de 30
CHONDROSULF, gélule, boîte de 84
CHONDROSULF, granulé pour suspension buvable, sachets, boîte de 84
JONCTUM 200 mg gélule, boîte de 45
KETUM gel à 2,5 %, tube de 60 g (2 dossiers)
UTEPLEX, solution buvable, ampoules de 2 ml, boîte de 45
ZONDAR 50 mg, gélule, boîte 30

Annexe 4-23

COMMISSION DE LA TRANSPARENCE

Direction des Etudes Médico-Economiques
et de l'Information Scientifique

Service médical rendu par la spécialité

Avis de la Commission

19 novembre 1999

MEDIATOR, comprimé enrobé,
Boîte de 30

benfluorex

LES LABORATOIRES SERVIER (BIOPHARMA)

Indication (s) :
- Adjuvant du régime adapté dans les hypertriglycéridémies.
La poursuite du régime est toujours indispensable.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.
- Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Après avoir étudié l'ensemble des indications, la Commission a retenu pour cette spécialité, les indications ci-dessous.

INDICATION : Adjuvant du régime dans le diabète asymptomatique avec surcharge pondérale. Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Caractère habituel de gravité de l'affection traitée :

L'affection concernée par cette spécialité engage le pronostic vital du patient immédiatement ou par suite de complications.

Efficacité/Sécurité d'emploi de la spécialité :

Cette spécialité entre dans le cadre d'un traitement curatif.

L'efficacité de cette spécialité dans cette indication est faible

Place dans la stratégie thérapeutique :

Cette spécialité est un médicament d'appoint.

Il existe des alternatives thérapeutiques médicamenteuses ou non médicamenteuses à cette spécialité.

Intérêt en termes de santé publique :

Sans objet.

Annexe 4-23

INDICATION :
- Adjuvant du régime adapté dans les hypertriglycéridémies.
La poursuite du régime est toujours indispensable.
Remarque : l'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

Caractère habituel de gravité de l'affection traitée :

L'affection concernée par cette spécialité n'engage pas le pronostic vital du patient, n'entraîne pas de complications graves , ni de handicap, ni de dégradation marquée de la qualité de vie.

Efficacité/Sécurité d'emploi de la spécialité :

Cette spécialité entre dans le cadre d'un traitement préventif.

L'efficacité de cette spécialité dans cette indication est moyenne.

Place dans la stratégie thérapeutique :

Cette spécialité est un médicament d'appoint.

Il existe des alternatives thérapeutiques médicamenteuses ou non médicamenteuses à cette spécialité.

Intérêt en termes de santé publique :

Sans objet.

Annexe 4-23.

Conclusion de la Commission de la Transparence

Le service médical rendu de cette spécialité a été apprécié en prenant en compte l'efficacité et les effets indésirables du médicament, sa place dans la stratégie thérapeutique, notamment au regard des autres thérapies disponibles, la gravité de l'affection à laquelle il est destiné, le caractère préventif, curatif ou symptomatique du traitement médicamenteux et son intérêt pour la santé publique.
Le niveau de service médical rendu est insuffisant au regard des autres médicaments ou thérapies disponibles pour justifier sa prise en charge.

médecin inspecteur régional et examen du tableau général de garde de l'établissement, autoriser, par période maximum d'un an, des dépassements de plafond dans certaines disciplines.

C. – Quel que soit l'établissement où elles ont été effectuées, les participations au service de garde sont exclusivement mandatées par l'établissement où le praticien effectue son service normal de jour.

D. – Pour les activités de service continu institué à titre dérogatoire en application de l'article 8 ci-dessus, les plages de travail effectuées au delà des obligations statutaires sont indemnisées sur la base du montant d'une garde ou d'une demi-garde, selon leur durée.

Art. 18. – Les appels faits aux praticiens à plein temps au bénéfice de leurs malades personnels admis dans les établissements dans le cadre de l'activité libérale qu'un praticien peut exercer à l'hôpital ne donnent pas lieu au remboursement de frais de transport ni à l'octroi d'indemnités kilométriques.

Les déplacements effectués pour assurer le service de garde ne donnent pas lieu au remboursement de frais de transport ni à l'octroi d'indemnités kilométriques. Toutefois, si le service de garde est organisé entre plusieurs hôpitaux conformément aux dispositions de l'avant-dernier alinéa de l'article 4 ci-dessus, les frais de déplacement des praticiens à temps plein ou à temps partiel appelés à se rendre dans un établissement autre que celui dans lequel ils exercent leurs fonctions sont remboursés sur la base d'indemnités kilométriques dans les conditions et limites prévues pour les membres du personnel hospitalier visés au titre IV du statut général des fonctionnaires.

Art. 19. – Les dispositions des articles 17 et 18 ci-dessus ne sont pas applicables aux praticiens hospitaliers logés par nécessité ou utilité de service.

CHAPITRE IV

Dispositions d'ordre comptable

Art. 20. – Chaque praticien effectuant une garde à domicile note sur un carnet à double feuillet, unique pour l'établissement et déposé au service des urgences :

- le nombre et l'heure des appels reçus au cours de la nuit ;
- ses heures d'arrivée et de départ de l'hôpital ;
- le nom des malades soignés et, par référence à la nomenclature des actes médicaux, l'indication des soins dispensés.

Art. 21. – Au plus tard le 10 de chaque mois, le directeur de l'établissement ou le directeur responsable du service de garde arrête l'état récapitulatif des participations au service de garde effectuées au cours du mois précédent. Cet état décompte pour chaque praticien le nombre de permanences à l'hôpital, effectuées sous déduction, le cas échéant, de celles incluses dans le service normal, conformément aux dispositions de l'article 16 ci-dessus, et celui des gardes par astreinte à domicile, avec l'indication du nombre des appels et heures de présence consécutifs à chaque garde. L'extrait qui le concerne est adressé à chaque praticien.

Lorsque cet état récapitulatif est arrêté par le directeur responsable d'un secteur de garde, il en est transmis copie à chaque directeur d'établissement concerné.

Art. 22. – Au vu de l'état récapitulatif visé à l'article précédent, le directeur liquide le montant des indemnités dues aux praticiens extérieurs rattachés en appliquant aux services faits le barème fixé à l'article 17 ci-dessus.

Les mandatements sont présentés au comptable sous forme d'état collectif pour chaque mois et sont accompagnés du tableau mensuel de service visé à l'article 15 ci-dessus, préalablement annoté des modifications qui lui auraient été apportées et arrêté par le directeur de l'établissement comme état des services faits.

CHAPITRE V

Champ d'application et calendrier

Art. 23. – Pour l'application des dispositions du présent arrêté :

- les fractions d'heures sont négligées ou comptées pour une heure selon qu'elles sont inférieures ou supérieures à la demi-heure ;
- la période hebdomadaire commence le lundi matin à 8 h 30 et s'achève le lundi suivant à la même heure ;
- la période mensuelle commence le premier lundi de chaque mois à 8 h 30 et s'achève le premier lundi du mois suivant à la même heure, chaque période mensuelle comportant ainsi quatre ou cinq semaines entières.

Art. 24. – Les dispositions des articles 16 et 17 du présent arrêté sont applicables aux gardes médicales effectuées dans les services de réanimation des hôpitaux publics par les praticiens et les internes autorisés à participer au service de garde de réanimation en application de l'article 3 de l'arrêté du 21 janvier 1976.

En outre, les permanences à l'hôpital pendant l'après-midi sont indemnisées sur la base de la demi-garde. Elles ne peuvent faire l'objet de récupération.

Art. 25. – Le bénéfice du repos de sécurité, dans les conditions fixées par l'article 1er du présent arrêté, est ouvert à tous les praticiens visés au premier alinéa de l'article 9 à compter du 1er octobre 2003.

Dans les établissements ayant organisé leurs secteurs de garde conformément aux dispositions de l'avant-dernier alinéa de l'article 3 ci-dessus, le bénéfice du repos de sécurité peut, à titre dérogatoire, être ouvert avant la date fixée au premier alinéa du présent article, à compter de la mise en place d'une organisation des soins le permettant.

Art. 26. – L'arrêté du 15 février 1973 relatif à l'organisation et à l'indemnisation des services de garde dans les hôpitaux publics autres que les hôpitaux locaux est abrogé.

Art. 27. – Le directeur de l'hospitalisation et de l'organisation des soins au ministère de l'emploi et de la solidarité est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 14 septembre 2001.

La ministre de l'emploi et de la solidarité,
Pour la ministre et par délégation :
Par empêchement du directeur
de l'hospitalisation
et de l'organisation des soins :
Le sous-directeur des professions médicales
et des personnels médicaux hospitaliers,
P. BLÉMONT

Le ministre de l'économie,
des finances et de l'industrie,
Pour le ministre et par délégation :
Par empêchement de la directrice du budget :
La sous-directrice,
C. BUHL

Le ministre de l'éducation nationale,
Pour le ministre et par délégation :
Par empêchement du directeur
des personnels enseignants :
La sous-directrice,
J. COLLET-SASSÈRE

Arrêté du 14 septembre 2001 modifiant la liste des spécialités pharmaceutiques remboursables aux assurés sociaux

NOR : *MESS0123370A*

La ministre de l'emploi et de la solidarité et le ministre délégué à la santé,

Vu le code de la sécurité sociale, notamment les articles L. 162-17, L. 162-17-1, R. 161-50, R. 163-2 à R. 163-7 et R. 322-1 ;

Vu le code de la santé publique, notamment les articles L. 5123-1, L. 5121-8, L. 5121-13 et L. 5121-15 ;

Vu les avis de la Commission de la transparence,

Arrêtent :

Art. 1er. – La liste des spécialités pharmaceutiques remboursables aux assurés sociaux est modifiée conformément aux dispositions qui figurent en annexe.

Art. 2. – L'arrêté du 1er août 2000 est retiré en tant qu'il concerne les différentes formes figurant dans ce texte des spécialités : Tanakan, Piribedil, Olmifon, Gevatran, Praxilène, Cervoxan, Trivastal, Duxil, Nootropyl, Tramisal, Ginkogink et Geram.

Art. 3. – L'arrêté du 1er août 2000 est abrogé en tant qu'il concerne les différentes formes des autres spécialités que celles mentionnées à l'article 2 du présent arrêté.

Art. 4. – Le directeur général de la santé et le directeur de la sécurité sociale sont chargés, chacun en ce qui le concerne, de l'exécution du présent arrêté, qui sera publié ainsi que son annexe au *Journal officiel* de la République française.

Fait à Paris, le 14 septembre 2001.

La ministre de l'emploi et de la solidarité,
ÉLISABETH GUIGOU

Le ministre délégué à la santé,
BERNARD KOUCHNER

ANNEXE

MODIFICATION DU TAUX DE REMBOURSEMENT

Le taux de participation de l'assuré est celui prévu au 5° du deuxième alinéa de l'article R. 322-1 du code de la sécurité sociale pour les spécialités ci-dessous à compter de la date de publication du présent arrêté.

Les fabricants doivent apposer sur les spécialités concernées des vignettes avec la mention du taux de participation fixé à l'alinéa ci-dessus à compter de la même date.

Les stocks détenus à cette date des différentes formes de la spécialité Fonzylane comportant des vignettes avec la mention du taux prévu au 6° du deuxième alinéa de l'article R. 322-1 peuvent être écoulés et pris en charge au taux de participation figurant sur la vignette jusqu'au 1er octobre 2001.

A compter du 1er octobre 2001, les stocks détenus à cette date des différentes formes de la spécialité Fonzylane comportant des vignettes avec la mention du taux prévu au 6° du deuxième alinéa de l'article R. 322-1 ne peuvent être écoulés et pris en charge qu'au taux de participation prévu au premier alinéa ci-dessus.

328 442-3 Adlone (exifone), comprimés sécables (B/30) (laboratoires Pharmascience).

331 498-6 Axonyl 1 g/5 ml (piracétam), solution buvable Gé, 125 ml en flacon (laboratoires Parke-Davis).

352 844-0 Buflomedil Bayer 150 mg, comprimés (B/20) (laboratoires Bayer Classics).

352 845-7 Buflomedil Bayer 300 mg, comprimés (B/10) (laboratoires Bayer Classics).

351 537-7 Buflomedil Biogaran 150 mg, comprimés pelliculés (B/20) (laboratoires Biogaran).

351 538-3 Buflomedil Biogaran 300 mg, comprimés pelliculés (B/10) (laboratoires Biogaran).

352 829-1 Buflomedil EG 150 mg, comprimés (B/20) (EG Labo-laboratoires EuroGenerics).

352 831-6 Buflomedil EG 300 mg, comprimés (B/10) (EG Labo-laboratoires EuroGenerics).

352 698-4 Buflomedil G GAM 150 mg, comprimés pelliculés (B/20) (laboratoires G GAM).

352 699-0 Buflomedil G GAM 300 mg, comprimés pelliculés (B/10) (laboratoires G GAM).

352 686-6 Buflomedil GNR 150 mg, comprimés (B/20) (laboratoires GNR-pharma).

352 689-5 Buflomedil GNR 300 mg, comprimés (B/10) (laboratoires GNR-pharma).

343 084-7 Buflomedil Merck 150 mg, comprimés pelliculés (B/20) (laboratoires Merck Génériques).

347 408-1 Buflomedil Merck 300 mg, comprimés pelliculés (B/10) (laboratoires Merck Génériques).

331 334-3 Buflomedil Ratiopharm 150 mg, comprimés pelliculés (B/30) (laboratoires Lafon).

331 333-7 Buflomedil Ratiopharm 50 mg/5 ml, solution injectable, 5 ml en ampoule (B/10) (laboratoires Lafon).

354 049-3 Buflomedil RPG 150 mg, comprimés (B/20) (laboratoires Biogalénique).

354 050-1 Buflomedil RPG 300 mg, comprimés (B/10) (laboratoires Biogalénique).

327 173-9 Capergyl 4,5 mg (méthane, sulfonate de dihydroergotoxine), capsules molles, dose quotidienne unique (B/30) (laboratoires Thérica).

301 899-2 Carlytene 30 mg (moxisylyte), comprimés enrobés (B/32) (laboratoires Asta Medica).

321 490-2 Cervilane (lomifylline, dihydroergocristine mésilate), comprimés dragéifiés (B/40) (laboratoires Cassenne).

330 851-4 Cervoxan 60 mg (vinburnine), gélules (B/30) (laboratoires Pharmafarm).

320 240-2 Cervoxan, soluté injectable, 1 ml en ampoule (B/6) (laboratoires Smithkline Beecham).

321 796-4 Cristanyl (raubasine, méthane, sulfonate de dihydroergocristine), gouttes buvables, 30 ml en flacon (laboratoires Biogalénique).

323 175-7 Cyclergine (cyclandélate), gélules Gé (B/60) (laboratoires Patrick Poirier).

320 175-6 Cyclospasmol 400 mg (cyclandélate), gélules (B/50) (laboratoires Yamanouchi Pharma).

329 012-2 Di-Actane 100 mg (oxalate de naftidrofuryl), gélules Gé (B/20) (laboratoires Ménarini France).

327 489-6 Di-Actane 200 mg (oxalate de naftidrofuryl), gélules Gé (B/20) (laboratoires Ménarini).

339 948-0 Dihydroergotoxine RPG 1 mg/ml, 1 flacon de 50 ml (laboratoires Biogalénique).

303 430-1 Duvadilan 10 mg (chlorhydrate d'isoxsuprine), comprimés sécables (B/50) (laboratoires Solvay Pharma).

322 209-5 Duxil (almitrine, raubasine), suspension buvable en flacon compte-gouttes (48 ml) (laboratoires Servier).

322 200-8 Duxil (almitrine, raubasine), comprimés (B/30) (laboratoires Servier).

327 169-1 Ergodose 4,5 mg dose quotidienne unique (mésilate de dihydroergotoxine), capsules molles (B/30) (laboratoires Murat).

346 595-2 Fonzylane 150 mg (chlorhydrate de buflomédil), comprimés pelliculés (B/20) (laboratoires L. Lafon).

346 594-6 Fonzylane 300 mg (chlorhydrate de buflomédil), comprimés pelliculés (B/10) (laboratoires L. Lafon).

346 596-9 Fonzylane 50 mg/5 ml (chlorhydrate de buflomédil), solution injectable en ampoule de 5 ml (B/2) (laboratoires L. Lafon).

322 018-5 Gabacet (piracétam), soluté buvable en ampoule (B/20) (laboratoires Synthélabo France).

322 569-1 Gabacet 1 g/5 ml (piracétam), soluté injectable en ampoule (B/12) (laboratoires Synthélabo France).

322 571-6 Gabacet 400 mg (piracétam), gélules (B/60) (laboratoires Synthélabo France).

329 943-6 Geram 1 g/5 ml (piracétam), solution injectable, 5 ml en ampoule (B/12) (laboratoires Vedim).

329 937-6 Geram 20 g/100 ml (piracétam), solution buvable Gé, 125 ml en flacon avec mesurette graduée (laboratoires Vedim Pharma).

329 939-9 Geram 400 mg (piracétam), gélules (B/60) (laboratoires Vedim).

329 941-3 Geram 800 mg (piracétam), comprimés pelliculés (B/90) (laboratoires Vedim).

329 940-7 Geram 800 mg (piracétam), comprimés pelliculés (B/45) (laboratoires Vedim).

321 898-1 GEVATRAN 100 mg (oxalate de naftidrofuryl), gélules (B/20) (laboratoires Lipha Santé).

325 761-0 GEVATRAN 200 mg (oxalate de naftidrofuryl), gélules (B/20) (laboratoires Lipha Santé).

328 457-0 GINKOGINK 40 mg/ml (ginkgo biloba), solution buvable en flacon de 30 ml (laboratoires Urpac-Astier).

328 459-3 GINKOGINK 40 mg/ml (ginkgo biloba), solution buvable en flacon de 90 ml (laboratoires Urpac-Astier).

335 700-4 Hatial LP 400 mg (pentoxifylline), comprimés à libération prolongée Gé (B/30) (société Wyeth Lederlé).

305 122-2 Hydergine 1 mg/ml (mésilate de dihydroergotoxine), solution buvable en gouttes, 1 flacon de 50 ml avec mesurette graduée (société Novartis Pharma SA).

325 280-2 Hydergine 4,5 mg dose quotidienne unique (mésilate de dihydroergotoxine), comprimés (B/30) (société Novartis Pharma SA).

322 183-6 Iskedyl (mésilate de dihydroergocristine, raubasine), comprimés (B/100) (laboratoires Pierre Fabre Médicament).

314 183-0 Iskedyl (mésilate de dihydroergocristine, raubasine) soluté injectable en ampoule (B/6) (laboratoires Pierre Fabre Médicament).

305 425-5 Iskedyl (raubasine, méthanesulfonate de dihydroergocristine), gouttes en flacon de 30 ml (laboratoires Pierre Fabre Médicament).

333 995-7 Iskedyl (raubasine, méthanesulfonate de dihydroergocristine), solution buvable en flacon de 140 ml avec mesurette graduée (laboratoires Pierre Fabre Médicament).

333 523-8 Iskedyl (raubasine, méthanesulfonate de dihydroergocristine), solution buvable en flacon de 70 ml avec mesurette graduée (laboratoires Pierre Fabre Médicament).

330 077-7 Iskedyl Fort (mésilate de dihydroergocristine, raubasine), comprimés (B/112) (laboratoires Pierre Fabre Médicament).

330 076-0 Iskedyl Fort (mésilate de dihydroergocristine, raubasine), comprimés (B/56) (laboratoires Pierre Fabre Médicament).

341 238-7 Iskedyl Fort (raubasine, mélisate de dihydroergocristine), comprimés (B/56) (laboratoires Pierre Fabre Médicament).

341 237-0 Iskedyl Fort (raubasine, mésilate de dihydroergocristine), comprimés (B/28) (laboratoires Pierre Fabre Médicament).

346 597-5 Loftyl 150 mg (chlorhydrate de buflomédil), comprimés pelliculés Gé (B/20) (laboratoires Abbott).

346 442-1 Naftidrofuryl Merck 100 mg, gélules (B/20) (laboratoires Merck Génériques).

346 443-8 Naftidrofuryl Merck 200 mg, comprimés pelliculés (B/20) (laboratoires Merck Génériques).
343 741-8 Naftidrofuryl RPG 100 mg, gélules (B/20) (laboratoires Biogalénique).
325 765-6 Naftilux 200 mg (naftidrofuryl), gélules (B/20) (laboratoires Thérabel Lucien Pharma).
352 528-1 Nicergoline Biogaran 10 mg, gélules (B/30) (laboratoires Biogaran).
352 529-8 Nicergoline Biogaran 10 mg, gélules (B/90) (laboratoires Biogaran).
352 526-9 Nicergoline Biogaran 5 mg, gélules (B/30) (laboratoires Biogaran).
353 435-7 Nicergoline EG 10 mg, gélules (B/90) (EG Labo-laboratoires EuroGenerics).
353 434-0 Nicergoline EG 10 mg, gélules (B/30) (EG Labo-laboratoires EuroGenerics).
353 837-8 Nicergoline EG 5 mg, gélules (B/30) (EG Labo-laboratoires EuroGenerics).
345 817-1 Nicergoline RPG 10 mg, gélules (B/90) (laboratoires Biogalénique).
338 106-6 Nicergoline RPG 10 mg, gélules (B/30) (laboratoires Biogalénique).
337 387-1 Nicergoline RPG 5 mg, gélules (B/30) (laboratoires Biogalénique).
313 056-5 Nootropyl (piracétam), gélules (B/60) (laboratoires UCB Pharma).
313 057-1 Nootropyl (piracétam), soluté injectable, 5 ml en ampoule (B/12) (laboratoires UCB Pharma).
331 441-4 Nootropyl 1,2 g/6 ml (piracétam), solution buvable en ampoules (B/30) (laboratoires UCB Pharma).
320 955-1 Nootropyl 20 % (piracétam), soluté buvable en flacon de 125 ml (laboratoires UCB Pharma).
326 861-9 Nootropyl 800 mg (piracétam), comprimés pelliculés (B/90) (laboratoires UCB Pharma).
326 637-1 Nootropyl 800 mg (piracétam), comprimés pelliculés (B/45) (laboratoires UCB Pharma).
324 824-9 Novodil (cyclandélate), gélules Gé (B/50) (laboratoires Augot).
324 876-9 Olmifon (adrafinil), comprimés pelliculés sécables (B/40) (laboratoires Lafon).
324 875-2 Olmifon (adrafinil), comprimés pelliculés (B/20) (laboratoires Lafon).
317 169-9 Optamine 1 mg/ml (mésilate de dihydroergotoxine), solution buvable en gouttes Gé, 50 ml en flacon + mesurette graduée (laboratoires Théraplix).
329 509-4 Oxadilène (chlorhydrate de butalamine, chlorhydrate de papavérine), gélules (B/30) (institut de recherche Corbière).
335 522-9 Oxyphar (mésilate de dihydroergotoxine), solution buvable en flacon Gé, 50 ml (laboratoires Diophar).
334 873-2 Pentoflux LP 400 mg (pentoxifylline), comprimés enrobés à libération prolongée Gé (B/30) (laboratoires du docteur E. Bouchara).
349 850-3 Pentoxifylline Bayer LP 400 mg, comprimés pelliculés à libération prolongée (B/30) (laboratoires Bayer Classics).
335 922-7 Pentoxifylline BGR LP 400 mg, comprimés à libération prolongée (B/30) (laboratoires Biogaran).
351 284-1 Pentoxifylline Biogaran LP 400 mg, comprimés pelliculés à libération prolongée (B/30) (laboratoires Biogaran).
335 467-8 Pentoxifylline GNR LP 400 mg, comprimés pelliculés à libération prolongée (B/30) (laboratoires GNR-pharma).
349 767-9 Pentoxifylline Merck LP 400 mg, comprimés pelliculés à libération prolongée (B/30) (laboratoires Merck Génériques).
323 301-2 Perenan, gélules (B/30) (laboratoires Sanofi Winthrop).
325 113-9 Perenan, solution buvable en gouttes, 50 ml en flacon (laboratoires Sanofi Winthrop).
349 727-7 Piracetam Biogaran 400 mg, comprimés pelliculés (B/90) (laboratoires Biogaran).
349 734-3 Piracetam Biogaran 800 mg, comprimés pelliculés sécables (B/90) (laboratoires Biogaran).
349 732-0 Piracetam Biogaran 800 mg, comprimés pelliculés sécables (B/45) (laboratoires Biogaran).
349 715-9 Piracetam EG 400 mg, comprimés pelliculés (B/90) (EG Labo-laboratoires EuroGenerics).
349 719-4 Piracetam EG 800 mg, comprimés pelliculés sécables (B/45) (EG Labo-laboratoires EuroGenerics).
353 277-2 Piracetam G GAM 800 mg, comprimés pelliculés sécables (B/45) (laboratoires G GAM).
347 383-9 Piracetam GNR 20 %, solution buvable, 125 ml en flacon avec pipette doseuse (laboratoires GNR-pharma).
351 261-1 Piracetam RPG 400 mg, comprimés pelliculés (B/90) (laboratoires Biogalénique).
351 265-7 Piracetam RPG 800 mg, comprimés pelliculés sécables (B/45) (laboratoires Biogalénique).
330 823-0 Piribedil Biogaran 20 mg, comprimés enrobés (B/30) (laboratoires Biogaran).
330 880-4 Piribedil Biogaran 3 mg/ml, solution injectable, 1 ml en ampoule (B/12) (laboratoires Biogaran).
330 829-9 Piribedil Biogaran 50 mg LP, comprimés enrobés à libération prolongée (B/30) (laboratoires Biogaran).
332 879-3 Praxilène 100 mg, gélules sous plaquettes thermoformées (B/20) (laboratoires Lipha Santé).
324 264-3 Praxilène 200 mg (oxalate acide de naftidrofuryl), comprimés pelliculés (B/20) (laboratoires Lipha Santé).
342 055-3 Praxilène 200 mg (oxalate acide de naftidrofuryl), comprimés pelliculés (B/90) (laboratoires Lipha Santé).
317 873-8 Rheobral (vincamine, troxérutine), gélules (B/60) (laboratoires Niverpharm).
317 872-1 Rheobral (vincamine, troxérutine), gélules (B/30) (laboratoires Niverpharm).
320 911-4 Rutovincine (vincamine, troxérutine, acide ascorbique), comprimés enrobés (B/60) (laboratoires Pamex SARL).
315 039-0 Segolan (dihydroergotoxine), gouttes, 75 ml en flacon (laboratoires Wyeth Byla).
337 257-0 Sermion 10 mg (nicergoline), gélules (B/90) (laboratoires Rhône-Poulenc Rorer).
335 638-7 Sermion 10 mg (nicergoline), gélules (B/30) (laboratoires Spécia).
337 390-2 Sermion 5 mg (nicergoline), gélules sous plaquettes thermoformées (B/30) (laboratoires Spécia).
317 613-6 Sermion injectable (nicergoline), préparation injectable, 1 flacon + 1 ampoule de solvant de 2,5 ml (laboratoires Spécia).
332 621-6 Sermion Lyoc 10 mg (nicergoline), lyophilisats oraux (B/30) (laboratoires Aventis).
317 064-2 Sermion Lyoc, lyophilisat oral dosé à 5 mg, 30 doses unitaires (laboratoires Spécia).
315 495-6 Stratene 100 mg (citrate monohydraté de cétiédil), gélules (B/24) (laboratoires Gerda).
310 219-0 Sureptil (cinnarizine, acéfylline heptaminol), comprimés (B/50) (laboratoires Synthélabo France).
312 370-8 Sureptil (cinnarizine, acéfylline heptaminol), solution buvable, gouttes en flacon de 100 ml (laboratoires Synthélabo France).
329 906-3 Tanakan 40 mg (extrait de ginkgo biloba), comprimés enrobés (B/90) (société Beaufour Ipsen Pharma).
329 904-0 Tanakan 40 mg (extrait de ginkgo biloba), comprimés enrobés (B/30) (société Beaufour Ipsen Pharma).
330 279-9 Tanakan 40 mg/ml (extrait de ginkgo biloba), solution buvable, 90 ml en flacon avec mesurette graduée (société Beaufour Ipsen Pharma).
316 324-0 Tanakan 40 mg/ml (extrait de ginkgo biloba), solution buvable, 30 ml en flacon avec mesurette graduée (société Beaufour Ipsen Pharma).
317 696-9 Torental 100 mg/5 ml (pentoxifylline), solution injectable en ampoule (B/6) (laboratoires Hoechst Houdé).
322 757-2 Torental LP 400 mg (pentoxifylline), comprimés enrobés à libération prolongée (B/20) (laboratoires Hoechst Houdé).
328 779-8 Tramisal (ginkgo biloba), solution buvable, 30 ml en flacon (laboratoires Urpac-Astier).
310 860-8 Trivastal 20 mg (piribédil), comprimés enrobés (B/30) (laboratoires Servier).
318 906-7 Trivastal 50 mg LP (piribédil), comprimés enrobés à libération prolongée (B/30) (laboratoires Servier).
316 990-0 Trivastal injectable 3 mg (monométhane sulfonate de piribédil), soluté injectable, 1 ml en ampoule (B/12) (laboratoires Servier).
315 698-4 Vadilex 10, soluté injectable, 2 ml en ampoule (B/10) (laboratoires Synthélabo France).
322 867-2 Vadilex 20, comprimés dragéifiés (B/30) (laboratoires Synthélabo France).
311 151-0 Vasculat, ampoules injectables (B/6) (laboratoires Boehringer Ingelheim France).
311 152-7 Vasculat, comprimés (B/40) (laboratoires Boehringer Ingelheim France).

311 153-3 Vasculat, gouttes, 30 ml en flacon (laboratoires Boehringer Ingelheim France).
314 792-7 Vasculogene (vincamine), comprimés enrobés à 10 mg (B/60) (laboratoires Pharma 2000).
317 377-0 Vasculogene Fort (vincamine), comprimés (B/60) (laboratoires Pharma 2000).
325 566-3 Vascunormyl 200 mg (cyclandélate), comprimés enrobés (B/50) (laboratoires Alcon).
343 183-5 Vasobral (mésilate de dihydroergocryptine A, caféine), comprimés sécables (B/60) (laboratoires Chiesi SA).
339 209-3 Vasobral (mésilate de dihydroergocryptine A, caféine), comprimés sécables (B/30) (laboratoires Chiesi SA).
318 250-4 Vasobral, soluté buvable, 50 ml en flacon (laboratoires Chiesi SA).
319 815-5 Vinca 20 mg (vincamine), comprimés pelliculés (B/45) (laboratoires Substipharm).
322 265-2 Vinca 30 mg retard (vincamine), gélules (B/60) (laboratoires Substipharm).
319 495-0 Vincafor Retard 30 mg (vincamine), gélules (B/30) (laboratoires Pharmafarm).
319 850-5 Vincarutine (vincamine, rutoside), gélules (B/45) (laboratoires Labomed).
330 822-4 Zenium 4,5 mg (mésilate de dihydroergotoxine), gélules Gé (B/30) (laboratoires Jumer).

Arrêté du 17 septembre 2001 modifiant l'arrêté du 2 août 2001 autorisant au titre de l'année 2001 l'ouverture de concours pour le recrutement d'éducateurs spécialisés des instituts nationaux de jeunes sourds et de l'Institut national des jeunes aveugles (femmes et hommes)

NOR : *MESG0123235A*

Par arrêté de la ministre de l'emploi et de la solidarité et du ministre de la fonction publique et de la réforme de l'Etat en date du 17 septembre 2001, les dispositions de l'arrêté du 2 août 2001 autorisant au titre de l'année 2001 l'ouverture de concours pour le recrutement d'éducateurs spécialisés des instituts nationaux de jeunes sourds et de l'Institut national des jeunes aveugles (femmes et hommes) sont modifiées ainsi qu'il suit :

Les épreuves écrites auront lieu le 6 décembre 2001.

La date de clôture des inscriptions est fixée au 31 octobre 2001.

Le dossier complet de candidature doit être adressé, uniquement par voie postale, au ministère de l'emploi et de la solidarité (DAGPB, bureau du recrutement, pièce 217), 10, place des Cinq-Martyrs-du-Lycée-Buffon, 75015 Paris, au plus tard le 31 octobre 2001 (le cachet de la poste faisant foi).

(Le reste sans changement.)

MINISTÈRE DE L'INTÉRIEUR

Décret n° 2001-847 du 11 septembre 2001 relatif à la durée de validité des passeports délivrés en Nouvelle-Calédonie, en Polynésie française, dans les îles Wallis et Futuna, à Mayotte et à Saint-Pierre-et-Miquelon

NOR : *INTM0100036D*

Le Premier ministre,

Sur le rapport du ministre de l'intérieur,

Vu le décret de la Convention nationale du 7 décembre 1792 relatif aux passeports à accorder à ceux qui seraient dans le cas de sortir du territoire français pour leurs affaires ;

Vu le décret n° 2001-185 du 26 février 2001 relatif aux conditions de délivrance et de renouvellement des passeports ;

Vu l'avis du gouvernement de la Nouvelle-Calédonie en date du 2 août 2001 ;

Vu l'avis du gouvernement de la Polynésie française en date du 11 juillet 2001,

Décrète :

Art. 1er. – La durée de validité des passeports délivrés en Nouvelle-Calédonie, en Polynésie française, dans les îles Wallis et Futuna, à Mayotte et à Saint-Pierre-et-Miquelon est de dix ans sous réserve des dispositions des articles 2 et 3 ci-après.

Art. 2. – La durée de validité des passeports délivrés dans les collectivités d'outre-mer visées à l'article 1er à un mineur ou portant inscription d'un mineur de moins de quinze ans est de cinq ans.

Art. 3. – La durée de validité des passeports délivrés dans les collectivités d'outre-mer visées à l'article 1er à titre exceptionnel et pour un motif d'urgence dûment justifié ou délivrés par une autorité qui n'est pas celle du lieu de résidence ou de domicile du demandeur est de six mois.

Art. 4. – Le ministre de l'intérieur et le secrétaire d'Etat à l'outre-mer sont chargés, chacun en ce qui le concerne, de l'exécution du présent décret, qui sera publié au *Journal officiel* de la République française.

Fait à Paris, le 11 septembre 2001.

LIONEL JOSPIN

Par le Premier ministre :

Le ministre de l'intérieur,
DANIEL VAILLANT

Le secrétaire d'Etat à l'outre-mer,
CHRISTIAN PAUL

Décret du 11 septembre 2001 approuvant des modifications apportées aux statuts d'une congrégation

NOR : *INTA0100240D*

Par décret en date du 11 septembre 2001, sont approuvés les nouveaux statuts de la congrégation dite « Province de France de la mission ouvrière Saint-Pierre et Saint-Paul », reconnue légalement par le décret du 22 juin 1992 et dont le siège est transféré à Montfermeil (Seine-Saint-Denis), 10, rue Grange.

Décret du 11 septembre 2001 approuvant des modifications apportées aux statuts d'une congrégation

NOR : *INTA0100241D*

Par décret en date du 11 septembre 2001, sont approuvés les nouveaux statuts de l'établissement particulier de la congrégation des sœurs du Sacré-Cœur de Montigny-lès-Metz, autorisé légalement par le décret du 6 décembre 1860, dont le siège est 9 et 11, rue des Couvents, à Montigny-lès-Metz (Moselle).

Arrêté du 20 juillet 2001 relatif aux pièces et informations à transmettre en vue de l'agrément et du versement de la prime à la création d'emplois

NOR : *INTM0100031A*

La ministre de l'emploi et de la solidarité et le secrétaire d'Etat à l'outre-mer,

Vu le code du travail, notamment les articles L. 421-2, L. 832-7, R. 831-20 et R. 831-21 et D. 831-5 ;

Vu la loi n° 2000-1207 du 13 décembre 2000 d'orientation pour l'outre-mer, et notamment ses articles 7 et 63 ;

Vu le décret n° 2001-499 du 11 juin 2001 portant application de l'article 7 de la loi n° 2000-1207 du 13 décembre 2000 d'orientation pour l'outre-mer et modifiant le code du travail (deuxième partie : Décrets en Conseil d'Etat) ;

Vu le décret n° 2001-502 du 11 juin 2001 portant application de l'article 7 de la loi n° 2000-1207 du 13 décembre 2000 d'orientation pour l'outre-mer,

Arrêtent :

Art. 1er. – La demande d'agrément de la prime à la création d'emploi signée est adressée au représentant de l'Etat dans le département ou dans la collectivité territoriale. A la demande est annexé un dossier qui doit comporter les pièces et informations suivantes :

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LIBELLÉS ABROGÉS		NOUVEAUX LIBELLÉS	
322 294-2	Vita 3, collyre, 10 ml en flacon (laboratoires H. Faure).	322 294-2	Vita 3, collyre, 10 ml en flacon (laboratoires Novar Ophthalmics).
311 422-4	Vitableu, collyre, 10 ml en flacon (laboratoires H. Faure).	311 422-4	Vitableu 0,1 %, collyre, 10 ml en flacon (laboratoir Novartis Ophthalmics).
321 574-1	Vitacic, collyre, 0,4 ml en récipient unidose (B/20) (laboratoires Ciba Vision Ophtalmics).	321 574-1	Vitacic, collyre, 0,4 ml en récipient unidose (B/20) (labo toires Novartis Ophtalmics).
322 178-2	Vitacic, collyre, 5 ml en ampoule (B/1) (laboratoires Ciba Vision Ophthalmics).	322 178-2	Vitacic, collyre, 5 ml en ampoule (B/1) (laboratoires Novar Ophthalmics).
342 750-3	Vitalens, collyre en flacon de 10 ml (laboratoires Ciba Vision Ophthalmics).	342 750-3	Vitalens, collyre en flacon de 10 ml (laboratoires Novar Ophthalmics).
311 458-9	Vitaphakol, collyre, 10 ml en flacon (laboratoires H. Faure).	311 458-9	Vitaphakol, collyre, 10 ml en flacon (laboratoires Novar Ophthalmics).
311 460-3	Vitargenol 5 %, collyre, 15 ml en flacon (laboratoires H. Faure).	311 460-3	Vitargenol 5 %, collyre, 15 ml en flacon (laboratoir Novartis Ophthalmics).
335 194-1	Vitarutine, collyre, 10 ml en flacon (laboratoires H. Faure).	335 194-1	Vitarutine (nicotinamide, sulforutoside sodique), collyr 10 ml en flacon (laboratoires Novartis Ophthalmics).
335 196-4	Vitasedine, collyre, 10 ml en flacon (laboratoires H. Faure).	335 196-4	Vitasedine, collyre, 10 ml en flacon (laboratoires Novar Ophthalmics).
317 754-9	Vitaseptol, collyre, 10 ml en flacon (laboratoires H. Faure).	317 754-9	Vitaseptol, collyre, 10 ml en flacon (laboratoires Novar Ophthalmics).
335 195-8	Vitazinc, collyre, 10 ml en flacon (laboratoires H. Faure).	335 195-8	Vitazinc, collyre, 10 ml en flacon (laboratoires Novar Ophthalmics).

DEUXIÈME PARTIE

Modifications du taux de remboursement

Pour les spécialités ci-dessous, le taux de participation de l'assuré prévu au premier alinéa et au 6° du deuxième alinéa de l'article R. 322-1 du code de la sécurité sociale est abrogé et remplacé par celui prévu au 5° du deuxième alinéa de l'article R. 322-1 du code de la sécurité sociale, à compter du 1er janvier 2002.

Les fabricants doivent apposer sur les spécialités concernées des vignettes avec la mention du taux de participation fixé à l'alinéa ci-dessus à compter de la même date.

Les stocks détenus à cette date comportant des vignettes avec la mention de l'ancien taux peuvent être écoulés et pris en charge au taux de participation figurant sur la vignette jusqu'au 2 mars 2002.

A compter du 3 mars 2002, les stocks détenus à cette date comportant des vignettes avec la mention de l'ancien taux de participation ne peuvent être écoulés et pris en charge qu'au nouveau taux de participation.

CODE CIP	PRÉSENTATION
300 027-1	Abufène (bêta-alanine), comprimés à 0,20 g (B/24) (laboratoires Doms-Adrian).
325 144-1	Aclacinomycine (chlorhydrate d'aclarubicine), préparation injectable, poudre en flacon + 5 ml de solvant en ampoule (B/1) (laboratoires Bellon).
338 255-1	Afebryl, comprimés effervescents (B/16) (laboratoires Galéphar).
328 209-7	Amicic, collyre, 5 ml en flacon (laboratoires Novartis Ophthalmics).
300 385-5	Amphocycline (amphotéricine B, tétracycline), comprimés enrobés (B/16) (laboratoires Bristol-Myers Squibb).
311 601-6	Angiophtal, collyre, 10 ml en flacon (laboratoires Merck Sharp & Dohme-Chibret).
321 582-4	Angitrine 2,5 mg (trinitrine), gélules (B/60) (laboratoires Laphal).
306 127-8	Antinerveux Lesourd, liquide, 45 ml en flacon (laboratoires Lesourd).

CODE CIP	PRÉSENTATION
301 307-8	Antiseptique Calmante, pommade ophtalmique, 5 g tube (laboratoires Chauvin).
300 563-0	Anxoral, comprimés dragéifiés (B/50) (laboratoires Ipra
342 132-8	Aureomycine Evans 3 % (chlorhydrate de chlortétrac cline), pommade, 15 g en tube (laboratoires Cellte Pharma).
300 907-1	BOP, comprimés dragéifiés (B/60) (laboratoires Pautr PPDH SA).
322 970-8	Bedelix, poudre pour suspension buvable en sache (B/30) (société Beaufour Ipsen Pharma).
322 971-4	Bedelix, poudre pour suspension buvable en sache (B/60) (société Beaufour Ipsen Pharma).
320 310-0	Bétadine (polyvidone iodée), ovules (B/8) (laboratoir Asta Medica).
314 513-0	Bétadine, comprimés gynécologiques (B/8) (laboratoir Asta Medica).
301 085-5	Bétadine, solution gynécologique, 125 ml en flacon (lab ratoires Asta Medica).
355 699-1	Bétasept 10 % (povidone iodée), solution vaginal 125 ml en flacon (laboratoires Asta Medica).
301 102-7	Betneval à la néomycine, crème dermique 1 pour mill 10 g en tube (laboratoires Glaxo Wellcome).
324 736-2	Betneval-néomycine (bétaméthasone-néomycine, sulfat crème dermique, 30 g en tube (laboratoires Glaxo We come).
301 105-6	Betneval à la néomycine, pommade 1 pour mille, 10 g tube (laboratoires Glaxo Wellcome).
324 737-9	Betneval-néomycine (béthaméthasone-néomycine, s fate), pommade, 30 g en tube (laboratoires Glaxo We come).
301 103-3	Betneval à la néomycine, lotion dermique 1 pour mil 15 g en flacon (laboratoires Glaxo Wellcome).
301 165-9	Biocarde, gouttes, 30 ml en flacon (laboratoires Lehning
338 457-6	Boroclarine (phényléphrine, acide borique, borax), c lyre, 10 ml en flacon (laboratoires Novartis Ophth mics).

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CODE CIP	PRÉSENTATION
301 663-9	Calcibronat 0,124 g/ml (bromo-galactogluconate de calcium), solution injectable IV, 10 ml en ampoule (B/5) (société Novartis Santé familiale SA).
301 664-5	Calcibronat 0,124 g/ml (bromo-galactogluconate de calcium), solution injectable IV, 5 ml en ampoule (B/10) (société Novartis Santé familiale SA).
301 662-2	Calcibronat 13,3 % (bromo-galactogluconate de calcium), sirop, 200 ml en flacon (société Novartis Santé familiale SA).
308 309-6	Calendula 4 %, pommade dermique, 20 g en tube (laboratoires Boiron).
315 665-9	Calendula DIG, pommade, 20 g en tube (laboratoires Boiron).
306 176-9	Calendula LHF, pommade, 20 g en tube (laboratoires Boiron).
313 790-0	Calmixène (pimélixène), sirop en flacon de 150 ml avec godet doseur (société Novartis Pharma SA).
301 817-6	Canol, comprimés (B/30) (laboratoires Jolly-Jatel).
350 866-7	Cantéine, comprimés pelliculés (B/60) (laboratoires Bailleul).
346 245-1	Cantéine, solution buvable, 100 ml en flacon + cuillère-mesure (laboratoires Bailleul).
313 059-4	Catecol, collyre, 10 ml en flacon (laboratoires Alcon).
301 925-3	Catalgine 0,50 g vitamine C (acétylsalicylate de sodium, bicarbonate de sodium, acide ascorbique), poudre pour solution buvable en sachets-dose (B/20) (laboratoires Lipha Santé).
336 658-7	Cataridol (iodure de sodium, chlorure de sodium), collyre, 10 ml en flacon (laboratoires Novartis Ophthalmics).
318 892-6	Cetarstat, collyre, 10 ml en flacon (laboratoires Chauvin).
313 096-7	Cebevir, collyre, lyophilisat en flacon + 10 ml de solvant en ampoule (B/1) (laboratoires Chauvin).
302 313-1	Cidermex (acétonide de triamcinolone, sulfate de néomycine), pommade, 10 g en tube (laboratoires Cellitech Pharma).
322 591-7	Clérédium 150 mg (dipyridamole), comprimés pelliculés sécables (B/60) (laboratoires Ipsed).
347 602-2	Codegic (acétylsalicylate de DL lysine, phosphate de codéine hémihydraté), poudre pour solution buvable en sachets-dose (B/16) (laboratoires Sanofi Synthélabo France).
302 504-1	Coltramyl 4 mg/2 ml (thiocolchicoside), solution injectable IM, 2 ml en ampoule (B/6) (laboratoires Thérapix).
320 499-6	Coronarine (dipyridamole), comprimés dragéifiés (B/120) (laboratoires Negma).
322 585-7	Corticotulle Lumière, pansement, compresses de 10 cm x 10 cm (B/5) (laboratoires Solvay Pharma).
329 427-8	Corticotulle Lumière, pansement, compresses de 20 cm x 20 cm (B/5) (laboratoires Solvay Pharma).
302 616-4	Cortisone Roussel 5 mg, comprimés (B/20) (laboratoires Aventis).
337 225-1	Covatine 50 mg (chlorhydrate de captodiamine), comprimés enrobés (B/45) (laboratoires A. Bailly-Speab).
302 654-3	Crataegol Boulet, liquide en flacon de 90 ml (laboratoires EPA Biotechnologies).
302 963-6	Dermo-Sulfuryl, pommade, 28 g en tube (laboratoires Monal).
303 089-8	Dicynone 250 mg (étamsylate), comprimés (B/20) (laboratoires Sanofi Synthélabo France).
303 088-1	Dicynone 250 mg/2 ml (étamsylate), solution injectable, 2 ml en ampoule (B/6) (laboratoires Sanofi Synthélabo France).
303 189-2	Dimegan, soluté injectable en ampoule (B/5) (laboratoires Dexo).
303 220-7	Diopaïne 1,5 %, collyre, 5 ml en ampoule (B/5) (laboratoires Novartis Ophthalmics).
335 523-5	Diphar 75 mg (dipyridamole), comprimés enrobés Gé (B/30) (laboratoires Dakota Pharm).
335 524-1	Diphar 75 mg (dipyridamole), comprimés enrobés Gé (B/100) (laboratoires Dakota Pharm).
323 093-0	Diprosone-néomycine, crème à 0,05 %, 30 g en tube (laboratoires Schering-Plough).
314 315-4	Diprosone-néomycine, crème à 0,05 %, 15 g en tube (laboratoires Schering-Plough).
323 091-8	Diprosone-néomycine, pommade à 0,05 %, 30 g en tube (laboratoires Schering-Plough).

CODE CIP	PRÉSENTATION
314 317-7	Diprosone-néomycine, pommade à 0,05 %, 15 g en tu (laboratoires Schering-Plough).
311 786-6	Dulciphak, collyre, 10 ml en flacon (laboratoires Aller France SA).
326 842-4	Efferalgan vitamine C, comprimés effervescents (B (laboratoires UPSA).
303 591-6	Effortil, comprimés (B/30) (laboratoires Boehringer In heim France).
303 592-2	Effortil, gouttes, 30 ml en flacon (laboratoires Boehrin Ingelheim France).
332 146-6	Entecet, comprimés enrobés (B/60) (laboratoires So Maxim).
323 773-1	Ephedromel, sirop, 200 ml en flacon (laboratoi Richelet).
323 774-8	Ephelodine, élixir, 100 ml en flacon (laboratoi Richelet).
303 855-2	Euphytose, comprimés enrobés (B/40) (laboratoi Roche Nicolas).
328 971-6	Euphytose, comprimés enrobés (B/120) (laboratoi Roche Nicolas).
303 856-9	Euphytose, solution buvable, 82 ml en flacon (labo toires Roche Nicolas).
319 286-2	Fiboran 50 mg, gélules (B/40) (laboratoires Nycon Amersham SA).
328 985-7	Fluocalcic (monofluorophosphate disodique, carbon de calcium), comprimés effervescents (B/60) (labo toires Yamanouchi Pharma).
329 899-7	Fongamil 1 %, poudre pour application locale, 20 g flacon (laboratoires Biorga).
304 114-6	Fortal 30 mg/1 ml (pentazocine), solution injectable, 1 en ampoule (B/2) (laboratoires Sanofi Synthél France).
304 112-3	Fortal 30 mg/1 ml (pentazocine), solution injectable, 1 en ampoule (B/10) (laboratoires Sanofi Synthél France).
311 018-9	Fungizone (amphotéricine B), lotion, 30 ml en fla (laboratoires Bristol-Myers Squibb).
304 215-7	Galirène, 10 ml en ampoule buvable (B/20) (laboratoi Alpharma).
316 417-9	Génésérine 3, gouttes en flacon de 30 ml (laboratoi Amido).
316 418-5	Génésérine 3, granules, tube de 60 g (laboratoi Amido).
355 595-1	Génésérine 4,5 mg salicylate d'éséridine anhyd comprimés (B/30) (laboratoires Amido).
304 570-1	Gomenoleo 2 %, soluté injectable, 5 ml en ampo (B/10) (laboratoires Gomenol).
304 573-0	Gomenoleo 5 %, soluté injectable, 5 ml en ampo (B/10) (laboratoires Gomenol).
322 214-9	Halog néomycine, crème, 30 g en tube (laboratoi Bristol-Myers Squibb).
314 685-8	Hamamelis Boiron, pommade, 20 g en tube (laboratoi Boiron).
314 638-8	Hamamelis compose Boiron, comprimés (B/50) (labo toires Boiron).
314 636-5	Hamamelis compose Boiron, gouttes buvables, 30 ml flacon (laboratoires Boiron).
314 637-1	Hamamelis compose Boiron, granules (B/80) (laboratoi Boiron).
304 915-9	HEPT-A-MYL 187,5 mg (chlorhydrate d'heptamin comprimés (B/20) (laboratoires Sanofi Synthél France).
304 916-5	HEPT-A-MYL 30,5 % (chlorhydrate d'heptaminol), solut buvable, 20 ml en flacon compte-gouttes (laboratoi Sanofi Synthélabo France).
305 206-1	Hypnasmine, suppositoires Adulte (B/12) (laboratoi Elerté).
322 273-5	Isoprinosine (inosine, acédobène, diméprano comprimés (B/18) (laboratoires Sanofi Synthél France).
322 274-1	Isoprinosine (inosine, acédobène, diméprano comprimés (B/40) (laboratoires Sanofi Synthél France).
322 473-4	Karayal, granulés (B/1 kg) (laboratoires Chiesi).
328 845-0	Keal 1 g (sucralfate), comprimés sécables Gé (B/30) (Labo-laboratoires EuroGenerics).
333 975-6	Keal 1 g (sucralfate), suspension buvable en sachets de 5 ml (B/30) (EG Labo-laboratoires EuroGenerics).

CODE CIP	PRÉSENTATION
333 976-2	Keal 2 g (sucralfate), suspension buvable, 10 ml en sachets (B/15) (EG Labo-laboratoires EuroGenerics).
318 912-7	Kenakort 0,2 %, soluté labiolique, 25 ml en flacon (laboratoires Bristol-Myers Squibb).
314 930-0	Keratyl 1 % (sulfate sodique de nandrolone), collyre en solution, 5 ml en flacon + embout compte-gouttes (laboratoires Chauvin).
345 814-2	Locoïden (butyrate d'hydrocortisone, sulfate de néomycine), crème en tube de 30 g (laboratoires Yamanouchi Pharma).
328 292-1	Lucrin 5 mg/ml (leuproréline), solution injectable pour voie sous-cutanée, 2,8 ml en flacon (B/1) (laboratoires Abbott France).
317 318-4	Magnesium Monal 2,2 %, solution buvable, 300 ml en flacon (société Novartis Santé familiale SA).
336 452-4	Martigene (chlorhydrate de phényléphrine, maléate de brompheniramine), collyre, 10 ml en flacon (laboratoires Novartis Ophthalmics).
334 011-0	Mibrel, 4 mg/2 ml (thiocolchicoside), solution injectable (IM) Gé, 2 ml en ampoules (B/6) (laboratoires Fornett).
306 900-9	Mucomyst (N-acétylcystéine), solution à 20 %, 5 ml en ampoule (B/6) (laboratoires Bristol-Myers Squibb).
324 361-9	Multitest préchargé (B/1) (laboratoires Aventis Pasteur MSD, SNC).
306 924-5	Mutesa, suspension buvable, 200 ml en flacon (laboratoires Wyeth France).
320 491-5	Myco-Ultralan, pommade, 30 g en tube (laboratoires Schering).
306 940-0	Mycolog (triamcinolone, néomycine, nystatine), pommade, 10 g en tube (laboratoires Bristol-Myers Squibb).
307 021-9	Natisedine (phénobarbital, extrait sec hydro-alcoolique de passiflore), comprimés (B/40) (laboratoires Elaipharm).
345 946-6	Néoducyl (chlorure de calcium, chlorure de magnésium, sorbitol), collyre, 10 ml en flacon (laboratoires Novartis Ophthalmics).
307 131-9	Néopeparyl Framycetine, solution pour instillations, 5 ml en flacon (laboratoires Martinet).
322 528-3	Nerisone C, crème, 30 g en tube (laboratoires Schering).
307 184-5	Neurocalcium, comprimés dragéifiés (B/40) (laboratoires biologiques de l'Ile-de-France).
307 185-1	Neurocalcium, granulés, B/100 g (laboratoires biologiques de l'Ile-de-France).
307 245-4	Nibiol 100 mg, comprimés dragéifiés (B/50) (laboratoires Debat).
307 244-8	Nibiol 50 mg, comprimés dragéifiés (B/60) (laboratoires Debat).
329 061-3	Norgagil (gomme de sterculia, actapulgite, méprobamate), granulés en sachets de 10 g (B/30) (laboratoires Norgine Pharma).
320 043-2	Octofène Enfant, suppositoires (B/8) (laboratoires Debat).
320 038-9	Octofène Nourrisson, suppositoires (B/8) (laboratoires Debat).
322 086-0	Octofène, suppositoires Adulte (B/10) (laboratoires Debat).
307 667-2	Ophtalmine, collyre, 20 ml en flacon (laboratoires Coopération pharmaceutique française).
326 605-2	Orbénine 1 g/5 ml (cloxacilline sodique monohydratée), poudre et solution pour solution injectable (IM), poudre en flacon + solvant en ampoule (B/1) (laboratoires Yamanouchi Pharma).
307 775-3	Palfium 5 mg (dextromoramide), comprimés (B/20) (laboratoires Sanofi Synthélabo France).
307 777-6	Paliuryl 25 %, solution buvable en gouttes, 30 ml en flacon (laboratoires Richelet).
307 779-9	Palpipax, comprimés pelliculés (B/40) (laboratoires Pfizer).
307 743-4	Paps, poudre (B/100 g) (laboratoires Richard).
307 681-8	Passiflorine, solution buvable, 125 ml en flacon (laboratoires Thératech).
322 548-1	Penticort néomycine, crème, 30 g en tube (laboratoires Lederlé).
322 536-6	Penticort, pommade, 30 g en tube (laboratoires Lederlé).
340 122-5	Perkod 75 mg (dipyridamole), comprimés enrobés Gé (B/100) (laboratoires RPG Aventis)
308 202-7	Persantine 25 mg, comprimés dragéifiés (B/40) (laboratoires Boehringer Ingelheim France).
308 203-3	Persantine 75 mg, comprimés dragéifiés (B/30) (laboratoires Boehringer Ingelheim France).

CODE CIP	PRÉSENTATION
319 982-9	Persantine 75 mg, comprimés dragéifiés (B/100) (laboratoires Boehringer Ingelheim France).
311 739-8	Phakan, soluté buvable, 20 ampoules de 10 ml 20 gélules (laboratoires Chauvin SA).
308 224-0	Phenergan 2,5 % (chlorhydrate de prométhazine), solution injectable en ampoules de 2 ml (B/5) (laboratoir Colltech Pharma).
308 331-1	Pilosuryl, solution, 250 ml en flacon (laboratoires Pie Fabre Médicament).
322 704-6	Poly-Karaya (gomme karaya, polyvinyl polypyrrolidon granulés, 10 g en sachets (B/30) (laboratoires San Synthélabo France).
348 301-6	Polysilane UPSA (diméticone), gel oral, 170 g en tu (laboratoires UPSA).
355 597-2	Polysilane UPSA (diméticone), gel oral, 15 g en sach dose (B/30) (laboratoires UPSA).
351 039-0	Povidone iodée Merck 10 %, solution vaginale, 125 ml flacon (laboratoires Merck Génériques).
308 574-1	Praxinor, comprimés laqués (B/20) (laboratoires Lip Santé).
343 455-5	Propionate de sodium Chibret 5 %, collyre en solutio 10 ml en flacon compte-gouttes (laboratoires Mer Sharp & Dohme-Chibret).
327 320-1	Rumafluor 22,1 mg, comprimés gastrorésistants (B/ (laboratoires Zyma).
326 856-5	Salipran (benorilate), poudre en sachets (B/6) (labor toires Celltech Pharma).
327 453-7	Sedarene, gélules (B/20) (laboratoires Cilla-Développ ment).
312 932-6	Septivon Lavril (trichlorocarbanilide), soluté pour usa externe, 250 ml en flacon (laboratoires Chefa Ardeval).
312 933-2	Septivon Lavril (trichlorocarbanilide), soluté pour usa externe, 500 ml en flacon (laboratoires Chefa Ardeval).
315 397-4	Solubacter (trichlorocarbanilide), solution à usa externe, 400 ml en flacon (laboratoires Boots Healt care).
311 781-4	Solubacter (trichlorocarbanilide), solution à usa externe, 150 ml en flacon (laboratoires Boots Healt care).
309 804-0	Sophtal, collyre, 10 ml en flacon (laboratoires Alcon).
341 903-0	Spasmine Enfant, suppositoires (B/10) (laboratoires Jol Jatel).
309 874-9	Spasmine Jolly, comprimés (B/30) (laboratoires Jol Jatel).
309 892-7	Spasmosédine, comprimés (B/40) (laboratoires Théran Deglaude).
302 548-9	Spiramycine Coquelusedal, suppositoires Nourriss (B/8) (laboratoires Eferté).
302 547-2	Spiramycine Coquelusedal, suppositoires Enfant (B (laboratoires Wyeth France).
302 546-6	Spiramycine Coquelusedal, suppositoires Adulte (B (laboratoires Wyeth France).
309 978-9	Sterlane, solution, 125 ml en flacon (laboratoires Ph masciences).
309 979-5	Sterlane, solution, 350 ml en flacon (laboratoires Ph masciences).
355 919-1	Sucralfate EG 1 g, comprimés sécables (B/30) (EG Lab laboratoires EuroGenerics).
356 918-5	Sucralfate EG 1 g, suspension buvable, 5 ml en sache dose (B/30) (EG Labo-laboratoires EuroGenerics).
331 592-2	Sucralfate GNR 1 g, comprimés (B/30) (laboratoires GN Pharma).
332 358-3	Sucralfate GNR 1 g, granulés pour suspension buval en sachets (B/30) (laboratoires GNR-Pharma).
340 733-4	Sucralfate RPG 1 g, comprimés sécables (B/30) (labor toires RPG Aventis).
340 734-0	Sucralfate RPG 1 g, suspension buvable, 5 ml en sach (B/30) (laboratoires RPG Aventis).
340 735-7	Sucralfate RPG 2 g, suspension buvable, 10 ml sachets (B/15) (laboratoires RPG Aventis).
328 792-4	Suprefact 100 microgrammes [1 mg/ml (acétate de bus réline), solution nasale, 10 ml en flacon + pom doseuse (B/1) (laboratoires Aventis).
328 508-1	Suprefact 100 microgrammes [1 mg/ml (acétate de bus réline), solution nasale, 10 ml en flacon + pom doseuse (B/4) (laboratoires Aventis).

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CODE CIP	PRÉSENTATION
322 293-6	Sympaneurol Papaverine, comprimés enrobés (B/60) (laboratoires DP Pharma).
310 246-8	Sympaneurol Papaverine, comprimés enrobés (B/20) (laboratoires DB Pharma).
348 621-0	Sympathyl, comprimés pelliculés (B/40) (laboratoires Innothera).
310 251-1	Sympavagol, comprimés enrobés (B/40) (société Novartis Santé familiale SA).
310 252-8	Sympavagol, solution buvable, 90 ml en flacon (société Novartis Santé familiale SA).
310 413-1	Terramycine solu-retard 250 mg, solution injectable (IM), 3 ml en ampoule (B/1) (laboratoires Pfizer).
346 464-5	Thiocolchicoside Byla 4 mg/2 ml, solution injectable (IM), 2 ml en ampoule (B/6) (société Wyeth Lederlé).
310 719-3	Topifram (desoximétasone, sulfate de framicétine, gramicidine), crème, 15 g en tube (B/1) (laboratoires Aventis).
340 972-9	Tranquital, comprimés enrobés (B/30) (société Novartis Santé familiale SA).
340 973-5	Tranquital, comprimés enrobés (B/100) (société Novartis Santé familiale SA).
345 229-2	Trimadiaz Antrima (sulfadiazine, triméthoprime), comprimés (B/10) (laboratoires Doms-Adrian).
345 228-6	Trimadiaz Antrima Nourrisson et Enfant (sulfadiazine, triméthoprime), suspension buvable, 50 ml en flacon avec cuillère-mesure (laboratoires Doms-Adrian).
310 906-8	Trophysan L glucidique 50, soluté injectable, 500 ml en flacon (B/1) (laboratoires Baxter SA).
310 911-1	Trophysan L simple, soluté injectable, 500 ml en flacon (B/1) (laboratoires Baxter SA).
329 429-0	Tulle gras Lumière, pansement, compresses de 20 cm × 20 cm (B/10) (laboratoires Solvay Pharma).
314 234-4	Tulle gras Lumière, pansement, compresses de 10 cm × 10 cm (B/10) (laboratoires Solvay Pharma).
314 489-2	Ulcar 1 g (sucralfate), comprimés (B/30) (laboratoires Aventis).

CODE CIP	PRÉSENTATION
332 839-1	Ulcar 1 g (sucralfate), suspension buvable en sach (B/30) (laboratoires Aventis).
342 433-8	Vagostabyl, comprimés enrobés (B/40) (laboratoires Le quin Mediolanum).
322 294-2	Vita 3, collyre, 10 ml en flacon (laboratoires Nova Ophthalmics).
311 422-4	Vitableu 0,1 %, collyre, 10 ml en flacon (laboratoi Novartis Ophthalmics).
321 574-1	Vitacic, collyre, 0,4 ml en récipient unidose (B/20) (labo toires Novartis Ophtalmics).
322 178-2	Vitacic, collyre, 5 ml en ampoule (B/1) (laboratoi Novartis Ophthalmics).
342 750-3	Vitalens, collyre en flacon de 10 ml (laboratoires Nova Ophthalmics).
336 621-0	Vitamine B12 Allergan France 0,2 mg/0,4 ml, collyre, ml en récipient unidose (B/20) (laboratoires Aller France SA).
311 343-7	Vitamine B12 Dulcis 0,50 pour mille, collyre, 5 ml flacon (laboratoires Allergan France SA).
348 550-6	Vitamine B12 Thea 0,05 % (0,2 mg/0,4 ml), collyre, 0,4 en récipient unidose (B/20) (laboratoires Thea).
311 458-9	Vitaphakol, collyre, 10 ml en flacon (laboratoires Nova Ophthalmics).
311 460-3	Vitargenol 5 %, collyre, 15 ml en flacon (laboratoi Novartis Ophthalmics).
335 194-1	Vitarutine (nicotinamide, sulforutoside sodique), colly 10 ml en flacon (laboratoires Novartis Ophthalmics)
335 196-4	Vitasedine, collyre, 10 ml en flacon (laboratoires Nova Ophthalmics).
317 754-9	Vitaseptol, collyre, 10 ml en flacon (laboratoires Nova Ophthalmics).
335 195-8	Vitazinc, collyre, 10 ml en flacon (laboratoires Nova Ophthalmics).

Arrêté du 20 décembre 2001 fixant le prix de vente au public, toutes taxes comprises, des greffons veineux de ve saphène d'origine humaine inscrits au titre III de la liste des produits et prestations remboursables prévue à l'art L. 165-1 du code de la sécurité sociale

NOR : *MESS0124397A*

Le ministre de l'économie, des finances et de l'industrie, la ministre de l'emploi et de la solidarité et le ministre délégué à la sa

Vu le code de la sécurité sociale, et notamment ses articles L. 162-38, L. 165-1 à L. 165-5 et R. 165-1 à R. 165-30 ;

Vu le code de la santé publique ;

Vu le livre IV du code de commerce ;

Vu le décret n° 86-1309 du 29 décembre 1986 fixant les conditions d'application de l'ordonnance n° 86-1243 du 1er décembre 1 susvisée ;

Vu le décret n° 88-854 du 28 juillet 1988 fixant les sanctions applicables aux infractions aux arrêtés prévus par l'article L. 162-38 du c de la sécurité sociale ;

Vu l'avis du comité économique des produits de santé du 26 octobre 2001,

Arrêtent :

Art. 1er. – Le prix de vente maximum au public, toutes taxes comprises, des greffons veineux de veine saphène d'origine humaine ins au titre III de la liste des produits et prestations remboursables prévue à l'article L. 165-1 du code de la sécurité sociale est fixé comme s

CODE	RÉFÉRENCE	SOCIÉTÉ	PRIX LIMITE DE VENTE au public TTC (en euros)	DATE DE FIN de prise en charge
		Greffon de veine saphène		
303803.1	Veine saphène.....	Bioprotec	1 372,04	1er août 2002

Annexe 4-26

MINISTERE DE L'EMPLOI
ET DE LA SOLIDARITE

REPUBLIQUE FRANCAISE

PARIS, le 10 OCT. 2001

DIRECTION DE LA SECURITE SOCIALE
DIRECTION GENERALE DE LA SANTE

Monsieur le Président,

La commission de la transparence, dans le cadre de la procédure de réévaluation décidée par la ministre de l'emploi et de la solidarité en 1998, a considéré notamment que le service médical rendu des spécialités dont la liste est fixée en annexe était insuffisant pour justifier une prise en charge par l'assurance maladie. La ministre de l'emploi et de la solidarité a décidé de tirer les conséquences de ces avis en prenant plusieurs mesures dont notamment une baisse du taux de remboursement.

Nous vous informons donc que nous envisageons de porter à 65% la participation de l'assuré et, en conséquence, de baisser à 35% le taux de prise en charge par l'assurance maladie de ces spécialités.

Votre laboratoire étant concerné par cette mesure, nous vous informons que vous avez la possibilité de présenter des observations écrites ou demander à être entendu par la commission de la transparence dans le mois suivant la réception de la présente lettre, conformément aux dispositions de l'article R. 163-13 du CSS.

Vos observations écrites éventuelles et vos demandes d'audition devront être adressées au ministère de l'emploi et de la solidarité, 8, avenue de Ségur 75007 PARIS, Direction de la sécurité sociale, bureau 1C (pièce 5129) avec copie à l'Agence française de sécurité sanitaire des produits de santé.

Nous vous indiquons également que cette mesure serait appliquée au 1er janvier 2002 afin qu'elle coïncide avec les opérations de revignettage nécessitées par le passage à l'Euro.

Nous vous prions d'agréer, Monsieur le Président, l'expression de notre considération distinguée.

Le Directeur Général

Professeur Lucien ABENHAIM

L. ABENHAIM

P.L. BRAS

Le Directeur de la sécurité sociale

Pierre-Louis BRAS

M. Jacques SERVIER
Président Directeur Général
SERVIER S.A.S
22 Rue Garnier
92200 NEUILLY SUR SEINE

Annexe 4-27

LES LABORATOIRES SERVIER

RECHERCHE MÉDICALE ET CRÉATION DE MÉDICAMENTS

FL
MPP
MJ
copie pour audition à mettre à l'OJ du 28/11

Monsieur le Professeur L. Abenhaïm
Directeur Général de la Santé

Monsieur P-L. Bras
Directeur de la Sécurité Sociale

Ministère de l'Emploi et de la Solidarité
Bureau 1 C (Pièce 5129)
8, avenue de Ségur
75007 PARIS

Neuilly-sur-Seine, le 12 novembre 2001.

DEMEIS
Arrivé le 15 NOV. 2001
N°3050
Transmis à : CB

N/Réf. : IT/dst/01.1293
☎ 01 55 72 65 34
Fax : 01 55 72 33 02

Objet : **Notre spécialité :**
MEDIATOR,® comprimés enrobés
V/Courrier du 10.10.2001

Messieurs les Directeurs,

Par votre courrier du 10.10.2001 (reçu le 12.10.2001), vous nous informez que vous envisagez de baisser à 35% le taux de prise en charge par l'assurance maladie de notre spécialité :

MEDIATOR,® comprimés enrobés,

dans la mesure où la Commission de la Transparence, dans le cadre de la procédure de réévaluation décidée en 1998, a considéré que le service médical rendu par cette spécialité était insuffisant ; cette appréciation reposant sur l'avis rendu à propos de l'indication principale de notre spécialité à la date 19.11.1999 : "*Adjuvant du régime adapté dans le diabète asymptomatique avec surcharge pondérale*".

Or il s'avère que, depuis (cf. notre courrier en date du 11.09.01), l'indication de MEDIATOR® dans le diabète a été validée selon le nouveau libellé suivant :

"Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale". (cf. modification de l'A.M.M. du 12.06.01).

SERVIER

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Cette indication a été agréée sur la base d'un dossier synthétisant les principales études pharmacologiques et cliniques disponibles, qui permet de positionner MEDIATOR® comme une alternative utile à la metformine.

En effet, l'action principale de MEDIATOR® chez les diabétiques de type 2 est **un effet insulino-sensibilisateur**, qui a été démontré par trois études de clamp hyperinsulinémique eu- (1,2) ou iso-glycémique (3), réalisées en double aveugle contre placebo.

Son mode d'action in vitro est différent de celui de la metformine et des thiazolidinediones : il s'exerce via un effet direct sur le foie (modifications de l'activité et de l'expression génique d'enzymes clés du métabolisme hépatique du glucose et des acides gras) et un effet indirect sur le muscle par la diminution des flux de triglycérides (4-11).

MEDIATOR® est utilisé depuis de nombreuses années dans le traitement du diabète de type 2, mais la démonstration de son efficacité reposait essentiellement sur des études réalisées en double aveugle versus placebo, aux effectifs relativement limités, qui ont montré néanmoins un effet cliniquement significatif avec une différence d'évolution de l'HbA1c de l'ordre de 1% au terme de 3 mois de traitement, à différents stades de la maladie :

- en monothérapie chez des patients nouvellement diagnostiqués insuffisamment contrôlés par régime seul (12),
- en association aux sulfonylurées (13) ou à la metformine (14) chez des patients insuffisamment contrôlés sous sulfonylurées ou metformine en monothérapie,
- et en association à l'insuline chez des patients insulino-requérants (15-17).

Une étude à plus large échelle a été récemment réalisée, comparant en double aveugle l'efficacité et la sécurité d'emploi de MEDIATOR®, de la metformine et d'un placebo au cours de 6 mois de traitement (18).
Cette étude a inclus 722 patients à un stade relativement précoce de la maladie, afin de permettre l'inclusion d'un groupe placebo suivi 8 mois (2 mois de pré-inclusion et 6 mois de traitement). Cette population était assez similaire aux 1704 patients éligibles pour le traitement par la metformine dans l'étude UKPDS (valeurs moyennes à l'inclusion : IMC 31 kg/m^2, HbA_{1c} 7,2%, glycémie à jeun 8,1 mmol/L dans UKPDS, et respectivement 30 kg/m^2, 7,6% et 10 mmol/L dans cette étude).

Annexe 4-27

L'effet sur le contrôle glycémique au terme de 6 mois de traitement dans cette étude a confirmé celui observé dans les précédentes études, avec une différence d'évolution de l'HbA_{1c} de près de 1% entre MEDIATOR® et le placebo chez les patients dont l'HbA_{1c} était comprise entre 6% et 8,5% au terme de 2 mois de régime intensif. L'effet a été plus prononcé chez les patients dont l'hyperglycémie était plus sévère à l'inclusion (HbA_{1c} > 8%), avec une diminution en valeur absolue de 1,5%, et une différence de 1,7% avec le groupe placebo. Dans cette étude, la différence finale d'HbA_{1c} entre MEDIATOR® et metformine était de 0,28 ± 0,12% (test de non-infériorité : p = 0,037, avec une limite supérieure de l'I.C. à 90 % au-dessous de la limite d'équivalence clinique fixée à 0,5 %). Cliniquement, cette différence pourrait traduire une puissance de MEDIATOR® légèrement inférieure à la metformine, probablement due à l'utilisation d'un dosage (moyenne 2,65 comprimés par jour), inférieur au dosage recommandé (3 comprimés par jour).

Un **programme d'études complémentaires** répondant aux standards qui seraient actuellement requis pour tout nouveau traitement du diabète a été envisagé, afin de mieux préciser la place de MEDIATOR® par rapport à la metformine dans la stratégie thérapeutique telle que définie par les recommandations de l'A.F.S.S.A.P.S. (02.99) et de l'ANAES (03.00), y compris chez des patients à un stade plus avancé de la maladie :

Deux études incluant près de 700 patients sont d'ores et déjà en cours de mise en place :

1 - Une étude comparant MEDIATOR® au placebo chez des patients insuffisamment contrôlés sous sulfonylurées en monothérapie, et présentant des contre-indications relatives ou absolues à l'usage de la metformine (produit d'association de première intention dans les recommandations de l'A.F.S.S.A.P.S. - Février 1999 pour la prise en charge du patient diabétique de type 2).
La durée du suivi sera de 7 mois (6 mois de maintenance après une période de titration initiale). Cette étude permettra de confirmer les données préalablement obtenues avec des effectifs plus faibles, et le positionnement de MEDIATOR® en tant qu'alternative thérapeutique à l'usage de la metformine, quand cette dernière ne peut être utilisée compte tenu de ses précautions d'emploi ou contre-indications.

2 - Une étude comparant MEDIATOR® au placebo chez des patients insuffisamment contrôlés sous metformine en monothérapie. En effet, il apparaît aujourd'hui intéressant, au vu des études réalisées sur l'association de la metformine et des thiazolidinediones, de prescrire une association de deux insulino-sensibilisateurs.

Annexe 4-27

Or, le mode d'action de MEDIATOR® et de la metformine sur la sensibilité à l'insuline est complémentaire. MEDIATOR® constitue donc une alternative thérapeutique utile aux thiazolidinediones, puisqu'il présente très peu de contre-indications (pancréatites chroniques avérées et hypersensibilité au benfluorex ou à l'un de ses excipients), et ne nécessite pas de surveillance biologique particulière. La durée du suivi sera également de 7 mois.

Au total et en résumé :

- La place de MEDIATOR® chez le diabétique vient d'être confirmée (A.M.M. validée en date du 12.06.01).
- L'évaluation de son Service Médical Rendu est antérieure, tout comme la publication des «*Recommandations pour le traitement médicamenteux du diabète de type 2*» (AFSSAPS - février 1999) et la «*Stratégie de prise en charge du patient diabétique de type 2, à l'exclusion de la prise en charge des complications*» (ANAES - mars 2000), documents qui ne pouvaient, par conséquent, en faire état.
- Nous sommes prêts à nous engager, y compris par voie conventionnelle, sur la réalisation d'un programme d'études visant à confirmer et préciser la place de MEDIATOR® dans la stratégie thérapeutique du diabète. Nous nous tenons à votre disposition pour vous en exposer les synopsis. La mise en place des deux études ci-dessus mentionnées est en cours, en vue de résultats escomptés pour début 2004.

Dans ce cadre et compte tenu de ces nouveaux éléments, comme vous nous en offrez la possibilité, nous vous demandons de présenter ces observations à la Commission de la Transparence, en vue de la réévaluation du Service Médical Rendu par notre spécialité MEDIATOR®.

Dans l'attente, nous vous prions donc de bien vouloir surseoir à votre décision.

Nous vous prions d'agréer, Messieurs les Directeurs, l'expression de notre considération distinguée.

Pierre MONTES
Pharmacien Responsable Intérimaire

P.J. : *Annexe 1 : Références bibliographiques (1) à (18),*
Annexe 2 : A.M.M. du 12.06.01.

Cc. : *Monsieur le Directeur Général de l'A.F.S.S.A.P.S.*

Annexe 4-28

MINISTERE DE L'EMPLOI
ET DE LA SOLIDARITE

REPUBLIQUE FRANCAISE

DIRECTION DE LA SECURITE SOCIALE

Sous-direction du financement du système de soins
Bureau : 1C
personne chargée du dossier : C.Dumont/ Ch. Draicchio/ M.Larreur
tél : 01-40-56-42-05 fax 01-40-56-75-62:
e.mail :
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PARIS, 24 DEC. 2001

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NOTE
pour la Ministre et pour le Ministre délégué

A l'attention de M.Romaneix et Mme Wargon, conseillers techniques

Objet : Baisse du taux de remboursement de certains médicaments

Réf : Ma note en date du 28 novembre.

Comme je vous l'indiquais dans ma note susvisée, il n'a pas été possible de procéder à l'élaboration d'un arrêté unique portant à 35% le taux de remboursement de l'ensemble des médicaments dont le service médical rendu a été jugé insuffisant par la commission de la transparence dans le cadre de la procédure de réévaluation.

En effet, un certain nombre de laboratoires ont formulé des observations, suite au courrier du 10 octobre 2001 les informant de l'intention des pouvoirs publics de procéder à la baisse de taux des spécialités concernées qu'ils exploitent.

Le premier arrêté qui ne concerne donc que les médicaments pour lesquels les laboratoires n'ont pas formulé d'observations est en cours de publication.
Le 2ème arrêté concerne les médicaments pour lesquels les laboratoires nous ont fait parvenir des observations. Leurs génériques figureraient également dans ce second texte.
Les points suivants sont à noter :

1. Trois spécialités (hydracort, mediator, pepsane) ayant un niveau de Service Médical Rendu (SMR) insuffisant dans toutes leurs indications ont fait l'objet d'un nouvel examen de la commission de la transparence. Pour ces 3 produits l'avis de la commission de la transparence a été confirmé. Nous vous proposons de porter leur taux de remboursement à 35%.

Copie : Hélène Sainte- Marie, DGS

2. Le laboratoire Alpharma conteste la baisse du taux de la spécialité Galirène au motif que cette mesure [illegible] pour effet [illegible] un report de prescription vers des [illegible]

3. La spécialité Méthotrexate [illegible] a reçu un niveau de SMR insuffisant dans les indications de son AMM. Or ce produit est principalement utilisé depuis des années dans une indication hors AMM : la polyarthrite rhumatoïde. Il convient de noter que le laboratoire Aventis (anciennement Roger Bellon) n'a jamais déposé de demande de modification de son AMM afin d'obtenir cette indication. Il existe depuis 1995, un médicament ayant exactement la même composition : le Novatrex (Wyeth-Léderlé) qui lui a l'AMM dans l'indication de la polyarthrite rhumatoïde, est remboursable et a obtenu un niveau de SMR important. Le laboratoire Aventis nous a signalé que dans l'hypothèse où le taux de remboursement de Methotrexate serait ramené à 35% il en arrêterait la commercialisation. Cependant et compte tenu du fait que cette spécialité a été utilisée et remboursée dans une indication hors AMM pendant des années sans que le laboratoire ne fasse la moindre démarche pour régulariser cette situation. Je vous propose d'adresser un courrier au laboratoire en lui indiquant que s'il ne demande pas la modification de son AMM afin de régulariser sa situation dans un délai de 6 mois, le taux de remboursement de cette spécialité sera porté à 35%.

4. Le laboratoire Aventis nous a également saisi de la situation de la spécialité colimycine injectable qui a obtenu un niveau de SMR insuffisant dans les indications de son AMM mais qui est utilisé hors AMM dans une indication pédiatrique pour les enfants souffrant de mucoviscidose. Je vous propose de tenir le même raisonnement que pour Méthotréxate et de saisir le laboratoire d'une demande de régularisation de ses indications de l'AMM dans un délai de 6 mois en lui précisant qu'en l'absence de cette démarche le taux de remboursement de cette spécialité sera porté à 35%.

5. La spécialité Cognex utilisée dans le traitement de la maladie d'Alzheimer ne fait à l'heure actuelle plus l'objet d'initialisation de nouveaux traitements mais concerne des patients anciennement traités et qui supportent bien ce produit. S'agissant d'un médicament qui n'étant plus prescrit dans de nouveaux traitements va progressivement quitter le marché et compte-tenu de la gravité de la pathologie en cause, je vous propose de maintenir son taux de remboursement à 65%. De plus, la pathologie étant prise en charge à 100%, cette baisse de taux ne conduirait à aucune économie pour l'assurance maladie.

6. Les autres spécialités[1] pour lesquelles des observations ont été formulées présentent toutes la caractéristique d'avoir obtenu un niveau de SMR modéré ou faible dans certaines de leurs indications et insuffisant dans d'autres. La commission de la transparence a confirmé ses avis sans définir les indications prévalentes. Dans ces conditions, et à l'appui des documents dont nous disposons (analyse de la prescription médicale de la société IMS) et qui ont montré que les prescriptions les plus importantes pour ces spécialités étaient effectuées dans les indications ayant un niveau de service médical rendu modéré ou faible, je vous propose de maintenir le taux de remboursement de ces spécialités à 65%, à l'exception de Vitamine A faure pour laquelle les données sur la prescription indiquent que l'indication la plus prescrite est celle qui a un niveau de SMR insuffisant. La même décision sera appliquée à leurs génériques

[1] il s'agit de : Vastarel, Centrofène, Ikaran, Seglor, Prazinil et Vitamine A Faure, collyre.

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7. J'attire néanmoins votre attention sur la situation de la spécialité Vastarel (laboratoires Servier). En effet, si l'on considère uniquement les indications de son AMM (« traitement de l'angine de poitrine et vertiges) Vastarel est effectivement prescrit majoritairement dans l'indication : « traitement de l'angine de poitrine » pour laquelle ce médicament a eu un niveau de SMR modéré.

En revanche, il convient de noter que cette spécialité est **prescrite à plus de 50% dans des indications hors AMM sans justification de santé publique.**
En effet, les données sur la prescription dont nous disposons nous indiquent que VASTAREL est prescrit dans de multiples indications telles que les maladies hypertensives, les troubles mentaux organiques, l'infarctus du myocarde aigu et même pour 8,2% dans des indications non déterminées. L'utilisation de VASTAREL dans ces indications n'est validée, à ce jour, par aucune donnée scientifique. Je vous précise que les montants remboursés pour Vastarel étaient de 648 MF en 2000 pour des dépenses présentées au remboursement de 821 MF (source CNAMTS). Ces montants ne concernent que le régime général qui représente environ 70% de la dépense totale. On peut donc estimer la dépense totale à 925 MF pour l'ensemble des régimes en ce qui concerne les remboursements et à 1173 MF les dépenses présentées au remboursement. Le chiffre d'affaires TTC de la spécialité est de 1221 MF en 2000 (source GERS). On peut donc estimer que seulement 4% des achats de Vastarel ne sont pas remboursés alors que 51% des prescriptions sont réalisées en dehors des indications de l'AMM.
Une telle dérive me semble inacceptable.

Les solutions suivantes sont envisageables :

- Baisse du taux de remboursement de Vastarel à 35%

Cette décision serait fondée sur le fait que les indications dans lesquelles Vastarel est prescrit font généralement l'objet de traitement par des spécialités dont le niveau de smr a été jugé insuffisant (notamment en ce qui concerne les prescriptions dans les indications de vaso-dilatateur périphérique).
Toutefois cette option est extrêmement fragile juridiquement.
En effet, seule la commission de la transparence est habilitée à évaluer le niveau de smr d'un médicament. Toutefois, elle ne pourra pas donner un avis sur des indications hors AMM dans la mesure où une telle démarche reviendrait à se prononcer sur la validité même de ces indications ce qui n'entre pas dans son champ de compétence. Les ministres ne peuvent pas non plus porter une telle appréciation sans les avis des commissions compétentes (AMM et transparence).

- En revanche, il semble juridiquement possible de procéder à la radiation de la liste des spécialités remboursables de cette spécialité. En effet, le 3° de l'article R 163-5 du code de la sécurité sociale précise que les médicaments susceptibles d'entraîner des dépenses injustifiées ne peuvent faire l'objet d'une inscription sur la liste des spécialités remboursables. L'article R 163-7 d même code indique que les médicaments mentionnés au 3° de l'article R 163-5 peuvent faire l'objet d'une radiation de la liste des spécialités remboursables. Dans le cas d'espèce, le caractère injustifié des dépenses entraînées par les prescriptions hors AMM de Vastarel n'est pas contestable. De ce fait, la décision de radiation serait juridiquement fondée. Aussi, je vous propose de saisir le laboratoire Servier de mon intention de radier Vastarel de la liste des spécialités remboursables dés lors qu'il n'y aurait pas eu de régularisation de sa situation vis à vis de l'AMM. Le laboratoire aura alors un mois pour formuler des observations. Cette saisine suppose l'accord de la DGS sur ce scénario dans la mesure où ce type de courrier doit être signé conjointement par nos deux directions.
- En tout état de cause, ce courrier présentera l'avantage de mettre le laboratoire dans une position où il sera contraint, s'il veut éviter la radiation, de nous fournir des éléments

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justifiant les prescriptions hors AMM de son produit voire de demander une régularisation de ces indications à la commission d'AMM, ce qui permettra par la suite à la commission de la transparence de se prononcer sur le niveau de smr de cette nouvelle indication et donc d'aboutir très probablement à une baisse du taux de remboursement.

- Si toutefois cette proposition ne recueillait pas votre accord, il conviendrait de demander au Comité Economique des Produits de Santé de bien vouloir examiner la possibilité d'une baisse de prix de ce produits.

8. Concernant la spécialité Succiminide Pharbiol (laboratoire Labomed), le niveau de SMR retenu par la commission de la transparence est insuffisant mais le laboratoire fait valoir que dans l'indication : lithiases oxaliques il n'existe aucune alternative thérapeutique médicamenteuse, la seule alternative est l'hospitalisation. Pour cette raison, l'an dernier, les pouvoirs publics ont demandé au laboratoire Labomed de maintenir ce produit sur le marché en lui accordant une hausse de prix pour l'y inciter. Dans ces conditions et par cohérence avec les décisions prises l'an dernier sur cette spécialité, il semble inopportun un an après et alors qu'il n'y a toujours pas d'alternative thérapeutique médicamenteuse de procéder à la baisse du taux de remboursement de ce produit.

9. Trois spécialités ont fait l'objet d'une notification complémentaire postérieure à celle du 10 octobre : Nopron, Vita-3 et Asthmasédine. A ce jour, seul le laboratoire NOVARTIS (Vita 3) a fait part de son accord sur la baisse du taux.et Vita-3 a pu être intégré dans le 1er arrêté.

Cette mesure devait prendre effet le 1er janvier 200, mais il est désormais impossible de respecter ce calendrier.
Je vous informe que j'ai donc indiqué aux laboratoires concernés que la décision de baisse de taux pour leurs spécialités n'étaient pas encore arrêtée.
Toutefois, il va de soi que je souhaiterais que cette mesure puisse être effective rapidement. Elle pourrait, par exemple, prendre place en même temps que la baisse de la marge des pharmaciens qui est envisagée. Aussi, je vous serais obligé de bien vouloir me faire parvenir votre avis sur les propositions contenues dans la présente note dans les meilleurs délais possibles

Le Directeur de la Sécurité Sociale,

Pierre-Louis BRAS

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Ministère des affaires sociales, du travail et de la solidarité

Ministère de la santé, de la famille et des personnes handicapées

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Paris - 8 AOUT 2002

NOTE POUR LE MINISTRE DE LA SANTE, DE LA FAMILLE ET DES PERSONNES HANDICAPEES

A l'attention de Monsieur Ph.Georges, directeur-adjoint de cabinet, MM.D.Eyssartier et J.de-Tournemire, conseillers techniques
Copie à M.P.Mayeur, conseiller technique au cabinet du ministre des Affaires sociales, du travail et de la solidarité.

Objet : Baisse du taux de remboursement des médicaments à service médical rendu insuffisant – mesures complémentaires à celles prises en 2001

La réévaluation du service médical rendu des médicaments par la commission de la transparence a conduit dans un premier temps, en août 2000, à baisser de 65% à 35% le taux de remboursement des vasodilatateurs.
Cet arrêté ayant fait l'objet d'une annulation par le Conseil d'Etat pour vice de forme, un deuxième arrêté a été pris pour ces produits en septembre 2001.
Pour la quasi-totalité des médicaments à service médical rendu insuffisant appartenant à d'autres classes thérapeutiques, le taux de remboursement a été porté à 35% par arrêté de décembre 2001.

Quelques produits bénéficient encore d'un taux de 65%.

Un certain nombre d'entreprises ont formulé des observations suite au courrier qui leur avait adressé en octobre 2001, les informant de l'intention des pouvoirs publics de procéder à la baisse des taux de remboursement des spécialités à SMR insuffisant qu'ils exploitaient.
Ces observations ont donné lieu à un nouvel examen par la commission de la transparence qui a confirmé ses avis précédents. La mise en place de cette procédure n'a toutefois pas permis que certains de ces produits puissent être rattachés à l'arrêté publié en décembre 2001.

Copie DGS (Hélène Sainte-Marie)

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Le cabinet précédent a été sollicité par la DSS en décembre 2001 ainsi que par la DGS en janvier 2002, pour accord sur la suite à donner aux propositions faites par les deux directions. Pour certains des médicaments concernés, ces propositions divergeaient. Le cabinet n'a pas fait part de sa position.

Il subsiste donc sur le marché quelques produits pour lesquels il serait nécessaire de prendre un arrêté ramenant leur taux de prise en charge de 65% à 35%, même si la décision était prise de dérembourser ultérieurement ces produits.

Une fiche jointe en annexe détaille les différents cas individuels en précisant la position de la DSS ainsi que celle de la DGS sur la base des observations faites par cette direction en janvier 2002. Il en ressort que pour six spécialités[1], la baisse de taux pourrait être immédiate. Elle est particulièrement nécessaire pour le Médiator(laboratoires Servier) dont les dépenses présentées au remboursement du régime général s'élevaient à 30 ME en 2001. Pour deux produits [2]des négociations devraient être menées avec les entreprises afin de les amener à déposer un dossier d'extension d'indication de leur autorisation de mise sur le marché ; ces produits sont en effet essentiellement prescrits hors AMM et le service médical rendu apprécié par la commission ne concerne bien entendu que les indications reconnues. Cinq produits [3]devraient être maintenus à 65% (ainsi que les médicaments faisant le cas échéant partie du même groupe générique).

J'appelle en particulier votre attention sur le cas du Vastarel des laboratoires Servier. En effet ce produit a eu un niveau de SMR modéré pour deux de ses indications qui représentent l'essentiel des prescriptions dans les indications de son AMM, le SMR pour ces autres indications étant insuffisnt. Par contre il est prescrit à plus de 50% dans des indications en dehors de celles de son AMM.La solution envisageable serait un passage à 35% justifié par le SMR modéré dans les indications prévalentes de l'AMM, assorti d'une menace de radiation si l'entreprise ne régularise pas la situation de son produit. L'enjeu est important car ce produit occupe en 2001 la 10ème place des produits remboursés.

Je vous remercie de me faire part de votre position sur chacun des cas évoqués.

Le chef de service,
oint au directeur de la sécurité sociale

Dominique LIP[illegible]

[1] Hydracort, Médiator, Pepsane, Galirène, Nopron et Asthmasedine
[2] Methotrexate et Colymicine injectable
[3] Cognex , Seglor, Ikaran, Prazinil, et Succinimide Pharbiol

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DSS/FSS/1C

BAISSE DU TAUX DE REMBOURSEMENT DES MEDICAMENTS A SMR INSUFFISANT

I – Dossiers faisant l'objet d'une position commune DSS/DGS et n'ayant pas fait l'objet de remarques de la part de l'AFSSAPS

1 – Trois spécialités (Hydracort, Mediator, Pepsane) ayant un niveau de service médical rendu (SMR) insuffisant dans toutes leurs indications ont fait l'objet d'un nouvel examen de la commission de la transparence. Pour ces trois produits l'avis de la commission de la transparence a été confirmé. Nous vous proposons de porter leur taux de remboursement à 35%.

2 – Le laboratoire Alpharma conteste la baisse du taux de la spécialité **Galirène** au motif que cette mesure aura pour effet d'entraîner un report de prescription vers des anxiolytiques plus puissants. Cette remarque ne semble pas recevable aussi je vous propose de **ramener le taux de remboursement de cette spécialité à 35 %**, d'autres spécialités comparables ayant vu leur taux ramené à 35% en décembre 2001 .

3 – La spécialité **Cognex** utilisée dans le traitement de la maladie d'Alzheimer ne fait à l'heure actuelle plus l'objet d'initialisation de nouveaux traitements mais concerne des patients anciennement traités et qui supportent bien ce produit. S'agissant d'un médicament qui n'étant plus prescrit dans de nouveaux traitements va progressivement quitter le marché et compte tenu de la gravité de la pathologie en cause, je vous propose de **maintenir son taux de remboursement à 65 %** De plus, la pathologie étant prise en charge à 100 %, cette baisse de taux ne conduirait à aucune économie pour l'assurance maladie.

4– La spécialité **Methotrexate** (laboratoire Aventis) a eu un niveau de SMR insuffisant dans les indications de son AMM. Or, ce produit est principalement utilisé depuis des années dans une indication hors AMM : la polyarthrite rhumatoïde. Il convient de noter que le laboratoire Aventis (anciennement Roger Bellon) n'a jamais déposé de demande de modification de son AMM afin d'obtenir cette indication. Il existe depuis 1995, un médicament ayant exactement la même composition : le Novatrex (Wyeth-Léderlé) qui lui a l'AMM dans l'indication de la polyarthrite rhumatoïde, est remboursable et a obtenu un niveau de SMR important. Le laboratoire Aventis a signalé que dans l'hypothèse où le taux de remboursement de Méthotréxate serait ramené à 35 % il en arrêterait la commercialisation. Cependant et compte tenu du fait que cette spécialité a été utilisée et remboursée dans une indication hors AMM pendant des années sans que le laboratoire ne fasse la moindre démarche pour régulariser cette situation, je vous propose **d'adresser un courrier au laboratoire en lui indiquant que s'il ne demande pas la modification de son AMM afin de régulariser sa situation dans un délai de 6 mois, le taux de remboursement de cette spécialité sera porté à 35 %.** La DGS, soucieuse de ne pas créer une situation de monopole au profit de Wyeth-Lederle, estime également nécessaire de négocier avec Aventis pour lui demander de déposer une demande d'extension d'AMM et de maintenir son produit sur le marché. L'AFSSAPS estime correct le délai de 6 mois proposé ci-dessus.

5 – Concernant la spécialité **Succinimide Pharbiol** (laboratoire Labomed), le niveau de SMR retenu par la commission de la transparence est insuffisant mais le laboratoire fait valoir que dans l'indication « lithiases oxaliques » il n'existe aucune alternative thérapeutique médicamenteuse,

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eule alternative est l'hospitalisation. Pour cette raison, en 2000, les pouvoirs publics ont andé au laboratoire Labomed de maintenir ce produit sur le marché en lui accordant une se de prix pour l'y inciter. Dans ces conditions et par cohérence avec les décisions prises érieurement sur cette spécialité, il semble inopportun alors qu'il n'y a toujours pas alternative thérapeutique médicamenteuse de procéder à la baisse du taux de remboursement de ce produit. L'AFSSAPS mentionne toutefois que la place de ce médicament par rapport à d'autres alternatives thérapeutiques tels que la litotrypsie paraît limitée.

6 – Le laboratoire Aventis nous a saisi de la situation de la spécialité **Colimycine injectable** qui a obtenu un niveau de SMR insuffisant dans les indications de son AMM mais qui est utilisée hors AMM pour les enfants souffrant de mucoviscidose. La DSS propose de tenir un **raisonnement analogue à celui du Méthotréxate** . Toutefois, au vu des observations formulées par l'AFSSAPS, l'engagement à demander au laboratoire concernerait le dépôt dans un délai de 6 mois d'un programme de développement préalable à une demande d'extension d'AMM en lui précisant qu'en l'absence de cette démarche le taux de remboursement de cette spécialité sera porté à 35 %. La DGS estime pour sa part inopportun, dans le contexte de la politique d'encouragement des pouvoirs publics aux médicaments pédiatriques, de fixer un ultimatum au laboratoire alors qu'il n'aurait semble t'il maintenu son produit sur le marché que pour répondre à un besoin de santé publique à la demande des prescripteurs. Il semble toutefois difficile de maintenir la situation actuelle. Si l'utilisation de la Colimycine correspond à une pratique, une régularisation de l'AMM doit être demandée. Une négociation est à conduire avec l'entreprise .

7 –Certaines spécialités pour lesquelles des observations ont été formulées présentent la caractéristique d'avoir obtenu un niveau de SMR modéré ou faible dans certaines de leurs indications et insuffisant dans d'autres. La commission de la transparence a confirmé ses avis sans définir les indications prévalentes. Dans ces conditions, et à l'appui des documents dont nous disposons (analyse de la prescription médicale de la société IMS) et qui ont montré que les prescriptions les plus importantes pour ces spécialités étaient effectuées dans les indications ayant un niveau de SMR modéré ou faible, je vous propose de maintenir le taux de remboursement à 65 % pour Prazinil, Ikaran , et Seglor, (ainsi que pour les spécialités des mêmes groupes génériques, s'il y a lieu) tant que les décisions de baisse de taux ne seront pas prises pour les autres spécialités à SMR modéré ou faible .

8- Deux spécialités qui ont font l'objet d'une notification complémentaire postérieure à celle du 10 octobre (**Nopron**[4] et **Asthmasédine**) n'ont pas fait part d'observations et donc acceptent implicitement la baisse du taux.

II – Dossier faisant l'objet d'un désaccord entre DSS et DGS

Parmi les spécialités visées au point 7 ci-dessus, figure également la Vitamine A Faure collyre pour laquelle les données sur la prescription indiquent que l'indication la plus prescrite est celle qui a un niveau de SMR insuffisant, justifiant une baisse de taux de remboursement. La DGS n'est pas d'accord avec cette proposition car cette spécialité a un SMR modéré dans l'indication « xérosis conjonctival et cornéen » . Toutefois elle ne justifie pas que cette indication représente une part substantielle du volume prescrit et l'AFSSAPS mentionne qu'il s'agit d'une indication rare. Le passage à 35% est donc justifié au regard des règles adoptées par la commission de transparence pour attribuer les niveaux de service médical rendu.

[4] Nopron est en cours de négociation avec le CEPS en vue d'un déremboursement

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III - Spécialité Vastarel (laboratoires Servier).

Si l'on considère uniquement les indications de l'AMM (traitement prophylactique de la crise d'angine de poitrine ; traitement symptomatique d'appoint des vertiges et des acouphènes ; traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire) Vastarel est effectivement prescrit majoritairement (données sur la prescription médicale d'IMS) dans l'indication : « traitement de l'angine de poitrine » pour laquelle ce médicament a eu un niveau de SMR modéré.

En revanche, il convient de noter que cette spécialité est **prescrite à plus de 50% dans des indications hors AMM**.
En effet, les données sur la prescription dont nous disposons nous indiquent que VASTAREL est prescrit dans de multiples indications telles que les maladies hypertensives, les troubles mentaux organiques, l'infarctus du myocarde aigu et même pour 8,2 % dans des indications non déterminées. L'utilisation de VASTAREL dans ces indications n'est validée, à ce jour, par aucune donnée scientifique. Je vous précise que les montants remboursés pour Vastarel étaient de 83 ME en 2001 pour des dépenses présentées au remboursement de 104 ME (source CNAMTS). Ces montants ne concernent que le régime général qui représente environ 70 % de la dépense totale. On peut donc estimer la dépense totale à 118 ME pour l'ensemble des régimes en ce qui concerne les remboursements et à 149 ME les dépenses présentées au remboursement. Le chiffre d'affaires en prix public de la spécialité est environ de 155 ME en 2001 (source GERS). On peut en conclure que toutes les prescriptions, y compris celles qui sont réalisées en dehors des indications de l'AMM, sont prises en charge par l'assurance maladie.

- Il est possible juridiquement de procéder à une baisse de taux car la spécialité a un SMR modéré dans les indications de l'AMM où le produit est majoritairement prescrit. Cette baisse pourrait donc intervenir soit immédiatement, soit conjointement avec celles des autres spécialités de SMR modéré. Par ailleurs, je vous propose de menacer l'entreprise d'une radiation de son produit s'il ne régularise pas sa situation au regard des indications de l'AMM. Ce courrier présentera l'avantage de mettre le laboratoire dans une position où il sera contraint, s'il veut éviter la radiation, de nous fournir des éléments justifiant les prescriptions hors AMM de son produit voire de demander une régularisation de ces indications à la commission d'AMM, ce qui permettra par la suite à la commission de la transparence de se prononcer sur le niveau de SMR de cette nouvelle indication. S'il peut paraître difficilement envisageable de procéder, in fine, à la radiation de cette spécialité, il me semble que la menace de radiation est la seule voie possible pour responsabiliser le laboratoire Servier et l'engager à régulariser la situation de Vastarel vis à vis du remboursement ; Les génériques de cette spécialité (notamment Centrophène) se trouvant dans une situation comparable, je vous propose de leur appliquer la même procédure.

- Si toutefois, cette proposition ne recueillait pas votre accord, il conviendrait de demander au Comité Economique des Produits de Santé de bien vouloir examiner la possibilité d'une baisse de prix de ces produits. La DGS est favorable à une saisine du CEPS afin qu'il utilise les moyens en sa possession pour inciter la firme à déposer un dossier de demande d'extension d'AMM.

Annexe 4-30

Ministère des affaires sociales, famille
du travail et de la solidarité

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Ministère de la santé, de la
et des personnes handicapées

DSS/SD1/1C
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N° 02-7152 D

Paris, le 1 DEC. 2002

Note
pour le ministre

A l'attention de M. de Tournemire, conseiller technique
Copie : M.Eyssartier

Objet : Baisse de 65% à 35% des médicaments de SMR modéré ou faible
PJ : 2 lettres-type

Suite à vos instructions concernant le calendrier de mise en œuvre de la baisse du taux de remboursement des médicaments dont le niveau de service médical rendu a été jugé faible ou modéré par la commission de transparence, vous voudrez bien trouver ci-joint deux projets de lettres-type pour les industriels, leur faisant part de l'intention du Ministre de procéder à cette baisse et visant à recueillir leurs éventuelles observations ou demandes d'audition auprès de la commission de la transparence.
Le premier projet est destiné aux entreprises dont les médicaments ont un niveau de service médical rendu, pour l'ensemble de leurs indications, apprécié comme faible ou modéré par la commission de la transparence.
Le second projet sera adressé aux quelques entreprises dont les produits ont un niveau de service médical rendu faible ou modéré pour certaines indications et insuffisant pour d'autres. La plupart de ces produits ont été écartés en 2001 de la baisse de taux pour SMR insuffisant compte tenu de leur caractère particulier[1]. Ils doivent donc désormais faire l'objet de cette nouvelle notification, cette fois en raison de leurs indications à SMR faible ou modéré. Je vous avais d'ailleurs proposé, par note en date du 8 août 2002, de porter à 35% le taux de prise en charge de ces spécialités.
Par ailleurs, comme le prévoyait la même note, il conviendra de porter également à 35%, après information des entreprises, et sous réserve que ces spécialités ne figurent pas dans la première liste de médicaments à dérembourser, le taux de prise en charge de 6 produits à SMR insuffisant pour l'ensemble de leurs indications[2] mais n'ayant pas fait l'objet de baisse en décembre 2001.
Vous trouverez ci-joint une liste des produits concernés, qui est en cours de validation définitive. Le cas de quelques produits à niveau de SMR faible ou modéré pour certaines indications et important pour d'autres indications est également en cours d'examen.

Le chef de service
adjoint au directeur de la sécurité sociale

Dominique LIBAULT

Copie : M. MAYEUR

[1] Il s'agit des spécialités : DHE Sandoz et ses génériques (Seglor, Ikaran,Tamik) ainsi que de Vastarel et les produits contenant de la trimetazidine ou du chlorhydrate de trimetazidine et partageant les mêmes indications, de Prazinil , et de Vitamine A Faure.
[2] Il s'agit des spécialités Hydracort, Mediator, Pepsane, Galirène, Nopron et Asthmasédine.

Médicament	Niveau de SMR dans les indications de l'AMM	Niveau de SMR dans les indications hors AMM	Taux actuel de prise en charge	Proposition DSS 8/08/2002	position DGS au 8/08/2002	Mesure de déremboursement ou de baisse de taux	Proposition DSS février 2003
Seglor	modéré ou faible dans certaines indications et insuffisant dans d'autres		65%	maintien à 65% dans l'attente décision baisse de taux des SMR modéré ou faible		baisse de taux à 35% (lettre envoyée le 7/01/03)	clos
Ikaran	modéré ou faible dans certaines indications et insuffisant dans d'autres		65%	maintien à 65% dans l'attente décision baisse de taux des SMR modéré ou faible		baisse de taux à 35% (lettre envoyée le 7/01/03)	clos
Praxinil	modéré ou faible dans certaines indications et insuffisant dans d'autres		65%	maintien à 65% dans l'attente décision baisse de taux des SMR modéré ou faible		baisse de taux à 35% (lettre envoyée le 7/01/03)	clos
Vitamine A Faure	modéré ou faible dans certaines indications et insuffisant dans l'indication la plus prescrite		65%	35% car smr insuffisant pour la majorité des prescriptions	désaccord car SMR modéré dans l'indication "xérosis conjonctival et cornéen"	baisse de taux à 35% (lettre envoyée le 7/01/03)	clos
Succinimide Pharbiol	insuffisant		65%	maintien à 65% car pas d'alternative thérapeutique médicamenteuse dans l'indication de l'AMM			idem proposition 8/08/2002
Vastarel	modéré dans : -crise d'angine de poitrine (indication la plus prescrite parmi les indications de l'AMM), - vertiges et accouphènes; et insuffisant dans les autres	prescrite à plus de 50% dans des indications hors AMM	65%	35% et contact avec l'entreprise pour régularisation de la situation de l'AMM en menaçant de radiation	favorable à saisine du CEPS pour inciter le labo à demander des extensions d'AMM	baisse de taux à 35% (lettre envoyée le 7/01/03)	clos

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Ministère des affaires sociales,
du travail et de la solidarité

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Ministère de la santé, de la famille
et des personnes handicapées

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Paris, le 25 FEV. 2003

Note
pour le Ministre

A l'attention de M. de Tournemire, conseiller technique

Objet : Baisse du taux de remboursement des médicaments à service médical rendu insuffisant.

PJ : - notes du 8/08/2002 et du 11/12/2002.
- tableau

Suite à votre demande, je vous prie de bien vouloir trouver ci-joint la note du 8 août 2002 sur la baisse du taux de remboursement des médicaments à service médical rendu insuffisant.

Dans cette note, je vous proposais de baisser le taux de remboursement des quelques produits à service médical rendu insuffisant bénéficiant encore d'un taux de prise en charge à 65%, même si la décision était prise de les dérembourser ultérieurement.

Je vous indiquais que pour six de ces spécialités, la baisse de taux pouvait être immédiate. Sur ces six spécialités, deux ont fait l'objet d'une annonce de déremboursement par lettre du 3 février dernier[1] et une spécialité est radiée depuis le 31 décembre 2002[2]. Il subsiste donc trois produits[3] dont il conviendrait de baisser le taux à 35% dans l'attente d'un futur déremboursement. Je vous propose de notifier cette baisse aux entreprises concernées en même temps que celle envisagée pour les vasodilatateurs.

Par ailleurs, je vous rappelle que pour deux produits[4] des négociations devraient être menées avec les entreprises afin de les amener à déposer un dossier d'extension d'indication de leur autorisation de mise sur le marché.

Je vous remercie de me faire part de votre position sur chacun des points évoqués.

Le Directeur de la Sécurité Sociale

Dominique LIBAULT

1 Hydracort, Galirène
2 Nopron
3 Mediator, Pepsane, Asthmasedine.
4 Methotrexate et Colymicine injectable

Médicament	Niveau de SMR dans les indications de l'AMM	indications hors AMM	Taux actuel de prise en charge	Proposition DSS 3/08/2002	position DGS au 8/08/2002	Mesure de déremboursement ou de baisse de taux	Proposition DSS février 2003
Hydracort	insuffisant		65%	35%		déremboursement (lettre envoyée le 3/02)	clos
Mediator	insuffisant		65%	35%			3e vague de déremboursement en attendant, baisse de taux à 35% proposée
Pepsane	insuffisant		65%	35%			2e vague de déremboursement en attendant, baisse de taux à 35% proposée
Galirène	insuffisant		65%	35%		déremboursement (lettre envoyée le 3/02)	clos
Nopron	insuffisant		radié au 31/12/2002				clos
Asthmasedine	insuffisant		65%	35%			2e ou 3e vague de déremboursement en attendant, baisse de taux à 35% proposée
Methotrexate	insuffisant	oui- polyarthrite rhumatoïde	65%	contacter le labo pour demande modification AMM afin de régulariser sa situation dans un délai de 6 mois - sinon, baisse à 35%	contacter le labo pour demande d'extension d'AMM		idem proposition 8/08/2002 - attente décision cabinet
Colymicine injectable	insuffisant	oui - pour les enfants atteints de mucoviscidose	65%	contacter le labo pour demander le dépôt d'un programme de développement préalable à la demande d'extension d'AMM, dans un délai de 6 mois - sinon, baisse à 35%	contacter le labo mais sans fixer d'ultimatum		idem proposition 8/08/2002 - attente décision cabinet
Cognex	insuffisant		65%	maintien à 65% car pas d'économie potentielle + patients anciennement traités + pathologie grave prise en charge à 100%			idem proposition 8/08/2002

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Rapport pour la commission de transparence du 12/04/06.

Réevaluation du Service Médical Rendu

Nom du produit : Mediator 150 mg
Principe actif : Benfluorex
Laboratoire : Servier

Dr P. GIRAL
Unités de Prévention Cardio-vasculaire
Groupe hospitalier Pitié-Salpétrière - PARIS 13

Le benfluorex est un très ancien produit qui est commercialisé depuis 30 ans avec des indications larges et imprécises à la lumière des données récentes et un mode d'action inconnu.
Du fait des indications imprécises, la prescription du produit l'est aussi et il est nécessaire de préciser les indications et le service médical rendu dans le cadre de ces indications

Le présent rapport ne traite que de l'indication « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale. »
On considère que la précédente réévaluation des autres indications (adjuvant du régime adapté dans les hypertriglycéridémies) a considéré le SMR comme insuffisant (commission de transparence du 19/11/1999).
Les complications du diabète sont nombreuses et graves. La microangiopathie diabétique qui atteint essentiellement le rein et la rétine est directement en rapport avec l'hyperglycémie dont le niveau moyen est reflété par l'hémoglobine glyquée. L'étude majeure UKPDS a montré que l'abaissement de l'hémoglobine glyquée chez les diabétiques était associé avec un développement moindre de la microangiopathie. De ce fait, l'abaissement de l'hémoglobine glyquée représente un marqueur validé de l'amélioration de l'équilibre du diabète et d'une diminution de la survenue des complications spécifiques.

En fait 2 études récemment publiées modifient certainement l'approche du produit dans l'indication du diabète.
Il s'agit de 2 études réalisées en Europe et dans le monde hors US publiés en 2003 et 2006.
La plus importante vient d'être publié dans Diabetes Care qui est une des meilleures revues internationale consacré au diabète (Impact factor 2004 : 7).
Il s'agit d'une étude majoritairement européenne (85% des patients inclus) d'une durée globale de 15 mois, terminé en 2004, communiqué en congrès international en 2005 et publié en 2006. L'investigateur principal qui est aussi le premier signataire de l'article est le chef du service d'endocrinologie de l'hopital cardiovasculaire de Lyon. Ce service et ses publications font autorité dans le domaine de la diabétologie, la lipidologie et la prise en charge du risque CV.
Cette étude a inclus 325 (ou 327 dans le rapport d'étude ?) patients de type 2 non insulinotraités intolérant à la metformine, traité par sulfamide hypoglycémiant et dont le diabète n'est pas équilibré sous ce dernier traitement. (HBA1c à l'entrée = 8.32 % dans les 2 groupes, glycémie à jeun 9.87 mmol/l groupe benfluorex ; 9.67 dans le groupe placebo).
IL s'agit d'une étude en double insu benfluorex versus placebo d'une durée de 18 semaines. Une période d'extension (non publiée) a été effectuée et 95% des patients (n=282) ont participé à cette période d'extension).

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Cette étude satisfait aux standards actuels des études comparatives vs placebo et les résultats peuvent être considérés comme fiables.
Les 2 groupes de patients sont comparables pour toutes les variables étudiées.
Le résultat principal est dans le groups traité par benfluorex, une baisse de 1% de l'hémoglobine glyquée par rapport au groupe placebo (groupe benfluorex de 8.34 à 7.52% ; groupe placebo 8.33 à 8.52%). Presque 3 fois plus de patients (34% vs 12%) atteigne les objectifs d'hémoglobine glyquée (7%) dans le groupe traité vs groupe contrôle. D'autres paramètres en rapport avec le métabolisme glucidique sont améliorés de façon similaire glycémie a jeun, indice de HOMA.

	Benfluorex			
	n	Baseline	Final	Change
A1C overall (%)	161	8.34 ± 0.83	7.52 ± 1.04	-0.82 (0.08)
A1C> 8% (%)	93	8.93 ± 0.53	7.78 ± 1.11	−1.15 (0.11)
Age >65 years (%)	70	8.28 ± 0.80	7.42 ± 0.89	−0.86 (0.10)
Creatinine clearance ≤80 ml/min (%)	62	8.17 ± 0.76	7.38 ± 0.97	−0.78 (0.12)
FPG (mmol/l)	159	9.89 ± 2.57	8.67 ± 2.46	−1.22 (0.20)
HOMA-IR (index)	157	6.62 ± 7.99	4.87 ± 3.67	−1.75 (0.50)
LDL (mmol/l)	149	3.60 ± 0.80	3.33 ± 0.72	−0.27 (0.06)
HDL cholesterol (mmol/l)	151	1.25 ± 0.28	1.23 ± 0.30	−0.03 (0.02)
Triglycerides (mmol/l)	151	2.26 ± 1.62	2.21 ± 2.18	−0.11*

Data are estimates of the change for end minus baseline E(SE) for the within-group analysis and estimates of the SD for baseline. *Nonparametric test.

	Placebo			Between-group difference	
n	Baseline	Final	Change	*P* Value	
156	8.33 ± 0.87	8.52 ± 1.36	0.19 (0.11)	−1.01 (0.13)	< 0.001
89	8.96 ± 0.56	8.90 ± 1.39	−0.06 (0.15)	−1.10 (0.18)	< 0.001
82	8.31 ± 0.87	8.28 ± 1.24	−0.03 (0.13)	−0.81 (0.17)	< 0.001
78	8.32 ± 0.87	8.59 ± 1.34	0.27 (0.15)	−1.16 (0.20)	< 0.001
156	9.71 ± 2.39	10.22 ± 2.88	0.51 (0.23)	−1.65 (0.27)	< 0.001
150	6.35 ± 7.95	5.93 ± 5.35	−0.42 (0.65)	−0.81*	< 0.01
152	3.52 ± 0.89	3.56 ± 0.92	0.04 (0.05)	−0.28 (0.07)	< 0.001
152	1.28 ± 0.28	1.25 ± 0.31	−0.03 (0.02)	−0.01 (0.03)	NS
152	2.11 ± 1.32	2.13 ± 1.18	0.05*	−0.16 (0.07)	< 0.05

: difference for benfluorex minus placebo E(SE) of adjusted group means and are expressed as means ±

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Le rapport présenté par le laboratoire apporte des informations intéressantes complémentaires sur la période d'extension en ouvert. Les patients du groupe placebo ont donc reçu le benfluorex dans la suite de l'étude suivant un période d'extension de 16 semaines avec la possibilité après 8 semaines de rajouter de l'arcabose chez les patients considérés comme mal équilibrés. Sur les 160 patients initiaux de ce groupe, 149 ont basculé du placebo au benfluorex. A noter que 23 patients de ce groupe avec un diabète déséquilibré ont reçu de l'arcabose à partir de la 26éme semaine soit donc 8 semaines après le début de la prise du benfluorex. Globalement, dans ce groupe, l'HbA1C a diminué de 8.53 à 7.49 %, ce qui représente une baisse similaire à ce qui a été constatée dans la première période Pour les 140 patients du groupe benfluorex de la première période, le niveau d'HbA1C est resté stable (de 7.52% à 7.53%). La glycémie et l'indice de HOMA montrent des modifications similaires.

La deuxième étude est une étude Européenne (France très majoritaire, Italie et Hollande) d'une durée globale de 21 mois, terminé en 1998, et publié en 2003 (Acta diabetologica IF 0.3). Alors que cette étude comprend 3 bras, le laboratoire annonce qu'il n'a été autorisé à ne communiquer que les résultats sur 2 bras : benfluorex versus placebo ; par contre le troisième bras qui comportait la metformine dans un design de non infériorité n'est pas commenté dans le mémoire du laboratoire.
Comme cette étude est publiée, l'ensemble de ses résultats sera commenté. Le premier signataire (Del Prato S) est un des professeurs d'un des plus célèbre service de diabétologie d'Europe situé à Pise (Italie).
La durée de l'étude était de 6 mois et concernait des patients présentant un diabète de type 2 mal équilibré traité uniquement par régime.
Il s'agit donc d'une étude multicentrique, comportant 3 bras : placebo, benfluorex, metformine avec des effectifs suivant un rapport 1/2/2. 722 patients ont été inclus et la durée du traitement est de 6 mois. 573 patients ont terminé l'étude soit 149 (21%) patients qui ont arrêté prématurément l'essai ou qui ont été perdu de vue (9). La répartition des patients entre les groupes est la suivante (ITT/PP) : Placebo 144/105, benfluorex 294/232, metformine 284/284.
Après 6 mois de traitement Le critère principal l'HbA1C est significativement abaissé dans le groupe benfluorex et le groupe metformine par rapport au groupe placebo dans lequel il augmente (cf tableau).

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Table 2 Changes in HbA1C and secondary efficacy parameters following a 6-month treatment period with benfluorex or placebo

Group[a]	Entry[b]	Endpoint[b]	Endpoint difference[c] [95% CI]	Treatment effect (p)[d]
HbA_{1c}, %				
Benfluorex (n=258)	7.65 (1.58)	7.05 (1.46)	-0.86 (0.17) [-1.20; -0-52]	<0.001
Placebo (n=127)	7.43 (1.48)	7.91 (1.86)		
Fasting plasma glucose, mmol/l				
Benfluorex (n=253)	10.04 (2.04)	8.80 (2.29)	-1.33 (0.28) [-1.89; -0.77]	<0.001
Placebo (n=123)	9.74 (2.28)	10.13 (3.11)		
Fasting serum insulin, pmol/l				
Benfluorex (n=237)	78.6 (82.6)	61.1 (77.9)	9.07 (7.70) [-6.06; 24.21]	0.125
Placebo (n=109)	74.3 (108.3)	52.1 (32.9)		

Table 3 Changes in HbA_{1C} and secondary efficacy parameters following a 6-month treatment period with benfuorex vs. metformin. No equivalence limit was preset for parameters other than HbA_{1C}. These are only descriptive statistics

Group[a]	Entry[b]	Endpoint[b]	Endpoint difference[c] [95% CI]
HbA_{1c}, %			
Benfluorex (n=258)	7.65 (1.58)	7.05 (1.46)	0.28 (0.12) [0.07; 0.48]
Metformin (n=250)	7.79 (1.61)	6.77 (1.34)	
Fasting plasma glucose, mmol/l			
Benfluorex (n=253)	10.04 (2.01)	8.80 (2.29)	0.64 (0.19) [0.33; 0.95]
Metformin (n=246)	10.15 (2.47)	8.16 (1.90)	
Fasting serum insulin, pmol/l			
Benfluorex (n=237)	78.6 (82.60)	61.1 (77.90)	2.10 (5.64) [-7.19; 11.39]
Metformin (n=237)	79.7 (84.80)	59.0 (39.30)	

La baisse de l'HbA1C est de 0.86 % dans le groupe benfluorex et de la différence est de 1.01% par comparaison à l'évolution de l'HbA1C dans le groupe placebo ($p< 0.001$).
Une étude en non infériorité vs metformine a été effectuée avec un seuil de non infériorité fixé à 0.5% pour l'HbA1C. Comme il existait une différence de 0.28% (CI 0.07-0.48) entre benfluorex et metformine, il a été conclu à l'absence d'infériorité entre baisse de l'HBA1C induite par la metformine et le benfluorex.

Globalement ces 2 études montrent des résultats similaires avec une baisse significative de l'HbA1C induite par le benfluorex autour de 1% par rapport au groupe placebo. Clairement, ces 2 études réalisées dans des populations européennes diabétiques représentatives montrent des résultats favorables pour le benfluorex qui suggère que la baisse de l'HbA1C devrait entraîner une diminution des complications du diabète.

Paramètres lipidiques : il faut noter même si cela ne faisait pas l'objet du présent rapport que dans ces populations diabétiques présentant des dyslipidémies, la modification des paramètres lipidiques est très modeste, voire non significative dans l'étude de Del Prato. Cela pose la question des indications du produit dans les dyslipidémies surtout si l'on compare les résultats obtenus avec les autres classes d'hypolipémiants que ce soit en terme d'effet biologique (fibrate, statine, acide nicotinique) ou en terme clinique (statine ou gemfibrozil). A la lumière de ces résultats, il n'est pas acceptable que le benfluorex conserve cette indication dans les hypertriglycéridémies ce d'autant que le DOREMA

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montre que le benfluorex est prescrit dans 46.3% pour une dyslipidémie. Cela pourrait être considéré comme un perte de chance pour les patients redevable d'un traitement par un hypolipémiant cliniquement efficace !

Effets secondaires : la fréquence des diarrhées qui est un des effets secondaires les plus fréquents avec la metformine est significativement plus faible avec le benfluorex (2 fois moins dans les 2 études commentées) . Par contre, il existe une symptomatologie mal étiquetée (vertiges, hypoglycémie, asthénie ...) qui semble plus fréquente dans le groupe benfluorex que dans le groupe placebo voire même vs metformine dans l'étude de Del Prato.

Conclusion :
Au vu de ces 2 études de bonne qualité, le service médical rendu du benfluorex dans le diabète est validé car il entraîne une baisse similaire aux autres antidiabétiques oraux du principal marqueur biologique de complications qui est l'hémoglobine glyquée.
Mais il ne faut pas que le dossier s'arrête là et les indications du produit doivent être revue à la lumière de ces études car il existe plusieurs problèmes
1/ Quel est la place du benfluorex dans la stratégie de prise en charge du diabète de type 2 ?.
Il revient aux sociétés savantes et aux commissions chargées des recommandations de préciser exactement la place du benfluorex.
2/ Quelle est la place du benfluorex par rapport à la metformine ?
. Soit seconde intention, à réserver aux intolérants si on considère que le benfluorex n'est qu'un me too de la metformine avec peut être une meilleure tolérance digestive.
. Soit en addition, mais il faut que des essais montrent l'effet additif du benfluorex par rapport à la metformine et aux autres antidiabétique oraux
Ces questions sont d'ailleurs posées en conclusion de l'article du Pr Moulin
3/ Par contre les propriétés hypolipémiantes sont très modestes et les indications doivent être revues en précisant au minimum une seconde intention sous réserve que les études d'association avec les statines montrent un gain biologique.

Annexe 4-33

HAS

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

DOCUMENT PREPARATOIRE

12 avril 2006

Suite à la demande du ministre chargé de la Santé et de la Sécurité Sociale, la commission réexamine la spécialité suivante :

MEDIATOR 150 mg, comprimé enrobé
B/30 (CIP : 317 557-9)
B/100 (CIP : 317 559-1)

Laboratoire SERVIER

Benfluorex (chlorhydrate de)

liste I

Date de l'AMM : 22/04/1987

Conditions actuelles de prise en charge : Sécurité sociale (35%) ; Collectivités

Motif de la demande :Réévaluation du service médical rendu par la spécialité

Note : Le benfluorex est un dérivé de la fenfluramine (ex–PONDERAL) et de la dexfenfluramine (ex-ISOMERIDE), deux anorexigènes amphétaminiques retirés du marché du fait d'effets indésirables graves : hypertensions artérielles pulmonaires et valvulopathies cardiaques. (ces effets secondaires sévères connus peuvent se manifester plus de 10 ans après la dernière prise)
Le benfluorex est classé par l'OMS parmi les anorexigènes. Il est utilisé en France, hors AMM, comme traitement à visée amaigrissante.
En Espagne, la survenue sous benfluorex de troubles cardiaques graves, semblables à ceux observés avec la fenfluramine et la dexfenfluramine, est à l'origine du retrait du marché des spécialités pharmaceutiques contenant du benfluorex en mars 2003. En juin 2005, l'agence espagnole du médicament a annoncé l'interdiction des préparations magistrales à base de divers produits amaigrissants, dont le benfluorex, suite à la survenue d'effets indésirables graves.
La Commission Nationale de Pharmacovigilance (PV du 29 novembre 2005 ci joint) a souhaité une réévaluation du rapport bénéfice/risque du produit.

Chef de projet :

Direction de l'évaluation des actes et produits de santé

1 CARACTERISTIQUES DU MEDICAMENT

1.1. Principe actif

benfluorex (chlorhydrate de)

1.2. Indications remboursables

- Adjuvant du régime adapté dans les hypertriglycéridémies ;
- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque : L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

1.3. Posologie

Voie orale.

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante :

- 1ère semaine : 1 comprimé par jour, au cours du dîner ;
- 2ème semaine : 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner ;
- à partir de la 3ème semaine : 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.
En association à un régime adapté, Médiator constitue un traitement adjuvant : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

2 ANALYSE DES DONNEES DISPONIBLES

2.1. Efficacité

en attente d'éventuelles données de la firme

2.2. Effets indésirables (données RCP)

Les effets indésirables suivants ont été observés :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée) ;
- asthénie ;
- somnolence ;
- état vertigineux.

Toutefois, ces effets s'observent plus particulièrement à des posologies élevées. Une susceptibilité individuelle a également été observée.

3 SERVICE MEDICAL RENDU

3.1. Caractère habituel de gravité des affections traitées

La prise en charge des hypertriglycéridémies et du diabète ne se conçoit que dans le cadre d'une prise en charge globale des facteurs de risque (tabac, hypertension artérielle, obésité...)

Les hypertriglycéridémies sont souvent associées à un risque de maladie coronarienne. Les personnes avec des taux de triglycérides très élevés présentent un risque accru de développer une pancréatite. Les hypertriglycéridémies peuvent être isolées ou associées à une augmentation du taux de LDL-cholestérol.
En dehors de l'hypertriglycéridémie sévère, associée à un risque de survenue de pancréatite aiguë, il n'y a aucune urgence pour la prise en charge thérapeutique d'une anomalie isolée des triglycérides. Si le taux de triglycérides est le seul perturbé (taux de LDL-cholestérol en dessous des valeurs usuelles), il faut rechercher une cause associée : obésité ou surpoids, diabète, consommation excessive d'alcool.
Les complications les plus fréquentes et les plus graves du diabète sont cardiovasculaires, micro et macroangiopathiques.

3.2. Rapport efficacité/effets indésirables en attente d'éventuelles données de la firme

3.3. Place dans la stratégie thérapeutique

La prise en charge recommandée de la surcharge pondérale, déterminée par l'IMC, repose sur :
-la recherche de complications ou de facteurs de risques associés (HTA, dyslipidémie, diabète...)
- les mesures hygiéno-diététiques : activité physique, régime alimentaire, voire une psychothérapie de soutien.
Le traitement médicamenteux est indiqué en cas d'échec des mesures hygiéno-diététiques poursuivies pendant 3 mois. Mais ces dernières doivent être maintenues et associées au traitement médicamenteux.

La thérapeutique de première intention de l'hypertriglycéridémie inclut une thérapeutique diététique ainsi que la perte de poids, l'activité physique, la diminution des apports caloriques et de la consommation des graisses saturées et la restriction d'alcool. Lorsque l' hypertriglycéridémie est associée à une hypercholestérolémie, cette dyslipidémie mixte étant fortement athérosclérosante, un traitement médicamenteux doit être envisagé. Les médicaments de choix pour réduire les taux de triglycérides sont habituellement les fibrates. Dans le cas de dyslipidémie mixte, les statines associées aux fibrates sont recommandées.
Le mécanisme d'action du benfluorex comme hypolipémiant est indéterminé. Les données actuellement disponibles sont insuffisantes pour justifier son utilisation.[1]

Le programme alimentaire et une activité physique régulière constituent le traitement initial du diabète de type 2. Ils doivent être mis en oeuvre dès que le diagnostic de diabète de type 2 est confirmé et poursuivis indéfiniment.
Le régime diabétique est normoglucidique et hypolipidique. En cas de surpoids, il convient de mettre en place un régime hypocalorique.
Lorsque les mesures hygiéno-diététiques se révèlent insuffisantes, on prescrit un hypoglycémiant oral. En cas de surpoids important, la metformine en monothérapie a démontré son efficacité dans l'étude UKPDS. En cas de surpoids modéré, on peut choisir en première intention la metformine ou un inhibiteur des alphaglucosidases.

Une diminution significative du poids par rapport au placebo a été observée chez des patients obèses avec un diabète de type 2, ayant reçu de l'orlistat (diminuant l'absorption des TG alimentaires) ou de la sibutramine (utilisée pour stimuler la satiété).[2] Une méta-analyse[3] a évalué l'efficacité de certains médicaments (fluoxetine, orlistat, sibutramine) pour la perte de poids chez des patients obèses avec un diabète de type 2. Ces médicaments ont

[1] Prise en charge thérapeutique du patient dyslipidémique – recommandations Afssaps Mars 2005
[2] NICE – National Clinical Guidelines for Type 2 Diabetes - 2005
[3] Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus – Review Cochrane 2006

permis une perte de poids significative mais modeste. De plus, le profil de sécurité de la sibutramine est discutable.

Le benfluorex n'est cité dans aucune recommandation, il n'a donc pas de place reconnue dans la stratégie thérapeutique des traitements adjuvants du régime dans les hypertriglycéridémies et chez les diabétiques avec surcharge pondérale.

3.4. Intérêt en termes de santé publique

Compte tenu :

- d'un rapport efficacité/effets indésirables mal établi ;
- de l'absence de place dans la stratégie thérapeutique,

cette spécialité ne présente pas d'intérêt en termes de santé publique.

3.5. Recommandations de la commission de la transparence

Annexe 4-34

REEVALUATION DU SERVICE MEDICAL RENDU (SMR)
CONCERNANT LE MEDIATOR 150 mg

1. **Gravité des pathologies visées par les indications du Résumé des Caractéristiques du Produits de l'AMM**

Le Mediator a, actuellement, deux indications thérapeutiques :
- Le diabète avec surcharge pondérale,
- Les hypertriglycéridémies.

Le diabète avec surcharge pondérale est une pathologie fréquente et grave, dont la progression s'accélère dans les pays développés parallèlement à celle de l'excès pondéral.

Les hypertriglycéridémies sont plus rares et moins pathogènes. Leur association à une élévation du risque athérogène paraît essentiellement liée à la baisse du cholestérol HDL qui les accompagne habituellement.

2. **En fonction des données fournies par les laboratoires, analyse critique des études et des données comparatives, en particulier :**

La principale étude présentée par les laboratoires Servier dans ce dossier de réévaluation du SMR est celle publiée par Moulin en 2006 dans Diabetes Care.
Cette étude me semble :
- Concerner des sujets respectant le RCP de l'AMM,
- Avoir été conçue et réalisée selon une méthodologie correcte (avis complémentaire d'un expert statisticien indispensable),
- Concerner des sujets représentatifs d'une large population de malades vus en pratique, mais elle ne concerne ni les patients traités par la Metformine, ni ceux âgés de moins de 50 ans,
- Avoir adopté des critères diagnostiques adaptés à la pratique, des critères de jugement cliniquement adaptés et un comparateur (le placebo) acceptable.

Pour résumer, cette étude trouve que, par rapport au placebo, le Benfluorex :
- Améliore l'équilibre glycémique, avec une baisse moyenne de l'HbA1c de l'ordre de 1 % et de la glycémie de 1,65 mmol/l,
- Abaisse le LDL cholestérol (de l'ordre de 6%), les triglycérides et l'index HOMA-IR, reflet de l'insulinorésistance,
- Augmente le risque d'épisodes suggestifs d'hypoglycémie (8,5 % contre 3,8 % avec le placebo).

Les études antérieures montrent une efficacité proche de celle retrouvée par Moulin.
Les différences observées sont cliniquement pertinentes en ce qui concerne l'équilibre glycémique et le LDL cholestérol, mais cette étude ne permet pas de conclure sur un effet

vasculoprotecteur de ces effets liés au Benfluorex.
En revanche, la baisse des triglycérides est modeste (- 0,16 mmol/l par rapport au placebo) et n'a que peu de signification clinique.

3. Apport du médicament dans la stratégie thérapeutique

La prise en charge habituelle du « diabète avec surcharge pondérale » passe par plusieurs étapes :

- Avant tout, une prise en charge hygiéno-diététique associant activité physique et conseils nutritionnels destinés à favoriser une perte pondérale même partielle et à normaliser la glycémie.
- Le premier traitement médicamenteux reste la Metformine, qui a démontré une efficacité en termes d'événements cardiovasculaires et de mortalité,
- En cas d'échec partiel de la Metformine, association à un sulfamide hypoglycémiant ou à une glitazone, voire à l'acarbose,
- Ces trois classes thérapeutiques peuvent, par ailleurs, être utilisées en cas d'intolérance ou de contre-indication à la Metformine.

· Par rapport à la Metformine et aux glitazones, le Benfluorex agit également en tant qu'insulino-sensibilisateur, possède une efficacité voisine ou légèrement inférieure selon les études et, à l'inverse de ces deux molécules, n'a pas démontré jusqu'à présent posséder un effet bénéfique sur la morbidité cardiovasculaire.

· Point positif pour le Benfluorex : il n'est contre-indiqué ni en cas d'insuffisance cardiaque (alors que les glitazones le sont), ni en cas d'insuffisance rénale, cardiaque ou respiratoire (alors que la Metformine l'est). Dans ces populations, il peut donc avoir des indications privilégiées.

4. Conclusion

En pratique quotidienne, le Benfluorex me paraît, d'après ces études, avoir un intérêt en association aux sulfamides hypoglycémiants en cas d'intolérance ou de contre-indication à la Metformine et aux glitazones.
Concernant l'effet du Benfluorex sur les triglycérides, il n'a que peu de signification clinique et on pourrait discuter la pertinence de cette indication.

Le Benfluorex a un coût moyen de prescription largement inférieur aux glitazones (voir tableau 6 page 24 du volume 1/3) et une souplesse d'utilisation potentiellement utile dans le cadre de la médecine générale ; il manque cependant une démonstration d'efficacité en termes de morbidité/mortalité.

Dr jacques Fricker
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75008 PARIS

Annexe 4-35

COMMISSION DE LA TRANSPARENCE

26 avril 2006

RELEVE DES VOTES

ATEPADENE
(15 votants)

Détermination du SMR	
SMR insuffisant	15

ZAVEDOS
(16 votants)

Avis favorable à la sortie de réserve hospitalière	16

Détermination du SMR	
SMR important	16

Détermination du niveau d'ASMR	
ASMR III	11
ASMR IV	5

INDUCTOS – EI - Audition
(18 votants)

SMR faible	6
SMR modéré	11
SMR important	1

Maintien de l'ASMR V	18

ULTRAVIST
(19 votants)

Détermination du SMR	
SMR important	19

Détermination du niveau d'ASMR	
Pas d'ASMR	19

REEVALUATION

MUCOMYST
(16 votants)

Détermination du SMR	
SMR faible	16

PNEUMOREL
(16 votants)

Détermination du SMR	
SMR insuffisant	16

SURBRONC
(16 votants)

Détermination du SMR	
SMR insuffisant	16

GOMENOLEO - GOMENOL
(16 votants)

Détermination du SMR	
SMR insuffisant	16

RINUREL
(16 votants)

Détermination du SMR	
SMR insuffisant	16

RINUTAN
(16 votants)

Détermination du SMR	
SMR insuffisant	16

THIOVALONE
(16 votants)

Détermination du SMR	
SMR insuffisant	16

CLERIDIUM
(16 votants)

Détermination du SMR	
SMR insuffisant	16

CORONARINE
(16 votants)

Détermination du SMR	
SMR insuffisant	16

PERSANTINE, comprimé
(16 votants)

Détermination du SMR	
SMR insuffisant	16

PROTANGIX
(16 votants)

Détermination du SMR	
SMR insuffisant	16

PERSANTINE, solution injectable
(16 votants)

Détermination du SMR	
SMR faible	14
SMR modéré	1
Abstention	1

COVATINE
(16 votants)

Détermination du SMR	
SMR insuffisant	16

MEDIATOR
(16 votants)

Adjuvant du régime adapté dans les hypertriglycéridémies

Détermination du SMR	
SMR insuffisant	16

Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale

Détermination du SMR	
La CT se prononcera ultérieurement	16

PRAXINOR
(16 votants)

Détermination du SMR	
SMR insuffisant	16

TERRAMYCINE
(16 votants)

Détermination du SMR	
SMR important	16

Relevé d'avis du 12-04-06 - Réévaluation
(16 votants)

Adoption sous réserve des modifications demandées	16

Benfluorex = Médiator ® 150 mg

Réévaluation du service médical rendu

Avril 2006

Dr H. Narbonne

Introduction

Le diabète est une maladie chronique qui touche plus de 2 millions de Français (et certainement beaucoup plus si on inclut ceux chez qui le diagnostic n'a pas encore été posé).
Le diabète est une maladie gravissime au vue des complications qu'elle entraine : première cause de cécité chez l'adulte, première cause d'amputation non traumatique, une des causes principales de mise en dialyse et de maladie coronarienne. 51% des patents ont une hypercholestérolémie, 54% une HTA.
Le cout de la prise en charge du diabète est majeur car il existe des dépenses médicamenteuses, des dépenses en relations avec les professionnels de santé mais aussi par un nombre important d'hospitalisation (28% ont été hospitalisés au moins une fois en 2001), et également par un nombre important de mise en invalidité (11% en 2001). Au total, la prise en charge d'un patient diabétique en 2001 revient 1,9 fois plus chère qu'un non diabétique (Entred 2001).
Afin d'éviter l'apparition de complication, l'ANAES recommande d'obtenir un taux d'HbA1c < 6,5% dans le diabète de type 2 (ANAES 2000). Or, dans la population française, > 1/3 des diabétiques ont une HbA1c > 8% (Detournay 2005). Il est donc important de connaître et d'évaluer parfaitement l'ensemble des molécules pouvant y participer, dont le benfluorex.

I - Mécanismes d'action

L'effet du benfluorex s'exerce sur les lipides par 2 effets : un direct par action sur certains enzymes du métabolisme lipidique (Geelen 1983, Arnaud,1990, Sommariva 1986), un indirect par diminution de l'insulinorésistance. En effet, le benfluorex agit au niveau hépatique en diminuant la glycogénolyse hépatique (Bailey 1992) et au niveau périphérique en augmentant la captation et l'oxydation du glucose (Bailey 1992, Storlien 1993).
Néanmoins, sur le plan clinique, peu d'études convaincantes ont montré une baisse significative de l'insulinémie.

II - Efficacité

A – Effet sur la glycémie

1 – Efficacité de la molécule

Le tableau 1 résume les études qui semblent les plus intéressantes. Il faut noter d'emblée le très faible nombre de patients dans les études (seules 3 études ont plus de 100 patients), de la très faible durée des études (entre 3 et 6 mois) même s'il ne semble pas que l'effet de la molécule diminue avec le temps.
Concernant les critères d'efficacité, l'HbA1c diminue de 0,35 à 1,01% dans les groupes traités par le benfluorex (cette variation peut aller de 0,35 à 1,68% en calcul de variation inter groupe en sachant que dans cette dernière étude où le delta est si important, on note une forte augmentation de l'HbA1c dans le groupe contrôle).
La glycémie à jeun baisse elle aussi significativement dans toutes les études de 0,7 à 1,6 mmol/l allant jusqu'à 1,68 mmol/l en delta inter groupe (mais avec la même restriction que pour l'HbA1c).
Enfin, je trouve plus que surprenant de référencer une étude (celle de Louvet) qui porte sur un nombre ridicule de patients (25), dont l'HbA1c du groupe contrôle augmente de façon majeure et qui n'a pas été publiée de surcroit.

2 – Comparaison par rapport aux autres antidiabétiques oraux de même mode d'action

La comparaison doit se faire essentiellement avec les autres molécules efficaces sur l'insulinorésistance, c'est-à-dire la metformine et les glitazones.

Concernant la metformine, les essais en monothérapie montrent une baisse autour de 1,5% de l'HbA1c (DeFronzo 1995, Campbell 2004). Cette amélioration de la glycémie s'accompagne d'une perte de poids modeste qui ne devient vraiment significative qu'en comparaison de la prise de poids des sulfamides. On note également très peu d'hypoglycémies et une amélioration du profil lipidique, notamment des triglycérides quand ils sont élevés (Defronzo 1991, Schneider 1990).
Enfin et surtout, le metformine a montré une baisse de la mortalité significative lors de l'étude de l'UKPDS (UKPDS 1998). Si on compare le benfluorex et la metformine, sur la seule étude que nous avons (Del Prato 2003), l'effet sur le poids et les triglycérides est équivalent, il n'y a pas d'infériorité du benfluorex sur l'HbA1c mais celle-ci semble nettement plus basse sous metformine (cf tableau 1).
Le mode d'action de ses 2 molécules est proche, jouant sur la sensibilité à l'insuline. Leurs effets secondaires les plus fréquents sont digestifs, dont la fréquence, est à peu près similaires, même peu être supérieurs pour la metformine. Par contre, la metformine a des contre indications (toute défaillance viscérale pouvant entrainer une acidose lactique) que n'a pas le benfluorex.

Concernant les glitazones, aucune étude comparative n'a été réalisée. Les glitazones, que ce soient la pio ou la rosiglitazone entrainent une baisse de l'HbA1c autour de 1,4% en monothérapie (Campbell 2004, Lebovitz 2001). La pioglitazone a un effet intéressant sur les triglycérides avec une baisse dc 19% et une augmentation du HDL de 14% (Campbell 2004). Par contre, un des effets secondaires important de cette gamme de médicament est une prise de poids certaine et non négligeable, entrainant une surcharge hydrique et une augmentation du risque d'insuffisance cardiaque (Dormandy 2005). Il est clair que le benfluorex n'a pas ces effets secondaires, mais également semble moins efficace.

B - Effet sur les triglycérides

Les triglycérides baissent dans la majorité des études, de façon pas toujours significative (tableau 1). Mais, il est certains que le taux de triglycérides dans ces études est peu élevé. La baisse devient plus importante dans les sous groupes où les triglycérides sont plus hauts.
Par ailleurs, chez les sujets non diabétiques hypertriglycéridémiques, le benfluorex semble abaisser les triglycérides mais ici encore très peu d'études et très peu de patients : 22 patients sur 80 jours (Ranquin 1987) avec une baisse des triglycérides de plus de 20% par rapport au placébo. Enfin, les études comparant le benfluorex aux fibrates ont été très largement critiquées pour des problèmes méthodologiques (Prescrire 1998).

C – Effet sur le poids

Le poids baisse très faiblement de 0,5 à 1,96 Kg, le plus souvent non significativement. Il n'y a donc absolument pas lieu de le prescrire dans un but d'amaigrissement.

III – Effets secondaires et contres indications

Les effets secondaires sont essentiellement digestifs, à type de diarrhée, de douleurs abdominales ou de nausées. La fréquence est autour de 13% ce qui reste 2 fois moins fréquents que sous Metformine (25%) (Del Prato2003).
A noter un cas rapporté de défaillance avec fibrose sévère trivalvulaire cardiaque, identique à celle décrite avec la fenfluramine et la dexfenfluramine (Ribera 2003).
Enfin, dans les contre indications figurent l'hypersensibilité à la molécule. Plus surprenante est la contre indication en cas de pancréatite chronique.

IV – Place dans l'arsenal thérapeutique

Du fait de son mode d'action, il pourrait avoir sa place en tant qu'insulinosensibilisateur à la place de la metformine en cas de contre indication ou d'intolérance de celle-ci, ou même en association avec la metformine. N'ayant pas d'effet secondaire grave dans une population de patients fragiles, il pourrait être utilisé en monothérapie ou en association. Actuellement, dans ce cas de figure, les glitazones peuvent être utilisées. Il est certains que les effets secondaires à type d'insuffisance cardiaque, de prise de poids conséquente et d'œdèmes de membres inférieurs engendrés par les glitazones en limitent la prescription. Néanmoins, l'efficacité du benfluorex en termes de baisse de l'HbA1c est moindre que les glitazones. Il manque donc une étude, avec un grand nombre de patients et sur une période d'étude minimum de 6 mois, comparant le benfluorex à une glitazone.
Sur le plan santé publique, l'effet maximal du benfluorex sur l'HbA1c étant autour de 1% de l'HbA1c, son utilisation permettrait une baisse de 20% de la mortalité cardiovasculaire (UKPDS). La récente étude PROACTIVE avec la pioglitazone a été partiellement négative (Dormandy 2005). Néanmoins, aucune étude de morbimortalité n'est disponible pour le benfluorex. Enfin, le prix du traitement par benfluorex est 1/3 moins cher que celui par une glitzone.

V – Conclusion

Le benfluorex est une molécule ayant une activité insulinosensibilisatrice certaine permettant une amélioration des glycémies et des triglycérides. L'importance de son action sur ces 2 paramètres reste à affirmer par de grandes études sur des périodes de plus de 6 mois, avec un panel important de patients, et surtout en se comparant non pas à un placébo mais à un compétiteur actif type glitazone. Il serait également intéressant d'avoir des études de morbimortalité. Ceci permettrait d'intégrer éventuellement le benfluorex dans l'arbre décisionnel de la prise en charge du diabète. Il pourrait s'intégrer en association avec la metformine, ou à sa place, ou à la place des glitazones. Néanmoins, actuellement, les glitazones ont fourni des études comparatives versus metformine très convainquantes, avec cependant un doute quant à l'efficacité en termes de mortalité pour la pioglitazone.
Actuellement, le benfluorex ne bénéficiant pas d'étude de ce type, il est difficile de lui trouver une place certaine.
Concernant le traitement de l'hypertriglycéridémie, le flou est encore plus grand, les études de très faible qualité. Cela ne veut pas dire que la molécule ne serait pas active, mais les études recouvrent un trop faible nombre de patients pour se prononcer.
Enfin, il est bien certains que son effet sur la perte pondérale est minime et il n'a aucune indication dans la prise en charge du surpoids ou de l'obésité.

Etudes	Nombre patients	Modalités	Durée (semaines)	Efficacité				Commentaires
				Δ HbA1c (%)	Δ Glycémie à jeun (mmol/l)	Δ Poids (Kg)	Δ Triglycérides (mmol/l)	
Moulin 2006	325	S + B vs P	18 + 16	- 1,01* (- 1,01)*	- 1,22 * (- 1,65)*	- 1,3* (- 0,6)*	- 0,05* (- 0,07)*	
Stucci 1996	68	S + B vs P	12	- 0,66* (- 0,8)*	- 1,39 * (-1,09)*	- 0,5 ** (- 0,3)**	+0,03 g/l ** (+0,03)**	Faible effectif, durée courte
Louvet 1996	25	S + B vs P	12	- 0,47* (- 1,68)*	- 1,6 * (- 1,82) *	- 0,7 ** (- 1) **	+ 0,10** (- 0,69 g/l) **	Effectif ridicule, non publiée, très forte augmentation HbA1c dans le groupe P
Velussi 1996	30	B vs P	12	- 0,9 *	- 0,7 *	- 0,7 **		
Roger 1999	127	M + B vs P	12	- 0,35* (- 0,35)*	- 1,18*			
Leutenegger 1998	76	I + B vs P	12	- 0,73* (-0,73)*			- 0,54* (-0,75)*	Faible effectif, groupes non appariés sur l'HbA1c
Del Prato 1993	722	B vs P	29	- 0,6* (- 1,08)*	- 1,24* (- 1,63)*	- 1,96 (- 1,16)	- 0,15* (- 0,42)**	21% de sortie d'étude Comparaison B vs M critiquable car on ne donne que 2,5 cp de M vs 2,65 cp de B.
		B vs M		- 0,6* (+ 0,4)**	- 1,24* (+ 0,33)**	- 1,96 (- 1 15)	- 0,15* (+0,02)**	

Δ variation inter groupe
* S
** NS
B = benfluorex
M = metformine
P = placébo

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Annexe 4-37 (4)

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

AVIS

10 mai 2006

Suite à la demande du ministre chargé de la Santé et de la Sécurité Sociale, la commission réexamine la spécialité suivante :

MEDIATOR 150 mg, comprimé enrobé
B/30 (CIP : 317 557-9)
B/100 (CIP : 317 559-1)

Laboratoire SERVIER

Benfluorex (chlorhydrate de)

liste I

Date de l'AMM : 22/04/1987

Conditions actuelles de prise en charge : Sécurité sociale (65%) ; Collectivités

Motif de la demande :Réévaluation du service médical rendu par la spécialité

Direction de l'évaluation des actes et produits de santé

Annexe 4-37

1 CARACTERISTIQUES DU MEDICAMENT

1.1. Principe actif

benfluorex (chlorhydrate de)

1.2. Indications remboursables

- Adjuvant du régime adapté dans les hypertriglycéridémies ;
- Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Remarque : L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée.

1.3. Posologie

La posologie est habituellement de 3 comprimés par jour. Cette posologie peut être prescrite d'emblée ou atteinte progressivement de la manière suivante :

- 1ère semaine : 1 comprimé par jour, au cours du dîner ;
- 2ème semaine : 2 comprimés par jour, 1 au cours du déjeuner, 1 au cours du dîner ;
- à partir de la 3ème semaine : 3 comprimés par jour, soit 1 au petit déjeuner, 1 au déjeuner, 1 au dîner.

En fonction des résultats biologiques, la posologie peut être diminuée à 2 comprimés par jour, voire 1 comprimé par jour.
En association à un régime adapté, Médiator constitue un traitement adjuvant : une surveillance régulière clinique et biologique de chaque patient sera instaurée.

2 RAPPEL DES AVIS DE LA COMMISSION

Avis de la Commission du 19 novembre 1999

Le service médical rendu de cette spécialité a été apprécié en prenant en compte l'efficacité et les effets indésirables du médicament, sa place dans la stratégie thérapeutique, notamment au regard des autres thérapies disponibles, la gravité de l'affection à laquelle il est destiné, le caractère préventif, curatif ou symptomatique du traitement médicamenteux et son intérêt pour la santé publique.
Le niveau de service médical rendu est insuffisant au regard des autres médicaments ou thérapies disponibles pour justifier sa prise en charge.

3 ANALYSE DES DONNEES DISPONIBLES

3.1. Efficacité

3.1.1. Dans l'indication : adjuvant du régime adapté dans les hypertriglycéridémies
Aucune donnée clinique n'a été fournie par le laboratoire.

3.1.2. Dans l'indication : adjuvant du régime adapté chez les diabétiques avec surcharge pondérale

1/ Etudes anciennes

L'étude VELUSSI[1] de phase IV randomisée en double aveugle a évalué l'efficacité de MEDIATOR versus placebo sur l'insulinémie et sur le métabolisme glucidique chez 30 patients diabétiques de type 2, hyperinsulinémiques et en surpoids.
La durée de l'étude a été de 3 mois.
L'évaluation a porté sur des critères multiples (glycémie à jeun, HbA1c, fructosamine, test de tolérance au glucose, insulinémie...)
Aucun critère principal de jugement n'est précisé.

L'étude LOUVET de phase IV (non publiée) randomisée en double aveugle a évalué l'efficacité de MEDIATOR versus placebo sur le contrôle métabolique de 25 patients diabétiques de type 2 insuffisamment contrôlés par un régime et par sulfonylurés.
La durée de l'étude a été de 3 mois.
L'évaluation a porté sur des critères multiples (glycémie à jeun, HbA1c, fructosamine, test de tolérance au glucose, insulinémie...)
Aucun critère principal de jugement n'est précisé.

L'étude TOMASI[2] de phase IV randomisée en double aveugle a évalué l'efficacité de MEDIATOR versus placebo sur le contrôle métabolique de 68 patients diabétiques de type 2 insuffisamment contrôlés par sulfonylurés.
La durée de l'étude a été de 12 semaines.
L'évaluation a porté sur des critères multiples (glycémie à jeun, HbA1c, fructosamine, test de tolérance au glucose, insulinémie...)
Aucun critère principal de jugement n'est précisé.

Conclusion
Compte tenu de l'absence de détermination d'un critère principal et du nombre important des critères d'évaluation, les résultats de ces études anciennes ne permettent pas de préciser une éventuelle quantité d'effet du benfluorex dans l'indication « en adjuvant du régime adapté chez les diabétiques avec surcharge pondérale».

2/ Etudes récentes

Le laboratoire a fourni les résultats de 2 études récentes dans l'indication : adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Etude MOULIN[3]
Cette étude randomisée en double aveugle a évalué l'efficacité et la tolérance de MEDIATOR versus placebo chez 325 patients diabétiques de type 2 en surcharge pondérale (IMC compris entre 25 et 40 kg/m^2), insuffisamment contrôlés par les sulfamides hypoglycémiants et ayant une intolérance ou une contre-indication à la metformine.
La durée de l'étude a été de 18 semaines.
L'étude a ensuite été poursuivie en ouvert pendant 16 semaines. L'ensemble des patients étaient traités par MEDIATOR. Les résultats du suivi en ouvert ne sont pas publiés.

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[1] Velussi M, De Monte A, Cernigoi AM. Therapeutic effect of benfluorex in type II diabetic patients on diet regimen alone. Journal of Diabetes and Its Complications 1996;10:261-266.
[2] Therapeutic benefit of benfluorex in type II diabetic patients. J Diab Complic 1996; 10 : 267-273
[3] Moulin Ph. et al. Efficacity of benfluorex in combination with sulfonylurea in type 2 diabetic patients. An 18-week, randomized, double-bind study. Diabetes Care 2006; 65 (3) : 515-520

Le critère principal d'efficacité a été le taux d'hémoglobine glyquée HbA1c.
A l'inclusion, les populations étaient comparables dans les 2 groupes.

	Groupe MEDIATOR (n=161)	Groupe placebo (n=156)
Taux d'HbA1c à l'inclusion (%)	8,34 ± 0,83	8,33 ± 0,87
Taux d'HbA1c à 18 semaines (%)	7,52 ± 1,04	8,52 ± 1,36
Variation du taux d'HbA1c	- 0,82	+0,19

Il a donc été observé une diminution de 1,01% du taux d'HbA1c (IC 95% [-1,26 ; -0 ,76], p<0,001) dans le groupe traité par MEDIATOR par rapport au groupe placebo.

En fin de traitement, un taux d'HbA1c ≤ 7% a été atteint chez 34,2% des patients du groupe MEDIATOR versus 11,5% des patients du groupe placebo (p<0,001).

Les effets indésirables les plus fréquents ont été gastro-intestinaux (15% dans le groupe MEDIATOR, 10% dans le groupe placebo).

Etude DEL PRATO[4]
Cette étude randomisée en double aveugle a évalué l'efficacité et la tolérance de MEDIATOR versus placebo chez 722 patients diabétiques de type 2 en surpoids (IMC compris entre 25 et 40 kg/m^2), insuffisamment contrôlés par un régime seul.
Cette étude a également comporté un bras metformine (n=250), afin de démontrer la non infériorité de MEDIATOR.
Le seuil de non infériorité a été fixé à 0,5% pour le taux d'HbA1c. Une différence de 0,28% (IC 95% [0,07 ; 0,48]) a été observée entre le benfluorex et la metformine. Le benfluorex n'a pas été inférieur à la metformine sur la diminution du taux d' HbA1c.
La durée de l'étude a été de 6 mois.

Le critère principal d'efficacité a été le taux d'hémoglobine glyquée HbA1c.

	Groupe MEDIATOR (n=258)	Groupe placebo (n=127)
Taux d'HbA1c à l'inclusion (%)	7,65 ± 1,58	7,43 ± 1,48
Taux d'HbA1c à 6 mois (%)	7,05 ± 1,46	7,91 ± 1,86
Variation du taux d'HbA1c	-0,60	+0,48

Une différence moyenne de 0,86% (IC 95% [-1,20 ; -0 ,52], p<0,001) entre les taux d'HbA1c a été observée entre les 2 groupes de traitement.

Les effets indésirables les plus fréquents ont été gastro-intestinaux (6,8% dans le groupe MEDIATOR, 2,8% dans le groupe placebo).

3.2. Effets indésirables

Selon le RCP, les effets indésirables suivants ont été observés :
- troubles digestifs (nausées, vomissements, gastralgies, diarrhée) ;
- asthénie ;
- somnolence ;
- état vertigineux.

[4] Del Prato S, Erkelens DW, Leutenegger M. Six month efficacy of benfluorex vs placebo or metformin in diet-failed type 2 diabetic patients. Acta Diabetol 2003; 40 : 20-27

Toutefois, ces effets s'observent plus particulièrement à des posologies élevées. Une susceptibilité individuelle a également été observée.

4 SERVICE MEDICAL RENDU

4.1. Dans l'indication : adjuvant du régime adapté dans les hypertriglycéridémies :

4.1.1. Caractère habituel de gravité des affections traitées

La prise en charge des hypertriglycéridémies ne se conçoit que dans le cadre d'une prise en charge globale des facteurs de risque (tabac, hypertension artérielle, obésité...)
Les hypertriglycéridémies sont souvent associées à un risque de maladie coronarienne. Les personnes avec des taux de triglycérides très élevés présentent un risque accru de développer une pancréatite. Les hypertriglycéridémies peuvent être isolées ou associées à une augmentation du taux de LDL-cholestérol.
En dehors de l'hypertriglycéridémie sévère, associée à un risque de survenue de pancréatite aiguë, il n'y a aucune urgence à la prise en charge thérapeutique d'une hypertriglycéridémie isolée. Si le taux de triglycérides est le seul perturbé (taux de LDL-cholestérol en dessous des valeurs usuelles), il faut rechercher une cause associée : obésité ou surpoids, diabète, consommation excessive d'alcool.

4.1.2. Rapport efficacité/effets indésirables

Cette spécialité entre dans le cadre d'un traitement à visée symptomatique.
En l'absence de données cliniques, l'efficacité de cette spécialité n'est pas établie.
La tolérance est acceptable.
Le rapport efficacité / effets indésirables de cette spécialité est mal établi.

4.1.3. Place dans la stratégie thérapeutique

La prise en charge recommandée de la surcharge pondérale, déterminée par l'IMC, repose sur :
-la recherche de complications ou de facteurs de risques associés (HTA, dyslipidémie, diabète...)
-les mesures hygiéno-diététiques : activité physique, régime alimentaire, voire une psychothérapie de soutien.

Le traitement médicamenteux est indiqué en cas d'échec des mesures hygiéno-diététiques poursuivies pendant 3 mois. Mais ces dernières doivent être maintenues et associées au traitement médicamenteux.

La thérapeutique de première intention de l'hypertriglycéridémie inclut une thérapeutique diététique ainsi que la perte de poids, l'activité physique, la diminution des apports caloriques et de la consommation des graisses saturées et la restriction d'alcool. Lorsque l' hypertriglycéridémie est associée à une hypercholestérolémie, cette dyslipidémie mixte étant fortement athérosclérosante, un traitement médicamenteux doit être envisagé. Les médicaments de choix pour réduire les taux de triglycérides sont habituellement les fibrates. Dans le cas de dyslipidémie mixte, les statines associées aux fibrates sont recommandées.

Le mécanisme d'action du benfluorex comme hypolipémiant est indéterminé. Les données actuellement disponibles sont insuffisantes pour justifier son utilisation.[5]

Le benfluorex n'est cité dans aucune recommandation, il n'a pas de place reconnue dans la stratégie thérapeutique des traitements adjuvants du régime dans les hypertriglycéridémies.

[5] Prise en charge thérapeutique du patient dyslipidémique – recommandations Afssaps Mars 2005

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4.1.4. Intérêt en termes de santé publique

Compte tenu :

- d'un rapport efficacité/effets indésirables mal établi,
- de l'absence de place dans la stratégie thérapeutique,

cette spécialité ne présente pas d'intérêt en termes de santé publique.

4.1.5. Recommandations de la commission de la transparence

Le service médical rendu par cette spécialité est insuffisant dans l'indication adjuvant du régime adapté dans les hypertriglycéridémies.

4.2 Dans l'indication : adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Dans la mesure où la Commission de la transparence dispose de nouvelles données par rapport à l'avis de 1999 concernant l'indication « adjuvant du régime adapté chez les diabétiques avec surcharge pondérale » dont un essai publié (étude Moulin), dans la mesure où une réévaluation du rapport bénéfice / risque est en cours à l'Afssaps, la Commission de la transparence ne réévaluera le service médical rendu de MEDIATOR dans l'indication diabète qu'après avis de la Commission d'AMM et prise en compte de la réévaluation du rapport bénéfice / risque de ce produit par l'Afssaps.

Annexe 4-37

CT - Liste de présence / Liens d'intérêts avec le laboratoire Servier

Membres à voix délibérative ayant participé à l'évaluation de MEDIATOR en 2006					
NOM	Présence			Liens / Servier (IP : Intervention ponctuelle, VI : versement à une institution)	
	CT 12/04 après-midi Audition préliminaire	CT 26/04/06 après-midi Vote du SMR	CT 10/05/06 après-midi Approbation du PV		
Président					
M. le Pr BOUVENOT	Présent	Présent	Présent	Néant	
Vice-présidents					
Mme le Pr LE JEUNNE	Présente	Présente	Présente	Néant	
M. le Pr MASSOL	Présent	Présent	Absent	Néant	
Membres titulaires					
Mme le Pr AUTRET-LECA	Absente	Présente	Absente	Néant	
M. le Pr JOURDAN	Présent	Présent	Présent	Néant	
M. le Pr POUCHAIN	Présent	Absent	Absent	Néant	
M. le Dr CARIOU	Présent	Présent	Absent	Néant	
M. le Pr CHOSIDOW	Absent	Présent	Présent	Néant	
M. le Pr DUBOC	Présent	Absent	Présent	IP : essais IRIS sur Perindopril et cardiomyopathies liées à l'X / Preterax et réserve coronaire chez l'hypertendu	
M. le Dr FALISSARD	Présent	Présent	Absent	IP : conseil sur l'utilisation des mesures subjectives pour l'évaluation des thérapeutiques / Formation d'internes à la recherche en psychiatrie	
M. le Pr VESPIGNANI	Présent	Présent	Absent	Néant	
M. le Pr BANNWARTH	Absent	Absent	Présent	Néant	
Mme le Dr KOENIG-LOISEAU	Présente	Présente	Présente	Néant	
M. le Pr MOLIMARD	Absent	Absent	Présent	Néant	
M. le Pr PETIT	Présent	Présent	Absent	Néant	
M. le Dr TREMOLIERES	Présent	Présent	Présent	Néant	
M. le Dr VETEL	Présent	Absent	Absent	Néant	
M. le Dr WIERRE	Présent	Présent	Présent	Néant	
M. le Dr WONG	Présent	Présent	Présent	Néant	
Mme le Pr WORONOFF-LEMSI	Présente	Présente	Présente	Néant	

Liste prenant en compte les présences effectives au moment de l'examen de médiator en Commission de la transparence

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Membres suppléants					
Mme le Pr GOMPEL	Absente	Absente	Absente	VI : 2002-2003, coordination essai clinique	
M. le Pr FLAHAULT	Absent	Absent	Absent	Néant	
M. le Dr NONY	Présent	Absent	Présent	VI : protocole « ivabradine »	
M. le Dr COURTEILLE	Présent	Présent	Absent	Néant	

Note : Deux membres à voix délibérative, MM. Fiessinger et Danchin (suppléants), n'ont pas participé à l'évaluation de MEDIATOR (absents lorsque le dossier MEDIATOR a été abordé)

Représentants des institutions					
Institution	**CT 12/04/06**	**CT 26/04/06 Vote du SMR**	**CT 10/05/06 Approbation du PV**		
DSS	V. HOUDRY	A. MEYER	A. MEYER		
DGS	O. BALLU	N. DAVID	N.DAVID		
DHOS	D. LAGARDE	D. LAGARDE	D. LAGARDE		
AFSSAPS	E. ABADIE	-	E. ABADIE S. FORNAIRON S. LAURAIRE		
LEEM	C. LASSALE	C. LASSALE	C. LASSALE		
CNAMTS	H. BOURDEL	H. BOURDEL	H. BOURDEL		
CANAM	C.VICREY	C. VICREY	C.VICREY G.R. AULELEY		
CCMSA	M. JEANTET	-	-		

Experts externes					
NOM	**Présence**			**Liens / Servier**	
	CT 12/04/06	**CT 26/04/06**	**CT 10/05/06**		
Philippe GIRAL	Présent et rapport écrit			Néant	
Jacques FRICKER		Rapport écrit		Néant	
Henri NARBONNE		Rapport écrit		Néant	

Liste prenant en compte les présences effectives au moment de l'examen de médiator en Commission de la transparence

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HAUTE AUTORITÉ DE SANTÉ

Le président de la commission de la transparence,
Membre du collège de la Haute Autorité de Santé

Saint-Denis, le 13 JUIL. 2006

à

Monsieur Xavier BERTRAND
Ministre de la santé et des solidarités

Objet : Réévaluation des spécialités à SMR insuffisant – Etape 3

Monsieur le Ministre,

La commission de la transparence vient d'achever la réévaluation des spécialités à service médical rendu insuffisant et principalement de prescription médicale obligatoire (étape 3).

Je vous prie donc de trouver ci-joint :

- un tableau récapitulatif par spécialité des résultats de cette réévaluation,
- les avis de la commission portant sur l'ensemble des 127 médicaments concernés.

Ces avis résultent d'une expertise de caractère exclusivement scientifique et vous sont adressés sans préjuger de la teneur des recommandations que le Collège de la Haute Autorité de santé vous fera parvenir à leur propos courant septembre. Dans cette attente, nous prenons toutes les dispositions nécessaires pour conserver le caractère confidentiel de ces avis.

Je vous remercie de la confiance témoignée et vous prie d'agréer, Monsieur le Ministre, l'assurance de ma très haute considération.

Professeur Gilles BOUVENOT

Copies : Mme Françoise WEBER, Conseillère Technique
Mr Laurent DEGOS, Président du Collège

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REEVALUATION DU SERVICE MEDICAL RENDU (3ème PHASE)

EXPLOITANTS	CODE CIP	NOM	SMR
ROCHE NICHOLAS S.A.	3008019	ASTHMASEDINE SOL BUV FL 90ML	Insuffisant
PFIZER	3314986	AXONYL 1G/5ML BUV FV125ML BT 1	Insuffisant
ARROW GENERIQUES	3574374	BUFLOMEDIL ARROW 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
ARROW GENERIQUES	3574279	BUFLOMEDIL ARW 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
BIOGARAN	3515377	BUFLOMEDIL BIOGARAN 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
BIOGARAN	3515383	BUFLOMEDIL BIOGARAN 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
EG LABO LABORATOIRES EUROGENERICS	3600048	BUFLOMEDIL EG 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
EG LABO LABORATOIRES EUROGENERICS	3600054	BUFLOMEDIL EG 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
G GAM	5661255	BUFLOMEDIL G GAM 150MG CPR PELLIC BT100	Faible dans l'AOMI Insuffisant dans les autres indications
G GAM	5661261	BUFLOMEDIL G GAM 300MG CPR PELLIC BT100	Faible dans l'AOMI Insuffisant dans les autres indications
G GAM	3526984	BUFLOMEDIL G.GAM 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
G GAM	3526990	BUFLOMEDIL G.GAM 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
GNR PHARMA	3526866	BUFLOMEDIL GNR 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
GNR PHARMA	3526895	BUFLOMEDIL GNR 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
IREX	3538562	BUFLOMEDIL IRX 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
IREX	3540487	BUFLOMEDIL IRX 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
L. LAFON	3313343	BUFLOMEDIL L. LAFFON 150MG CPR PELLIC BT20	Faible dans l'AOMI Insuffisant dans les autres indications
L. LAFON	3327078	BUFLOMEDIL L. LAFFON 300MG CPR PELLIC BT10	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK GENERIQUES	3430847	BUFLOMEDIL MERCK 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK GENERIQUES	3474081	BUFLOMEDIL MERCK 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3528210	BUFLOMEDIL QUA 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3633102	BUFLOMEDIL QUA 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3528256	BUFLOMEDIL QUA 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3633119	BUFLOMEDIL QUA 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
RATIOPHARM	5564718	BUFLOMEDIL RATIOPHARM 0,4 G/40 ML SOL INJ PERF BT5	Insuffisant
RPG AVENTIS	3540493	BUFLOMEDIL RPG 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
RPG AVENTIS	3540501	BUFLOMEDIL RPG 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
SANDOZ	3659745	BUFLOMEDIL SDZ 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
SANDOZ	3658326	BUFLOMEDIL SDZ 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
TEVA CLASSICS	3626763	BUFLOMEDIL TEVA 150MG CPR PELLIC BT20	Faible dans l'AOMI Insuffisant dans les autres indications
TEVA CLASSICS	3626786	BUFLOMEDIL TVC 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
WINTHROP MEDICAMENTS	3674354	BUFLOMEDIL WINTHROP 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
WINTHROP MEDICAMENTS	3674360	BUFLOMEDIL WINTHROP 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications

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EXPLOITANTS	CODE CIP	NOM	SMR
ZYDUS FRANCE	3528428	BUFLOMEDIL ZYD 150MG CPR BT20	Faible dans l'AOMI Insuffisant dans les autres indications
ZYDUS FRANCE	3528434	BUFLOMEDIL ZYD 300MG CPR BT10	Faible dans l'AOMI Insuffisant dans les autres indications
THERICA	3271739	CAPERGYL 4,5MG CAPS MOL BT 30	Insuffisant
VIATRIS	3018963	CARLYTENE 48 Comprimes drageifies a 10 mg	Insuffisant
VIATRIS	3018992	CARLYTENE 30 MG (MOXISYLYTE) 32 Comprimes enrobes	Insuffisant
ZYDUS FRANCE	3456410	CENTROPHENE 20MG CPR B60	Insuffisant dans les baisses d'acuité et troubles du champs visuel. Non réévaluée dans les autres indications ("angor" et "vertiges")
ZYDUS FRANCE	3464415	CENTROPHENE BUV FL 60ML	Insuffisant dans les baisses d'acuité et troubles du champs visuel. Non réévaluée dans les autres indications ("angor" et "vertiges")
ALMIRALL SAS	3308514	CERVOXAN 60MG GELU BT 30	Insuffisant
PIERRE FABRE MEDICAMENT	3224792	CIRKAN PREDNACINOLONE SUP BT 12	Insuffisant
DEXO S.A.	3225917	CLERIDIUM 150MG CPR BT 60	Insuffisant
AVENTIS	3024567	COLIMYCINE 1 000 000 UI PDR et SOL POUR PREPA INJ	Important
AVENTIS	3024538	COLIMYCINE 1,5MN CPR BT 10	Insuffisant dans l'indication « traitement de la diarrhée aiguë présumée d'origine bactérienne en l'absence de suspicion de phénomènes invasifs, en complément de la réhydratation » Modéré dans l'indication « Décontamination intestinale sélective lors des aplasies médullaires»
AVENTIS	3024573	COLIMYCINE 500 000 UI PDR et SOL POUR PREPA INJ	Important
NEGMA LERADS	3204996	CORONARINE, CPR ENROBES, B/120	Insuffisant
BAILLY-CREAT	3372251	COVATINE 50MG CPR BT 45	Insuffisant
PATRICK POIRIER	3231757	CYCLERGINE (cyclandélate), gélules, Gé_ (B/60) (laboratoires PATRICK POIRIER).	Insuffisant
MENARINI FRANCE	3290122	DI-ACTANE 100MG GELU BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
MENARINI FRANCE	3274896	DI-ACTANE 200MG GELU BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
SANOFI-SYNTHELABO FRANCE	3037073	ERCEFURYL 100MG GELU BT 30	Insuffisant
SANOFI-SYNTHELABO FRANCE	3213251	ERCEFURYL 200MG GELU BT 28	Insuffisant
SANOFI-SYNTHELABO FRANCE	3144900	ERCEFURYL 4% BUV SUSP FL90ML BT 1	Insuffisant
CEPHALON FRANCE	5560287	FONZYLANE 0,4 G/40 ML (CHLORHYDRATE DE BUFLOMEDIL) 5 FL 40 ml, SOL INJ PERF	Insuffisant
CEPHALON FRANCE	3465952	FONZYLANE 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
CEPHALON FRANCE	3465946	FONZYLANE 300MG CPR BT 10	Faible dans l'AOMI Insuffisant dans les autres indications
CEPHALON FRANCE	5581817	FONZYLANE 400 MG (CHLORHYDRATE DE BUFLOMEDIL) BT5, lyophilisat pour perfusion en flacon avec capuchon de transfert	Insuffisant
CEPHALON FRANCE	5575254	FONZYLANE 400 MG/120 ML (CHLORHYDRATE DE BUFLOMEDIL) BT10, 120 ml en poche, solution injectable pour perfusion	Insuffisant
CEPHALON FRANCE	5575248	FONZYLANE 400 MG/120 ML (CHLORHYDRATE DE BUFLOMEDIL) BT120 ml en poche, SOL INJ PERF	Insuffisant

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EXPLOITANTS	CODE CIP	NOM	SMR
CEPHALON FRANCE	3465969	FONZYLANE 50MG INJ AMP5ML BT 2	Insuffisant
SANOFI-SYNTHELABO FRANCE	3225691	GABACET 1G INJ AMP5ML BT 12	Insuffisant
SANOFI-SYNTHELABO FRANCE	3225716	GABACET 400MG GELU BT 60	Insuffisant
SANOFI-SYNTHELABO FRANCE	3220185	GABACET BUV AMP10ML BT 20	Insuffisant
EISAI S.A.	3043412	GENATROPINE 0,15 % (chlorhydrate d'atropine n-oxyde) , solution buvable, 20 ml en flacon avec seringue doseuse (laboratoires EISAI S.A.).	Insuffisant
EISAI S.A.	3043406	GENATROPINE 0,5 mg (chlorhydrate d'atropine n-oxyde), comprimés (B/60) (laboratoires EISAI S.A.).	Insuffisant
EISAI S.A.	3164179	GENESERINE 300MG BUV GTT FL30ML BT 1	Insuffisant
EISAI S.A.	3555951	GENESERINE 4,5MG CPR BT 30	Insuffisant
MERCK LIPHA SANTE SAS	3257610	GEVATRAN 200MG GELU BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
BEAUFOUR IPSEN PHARMA	3284570	GINKOGINK BUV FV30ML BT 1	Insuffisant
BEAUFOUR IPSEN PHARMA	3284593	GINKOGINK BUV FV90ML BT 1	Insuffisant
GOMENOL	3045747	GOMENOLEO 10 P. 100 1 Flacon de 250 ml, solute huileuse	Insuffisant
GOMENOL	3045569	GOMENOLEO 10 P. 100 1 Flacon de 50 ml, solute huileuse	Insuffisant
GOMENOL	3045693	GOMENOLEO 10 P. 100 ampoule, solution pour application locale	Insuffisant
GOMENOL	3045753	GOMENOLEO 2 P. 100 1 Flacon de 250 ml, solute huileuse	Insuffisant
GOMENOL	3045575	GOMENOLEO 2 P. 100 1 Flacon de 50 ml, solute huileuse	Insuffisant
GOMENOL	3045701	GOMENOLEO 2% LOC AMP5ML BT 10	Insuffisant
GOMENOL	3045799	GOMENOLEO 5 P. 100 1 Flacon de 250 ml, solute	Insuffisant
GOMENOL	3045606	GOMENOLEO 5 P. 100 1 Flacon de 50 ml, solute	Insuffisant
GOMENOL	3045730	GOMENOLEO 5% LOC AMP5ML BT 10	Insuffisant
MEDIPHA SANTE S.A.S.	3357004	HATIAL LP 400MG CPR BT30 (PENTOXIFILLYNE BIOGARAN)	Insuffisant
GOMENOL	3050814	HUILE GOMENOLEE 2% NAS FL22ML BT 1	Insuffisant
GOMENOL	3050820	HUILE GOMENOLEE 5% NAS FL22ML BT 1	Insuffisant
NOVARTIS PHARMA SAS	3051222	HYDERGINE 1MG/ML BUV FV50ML BT 1	Insuffisant
NOVARTIS PHARMA SAS	3252802	HYDERGINE 4,5MG CPR BT 30	Insuffisant
PIERRE FABRE MEDICAMENT	3054255	ISKEDYL BUV FL30ML BT 1	Insuffisant
PIERRE FABRE MEDICAMENT	3335238	ISKEDYL BUV FL70ML BT 1	Insuffisant
PIERRE FABRE MEDICAMENT	3221836	ISKEDYL CPR BT 100	Insuffisant
PIERRE FABRE MEDICAMENT	3412370	ISKEDYL FORT CPR BT 28	Insuffisant
PIERRE FABRE MEDICAMENT	3412387	ISKEDYL FORT CPR BT 56	Insuffisant
PIERRE FABRE MEDICAMENT	3141830	ISKEDYL INJ AMP2,5ML BT 6	Insuffisant
ABBOTT FRANCE	3465975	LOFTYL 150MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications

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EXPLOITANTS	CODE CIP	NOM	SMR
WINTHROP MEDICAMENTS	3263355	LUMIFUREX 200MG GELU BT 28	Insuffisant
SERVIER S.A.S.	3175591	MEDIATOR 100 Comprimes enrobes	Insuffisant dans l'indication adjuvant du régime adapté dans les hypertriglycéridémies. Dans l'indication "adjuvant du régime adapté chez les diabétiques avec surcharge pondérale": la Commission de la transparence ne réévaluera le service médical rendu de MEDIATOR dans cette indication qu'après avis de la Commission d'AMM et prise en compte de la réévaluation du rapport bénéfice / risque de ce produit par l'Afssaps.
SERVIER	3175579	MEDIATOR 150MG CPR BT 30	Insuffisant dans l'indication adjuvant du régime adapté dans les hypertriglycéridémies. Dans l'indication "adjuvant du régime adapté chez les diabétiques avec surcharge pondérale": la Commission de la transparence ne réévaluera le service médical rendu de MEDIATOR dans cette indication qu'après avis de la Commission d'AMM et prise en compte de la réévaluation du rapport bénéfice / risque de ce produit par l'Afssaps.
BRISTOL-MYERS SQUIBB	3069009	MUCOMYST INSTIL TRAC A.5ML BT 6	Faible
BIOGARAN	3605815	NAFTIDROFURYL BGA 200MG GELU20	Faible dans l'AOMI Insuffisant dans les autres indications
BIOGARAN	3605838	NAFTIDROFURYL BGA 200MG GELU90	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK GENERIQUES	3464421	NAFTIDROFURYL MERCK 100MG GELU BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK GENERIQUES	3464438	NAFTIDROFURYL MERCK 200MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK GENERIQUES	3474916	NAFTIDROFURYL MKG 200MG GELU90	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3603638	NAFTIDROFURYL QUA 100MG GELU20	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3603667	NAFTIDROFURYL QUA 200MG GELU20	Faible dans l'AOMI Insuffisant dans les autres indications
QUALIMED	3613306	NAFTIDROFURYL QUA 200MG GELU90	Faible dans l'AOMI Insuffisant dans les autres indications
RANBAXY PHARMACIE GE EX (RPG AVENTIS)	3711517	NAFTIDROFURYL RANBAXY 200MG CPR PELLIC BT20	Faible dans l'AOMI Insuffisant dans les autres indications
RANBAXY PHARMACIE GE EX (RPG AVENTIS)	3711552	NAFTIDROFURYL RANBAXY 200MG CPR PELLIC BT90	Faible dans l'AOMI Insuffisant dans les autres indications
THERABEL LUCIEN PHARMA	3266425	NAFTILUX 100 MG (NAFTIDROFURYL) 20 Gelules	Faible dans l'AOMI Insuffisant dans les autres indications
THERABEL LUCIEN PHARMA	3257656	NAFTILUX 200MG GELU BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
FOURNIER S.A.	3072454	NIBIOL 100MG CPR BT 50	Faible
BIOGARAN	3525281	NICERGOLINE BIOGARAN 10MG GELU BT 30	Insuffisant
BIOGARAN	3525298	NICERGOLINE BIOGARAN 10MG GELU BT 90	Insuffisant
BIOGARAN	3525269	NICERGOLINE BIOGARAN 5MG GELU BT 30	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3534340	NICERGOLINE EG 10MG GELU BT 30	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3534357	NICERGOLINE EG 10MG GELU BT 90	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3538378	NICERGOLINE EG 5MG GELU BT 30	Insuffisant

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EXPLOITANTS	CODE CIP	NOM	SMR
MERCK GENERIQUES	3613795	NICERGOLINE MKG 5MG GELU BT30	Insuffisant
MERCK GENERIQUES	3613766	NICERGOLINE MKG 10MG GELU BT30	Insuffisant
MERCK GENERIQUES	3613789	NICERGOLINE MKG 10MG GELU BT90	Insuffisant
QUALIMED	3613832	NICERGOLINE QUA 5MG GELU BT30	Insuffisant
QUALIMED	3613861	NICERGOLINE QUA 10MG GELU BT30	Insuffisant
QUALIMED	3613884	NICERGOLINE QUA 10MG GELU BT90	Insuffisant
RPG AVENTIS	3373871	NICERGOLINE RPG 5MG GELU BT30	Insuffisant
RPG AVENTIS	3381066	NICERGOLINE RPG 10MG GELU BT 30	Insuffisant
RPG AVENTIS	3458171	NICERGOLINE RPG 10MG GELU BT 90	Insuffisant
ARROW GENERIQUES	3581641	NIFUROXAZIDE ARW 200MG GELU 28	Insuffisant
ARROW GENERIQUES	3610526	NIFUROXAZIDE ARW 4% BUV FL90ML	Insuffisant
BIOGARAN	3540518	NIFUROXAZIDE BIOGARAN 200MG GELU BT 28	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3540889	NIFUROXAZIDE EG 200MG GELU BT 28	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3532849	NIFUROXAZIDE EG 4% SUSP BUV FL90ML BT 1	Insuffisant
G GAM	3530678	NIFUROXAZIDE G.GAM 200MG GELU BT 28	Insuffisant
G GAM	3532803	NIFUROXAZIDE G.GAM 4% BUV FL90ML BT 1	Insuffisant
IVAX SAS	3632976	NIFUROXAZIDE IVX 200MG GELU 28	Insuffisant
MERCK GENERIQUES	3498006	NIFUROXAZIDE MERCK 200MG GELU BT 28	Insuffisant
MERCK GENERIQUES	3532826	NIFUROXAZIDE MERCK 4% BUV FL90ML BT 1	Insuffisant
QUALIMED	3588554	NIFUROXAZIDE QUA 4% BUV FL90ML	Insuffisant
QUALIMED	3502239	NIFUROXAZIDE QUALIMED 200MG GELU BT 28	Insuffisant
RATIOPHARM	3475755	NIFUROXAZIDE RATIOPHARM 100MG GELU BT 30	Insuffisant
RATIOPHARM	3475761	NIFUROXAZIDE RATIOPHARM 200MG GELU BT 28	Insuffisant
RATIOPHARM	3251599	NIFUROXAZIDE RATIOPHARM 4% BUV FL90ML BT 1	Insuffisant
RPG AVENTIS	3404643	NIFUROXAZIDE RPG 200MG GELU BT 28	Insuffisant
RPG AVENTIS	3404117	NIFUROXAZIDE RPG 4% BUV FL90ML	Insuffisant
SANDOZ	3659679	NIFUROXAZIDE SANDOZ 200MG GELU BT 29	Insuffisant
TEVA CLASSICS	3611744	NIFUROXAZIDE TVC 200MG GELU 28	Insuffisant
TEVA CLASSICS	3611750	NIFUROXAZIDE TVC 4% BUV FL90ML	Insuffisant
WINTHROP MEDICAMENTS	3241632	NIFUROXAZIDE WINTHROP 200MG GELU BT14	Insuffisant
WINTHROP MEDICAMENTS	3241649	NIFUROXAZIDE WINTHROP 200MG GELU BT20	Insuffisant
WINTHROP MEDICAMENTS	3674696	NIFUROXAZIDE WINTHROP 200MG GELU BT28	Insuffisant
WINTHROP MEDICAMENTS	3674704	NIFUROXAZIDE WINTHROP 4% SOL BUV FL 90	Insuffisant
ZYDUS FRANCE	3497946	NIFUROXAZIDE ZYD 200MG GELU 28	Insuffisant
ZYDUS FRANCE	3556689	NIFUROXAZIDE ZYD 4% BUV FL90ML	Insuffisant
UCB PHARMA SA	3130571	NOOTROPYL (PIRACETAM) 12 Ampoules de 5 ml, solute injectable	Insuffisant
UCB PHARMA SA	3314414	NOOTROPYL 1200MG BUV AMP6ML BT 30	Faible dans les myoclonies Insuffisant dans les autres indications
UCB PHARMA SA	3209551	NOOTROPYL 20% BUV FL125ML BT 1	Faible dans les myoclonies Insuffisant dans les autres indications
UCB PHARMA SA	3130565	NOOTROPYL 400MG GELU BT 60	Insuffisant
UCB PHARMA SA	3268619	NOOTROPYL 800 MG (PIRACETAM) 90 Comprimes pelliculés	Insuffisant

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EXPLOITANTS	CODE CIP	NOM	SMR
UCB PHARMA SA	3266371	NOOTROPYL 800MG CPR BT 45	Insuffisant
CEPHALON FRANCE	3248752	OLMIFON CPR PELLIC BT 20	Insuffisant
CEPHALON FRANCE	3248769	OLMIFON CPR PELLIC BT 40	Insuffisant
BOUCHARA RECORDATI	3275588	PANFUREX 200MG GELU BT 28	Insuffisant
BOUCHARA RECORDATI	3275594	PANFUREX 200MG/5ML BUV FL90ML BT 1	Insuffisant
BOUCHARA RECORDATI	3348732	PENTOFLUX LP 400MG CPR BT 30	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3587922	PENTOXIF. EG LP 400MG CPR BT30	Insuffisant
TEVA CLASSICS	3614429	PENTOXIF. TVC LP 400MG CPR BT30	Insuffisant
BIOGARAN	3512841	PENTOXIFYLLINE BIOGARAN LP 400MG CPR BT 30	Insuffisant
GNR PHARMA	3354678	PENTOXIFYLLINE GNR LP 400MG CPR BT 30	Insuffisant
MERCK GENERIQUES	3497679	PENTOXIFYLLINE MERCK LP 400MG CPR BT 30	Insuffisant
QUALIMED	3573966	PENTOXIFYLLINE QUALIMED LP 400MG CPR BT 30	Insuffisant
RATIOPHARM	3582830	PENTOXIFYLLINE RATIOPHARM LP 400MG CPR BT 30	Insuffisant
RPG AVENTIS	3570525	PENTOXIFYLLINE RPG LP 400MG CPR BT 30	Insuffisant
SANDOZ	3679618	PENTOXIFYLLINE SANDOZ LP 400MG CPR BT 30	Insuffisant
BOEHRINGER INGELHEIM FRANCE	5623409	PERSANTINE 10 MG/2 ML (DIPYRIDAMOLE) 1 Boite de 10, solution injectable en ampoule	Faible
BOEHRINGER INGELHEIM FRANCE	3199829	PERSANTINE 75MG CPR BT 100	Insuffisant
BOEHRINGER INGELHEIM FRANCE	3082033	PERSANTINE 75MG CPR BT 30	Insuffisant
ARROW GENERIQUES	3577042	PIRACETAM ARW 20% BUV FL125ML	Faible dans les myoclonies Insuffisant dans les autres indications
ARROW GENERIQUES	3596223	PIRACETAM ARW 800MG CPR FV45	Insuffisant
BIOGARAN	3497277	PIRACETAM BIOGARAN 400MG CPR FV 90	Insuffisant
BIOGARAN	3497320	PIRACETAM BIOGARAN 800MG CPR FV 45	Insuffisant
EG LABO LABORATOIRES EUROGENERICS	3497194	PIRACETAM EG 800MG CPR FV 45	Insuffisant
G GAM	3532772	PIRACETAM G.GAM 800MG CPR BT 45	Insuffisant
GNR PHARMA	3473839	PIRACETAM GNR 20% BUV FL125ML BT 1	Faible dans les myoclonies Insuffisant dans les autres indications
GNR PHARMA	3595086	PIRACETAM GNR 800MG CPR FV45	Insuffisant
IVAX SAS	3623747	PIRACETAM IVX 20% BUV FL125ML	Faible dans les myoclonies Insuffisant dans les autres indications
IVAX SAS	3621079	PIRACETAM IVX 800MG CPR FV45	Insuffisant
MERCK GENERIQUES	3602544	PIRACETAM MKG 20% BUV FL125ML	Faible dans les myoclonies Insuffisant dans les autres indications
MERCK GENERIQUES	3595123	PIRACETAM MKG 400MG CPR FV60	Insuffisant
MERCK GENERIQUES	3595146	PIRACETAM MKG 400MG CPR FV90	Insuffisant
MERCK GENERIQUES	3595169	PIRACETAM MKG 800MG CPR FV45	Insuffisant
QUALIMED	3602538	PIRACETAM QUA 20% BUV FL125ML	Faible dans les myoclonies Insuffisant dans les autres indications
QUALIMED	3595206	PIRACETAM QUA 400MG CPR FV60	Insuffisant
QUALIMED	3595212	PIRACETAM QUA 400MG CPR FV90	Insuffisant

EXPLOITANTS	CODE CIP	NOM	SMR
QUALIMED	3595235	PIRACETAM QUA 800MG CPR FV45	Insuffisant
RPG AVENTIS	3512657	PIRACETAM RPG 800MG CPR FV 45	Insuffisant
RATIOPHARM	3617534	PIRACETAM RTP 800MG CPR FV45	Insuffisant
SANDOZ	3680840	PIRACETAM SANDOZ 20% BUV FL125ML BT 1	Faible dans les myoclonies Insuffisant dans les autres indications
SANDOZ	3679736	PIRACETAM SANDOZ 800MG CPR FV45	Insuffisant
TEVA CLASSICS	3596737	PIRACETAM TVC 800MG CPR FV45	Insuffisant
VEDIM PHARMA	3638476	PIRACETAM UCB 20% BUV FL125ML	Faible dans les myoclonies Insuffisant dans les autres indications
VEDIM PHARMA	3299399	PIRACETAM UCB 400MG CPR BT 60	Insuffisant
VEDIM PHARMA	3299407	PIRACETAM UCB 800MG CPR BT 45	Insuffisant
ZYDUS FRANCE	3541216	PIRACETAM ZYD 800MG CPR FV45	Insuffisant
ZYDUS FRANCE	3541570	PIRACETAM ZYD 800MG CPR FV45	Insuffisant
SERVIER	3137981	PNEUMOREL 0,2% SIR FL150ML BT 1	Insuffisant
SERVIER	3193011	PNEUMOREL 80 MG (CHLORHYDRATE DE FENSPIRIDE) 100 CPR	Insuffisant
SERVIER	3192974	PNEUMOREL 80MG CPR BT 30	Insuffisant
MERCK LIPHA SANTE SAS	5536917	PRAXILENE 100 MG (OXALATE ACIDE DE NAFTIDROFURYL) BT100 gelules	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK LIPHA SANTE SAS	3328793	PRAXILENE 100MG GELU BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK LIPHA SANTE SAS	5592376	PRAXILENE 200 MG (OXALATE ACIDE DE NAFTIDROFURYL) 50 Comprimes pelicules	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK LIPHA SANTE SAS	3242643	PRAXILENE 200MG CPR BT 20	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK LIPHA SANTE SAS	3420553	PRAXILENE 200MG CPR BT 90	Faible dans l'AOMI Insuffisant dans les autres indications
MERCK LIPHA SANTE SAS	5572095	PRAXINOR CPR BT 100	Insuffisant
MERCK LIPHA SANTE SAS	3085741	PRAXINOR CPR BT 20	Insuffisant
MERCK LIPHA SANTE SAS	5506810	PRAXINOR CPR BT 250	Insuffisant
MERCK LIPHA SANTE SAS	5592347	PRAXINOR CPR BT 50	Insuffisant
EXPANPHARM	3233176	PROTANGIX 60 mg (dipyridamole), capsules (B/30) (laboratoires EXPANPHARM).	Insuffisant
NIVERPHARM	3178721	RHEOBRAL GELU BT 30	Insuffisant
NIVERPHARM	3178738	RHEOBRAL GELU BT 60	Insuffisant
SUBSTANTIA	3248261	RINUREL, comprimés (B/24) (laboratoires SUBSTANTIA).	Insuffisant
PARKE-DAVIS	3246701	RINUTAN, comprimés (B/12) (laboratoires WARNER WELLCOME et PARKE DAVIS).	Insuffisant
MERCK MEDICATION FAMILIALE S.A.S.	3093924	SALICAIRINE (extrait hydro-alcoolique fluide de salicaire), solution buvable, 15 ml en flacon compte-gouttes (laboratoires MERCK MEDICATION FAMILIALE).	Insuffisant
AVENTIS	5525322	SERMION 20 Flacons, preparation injectable a 5 mg	Insuffisant
AVENTIS	5528734	SERMION 50 Flacons, preparation injectable a 5 mg	Insuffisant
AVENTIS	3372570	SERMION 10MG GELU BT 90	Insuffisant
AVENTIS	3356387	SERMION 10MG GELU TB 30	Insuffisant
AVENTIS	3326216	SERMION 10MG LYOT ORAL BT 30	Insuffisant
AVENTIS	3373902	SERMION 5MG GELU BT 30	Insuffisant
AVENTIS	3176136	SERMION 5MG INJ FL+AMP BT 1	Insuffisant
AVENTIS	3170642	SERMION 5MG LYOT ORAL BT 30	Insuffisant
PHARMA DEVELOPPEMENT	3425438	SUCCINIMIDE PHARBIOL 3G BUV SACH DOS BT 30	Insuffisant
BOEHRINGER INGELHEIM FRANCE	5557871	SURBRONC 15 MG/2 ML (AMBROXOL) 60 Ampoules de 2 ml, SOL INJ	Insuffisant

EXPLOITANTS	CODE CIP	NOM	SMR
BOEHRINGER INGELHEIM FRANCE	3304019	SURBRONC 15MG INJ AMP2ML BT 12	Insuffisant
BOEHRINGER INGELHEIM FRANCE	3318725	SURBRONC 30MG INJ AMP4ML BT 12	Insuffisant
BEAUFOUR IPSEN PHARMA	5574935	TANAKAN 40 MG (EXTRAIT DE GINKGO BILOBA) 500 CPR	Insuffisant
BEAUFOUR IPSEN PHARMA	3299040	TANAKAN 40MG CPR BT 30	Insuffisant
BEAUFOUR IPSEN PHARMA	3299063	TANAKAN 40MG CPR BT 90	Insuffisant
BEAUFOUR IPSEN PHARMA	3163240	TANAKAN 40MG/ML BUV FL 30ML BT1	Insuffisant
BEAUFOUR IPSEN PHARMA	3302799	TANAKAN 40MG/ML BUV FL90ML BT 1	Insuffisant
PFIZER	3104131	TERRAMYCINE SOLU-RETARD 250 mg, solution injectable (IM), 3 ml en ampoule (B/1) (laboratoires PFIZER).	Important
PFIZER	3465366	THIOVALONE BUC FL PULV 12ML BT 1	Insuffisant
AVENTIS	5592169	TORENTAL 100 MG/5 ML (PENTOXIFYLLINE) BT 5, solution injectable en ampoule	Insuffisant
AVENTIS	3176969	TORENTAL 100MG INJ AMP5ML BT 6	Insuffisant
AVENTIS	5560442	TORENTAL 300 MG/15 ML (PENTOXIFYLLINE) 10 Ampoules de 15 ml, solution injectable	Insuffisant
AVENTIS	5604688	TORENTAL 300 MG/15 ML (PENTOXIFYLLINE) BT 5, solution injectable en Ampoule de 15 ml	Insuffisant
AVENTIS	3227572	TORENTAL LP 400MG CPR BT 20	Insuffisant
URPAC-ASTIER	3287798	TRAMISAL BUV SOL FV30ML	Insuffisant
BOUCHARA RECORDATI	3452292	TRIMADIAZ ANTRIMA (sulfadiazine, triméthoprime), comprimés (B/10) (laboratoires BOUCHARA RECORDATI).	Insuffisant
BOUCHARA RECORDATI	3452286	TRIMADIAZ ANTRIMA Nourrisson et Enfant (sulfadiazine, triméthoprime), suspension buvable, 50 ml en flacon avec cuillère-mesure (laboratoires BOUCHARA RECORDATI).	Insuffisant
ARROW GENERIQUES	3610176	TRIMETAZIDINE ALMUS 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
ARROW GENERIQUES	3574575	TRIMETAZIDINE ARW 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
ARROW GENERIQUES	3574581	TRIMETAZIDINE ARW 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
BIOGARAN	3411181	TRIMETAZIDINE BGA 20MG CPR B 60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
BIOGARAN	3414423	TRIMETAZIDINE BGA 20MG/ML FL 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications

EXPLOITANTS	CODE CIP	NOM	SMR
EG LABO LABORATOIRES EUROGENERICS	3456367	TRIMETAZIDINE EG 20MG CPR BT60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
EG LABO LABORATOIRES EUROGENERICS	3456924	TRIMETAZIDINE EG 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
G GAM	5624308	TRIMETAZIDINE G GAM 20MG CPR PELLIC BT100	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
G GAM	3534506	TRIMETAZIDINE GGAM 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
G GAM	3521633	TRIMETAZIDINE GGAM 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
IVAX SAS	3603928	TRIMETAZIDINE IVX 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
IVAX SAS	3417031	TRIMETAZIDINE IVX 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
MERCK GENERIQUES	3509187	TRIMETAZIDINE MKG 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
MERCK GENERIQUES	3510374	TRIMETAZIDINE MKG 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
MERCK SHARP &DOHME CHIBRET	3416793	TRIMETAZIDINE MSD 20 MG (DICHLORHYDRATE DE TRIMETAZIDINE) 1 Boite de 100, Comprimes pellicules	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
QUALIMED	3571223	TRIMETAZIDINE QUA 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
QUALIMED	3571252	TRIMETAZIDINE QUA 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
RPG AVENTIS	3549867	TRIMETAZIDINE RPG 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications

REEVALUATION DU SERVICE MEDICAL RENDU (3ème PHASE)

EXPLOITANTS	CODE CIP	NOM	SMR
RATIOPHARM	3544025	TRIMETAZIDINE RTP 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
RATIOPHARM	3550528	TRIMETAZIDINE RTP 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
SANDOZ	3681791	TRIMETAZIDINE SANDOZ 20MG CPR B 60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
SANDOZ	3689278	TRIMETAZIDINE SANDOZ 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
TEVA CLASSICS	3614027	TRIMETAZIDINE TVC 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
TEVA CLASSICS	3614010	TRIMETAZIDINE TVC 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
WINTHROP MEDICAMENTS	3674905	TRIMETAZIDINE WINTHROP 20MG CPR B/60	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
WINTHROP MEDICAMENTS	3674911	TRIMETAZIDINE WINTHROP 20MG/ML 60ML	Insuffisant dans l'indication :« Traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire ». Non réévalué dans les autres indications
SERVIER	3108608	TRIVASTAL 20MG BT 30	Important dans l'indication "maladie de Parkinson" Insuffisant dans les autres indications
SERVIER	3169900	TRIVASTAL 3MG INJ AMP1ML BT 12	Insuffisant
SERVIER	3189110	TRIVASTAL 50 MG L.P. (PIRIBEDIL) 100 CPR LP	Important dans l'indication "maladie de Parkinson" Insuffisant dans les autres indications
SERVIER	3189067	TRIVASTAL 50MG LP BT 30	Important dans l'indication "maladie de Parkinson" Insuffisant dans les autres indications
SANOFI-SYNTHELABO FRANCE	3359629	VADILEX 20 (TARTRATE D'IFENPRODIL) 50 CPR	Insuffisant
SANOFI-SYNTHELABO FRANCE	3228672	VADILEX 20MG CPR DRG BT 30	Insuffisant
SANOFI-SYNTHELABO FRANCE	3156984	VADILEX 5MG INJ AMP2ML BT 10	Insuffisant
CHIESI S.A.	3406398	VASOBRAL (MESILATE DE DIHYDROERGOCRYPTINE A CAFEINE) 100 CPR SEC	Insuffisant
CHIESI S.A.	3392093	VASOBRAL CPR BT 30	Insuffisant
CHIESI S.A.	3431835	VASOBRAL CPR BT 60	Insuffisant
CHIESI S.A.	3182504	VASOBRAL SOL BUV FL50ML BT 1	Insuffisant

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REEVALUATION DU SERVICE MEDICAL RENDU (3ème PHASE)

EXPLOITANTS	CODE CIP	NOM	SMR
SERVIER	3220512	VASTAREL 20 MG (CHLORHYDRATE DE TRIMETAZIDINE) CPR ENROB BT100	Insuffisant dans le traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire . Modéré dans le traitement symptomatique d'appoint des vertiges et des acouphènes. Modéré dans le traitement prophylactique de la crise d'angine de poitrine.
SERVIER	3220506	VASTAREL 20MG CPR ENROB B/60	Insuffisant dans le traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire . Modéré dans le traitement symptomatique d'appoint des vertiges et des acouphènes. Modéré dans le traitement prophylactique de la crise d'angine de poitrine.
SERVIER	3227520	VASTAREL 20MG/ML BUV FL60	Insuffisant dans le traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire . Modéré dans le traitement symptomatique d'appoint des vertiges et des acouphènes. Modéré dans le traitement prophylactique de la crise d'angine de poitrine.
SERVIER	3572470	VASTAREL 35 MG (DICHLORHYDRATE DE TRIMETAZIDINE),CPR PELLIC LM BT100	Insuffisant dans le traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire . Modéré dans le traitement symptomatique d'appoint des vertiges et des acouphènes. Modéré dans le traitement prophylactique de la crise d'angine de poitrine.
SERVIER	3572458	VASTAREL 35MG LM CPR BT60	Insuffisant dans le traitement d'appoint des baisses d'acuité et des troubles du champ visuel présumés d'origine vasculaire . Modéré dans le traitement symptomatique d'appoint des vertiges et des acouphènes. Modéré dans le traitement prophylactique de la crise d'angine de poitrine.
SUBSTIPHARM	3198155	VINCA 20 CPR BT 45	Insuffisant
SUBSTIPHARM	3222652	VINCA 30 RETARD GELU BT 60	Insuffisant
PHARMA DEVELOPPEMENT	3198505	VINCARUTINE GELU BT 45	Insuffisant

SANTé-MéDICAMENT-DIABèTE-OBéSITé
Médiator: la Haute autorité de Santé se défend
01/12/2010 19:42:24 GMT+01:00
#747766 DVBP 4360 GXZ83 (4) AFP (457)

PARIS, 1 déc 2010 (AFP) - La Haute Autorité de Santé (HAS) rappelle mercredi qu'elle s'est prononcée contre le remboursement par la sécurité sociale du Mediator, jugeant qu'il ne présentait pas d'intérêt, en mettant en ligne les avis concernés ainsi qu'un document préparatoire sujet à controverse.

La HAS, qui héberge la Commission de transparence du médicament, souligne à ce propos que son travail se limite à dire si l'efficacité d'un médicament justifie son remboursement, la décision revenant au ministère de la Santé.

A la suite d'informations parues dans la presse concernant l'évaluation de Mediator par la Commission de transparence, la HAS rappelle qu'elle s'est "déclarée défavorable au remboursement de ce produit dans un avis du 10 mai 2006, publié sur son site".

La Commission avait déjà rendu un avis défavorable au remboursement (avis du 17 novembre 1999), qui n'avait pas non plus été suivi d'une décision de déremboursement par le ministère.

La note incluse dans le document préparatoire du 12 avril 2006, reproduite en partie par le Canard Enchaîné fait état, selon l'HAS "d'informations qui étaient déjà publiques à l'époque" et dont certaines ont été reprises par la presse professionnelle. Cette note précisait aussi que la Commission Nationale de Pharmacovigilance (Afssaps) souhaitait une réévaluation du rapport bénéfice/risque de ce médicament, souligne la HAS.

Selon cette note en ligne, "le benfluorex (ndlr Médiator) est un dérivé de la fenfluramine (ex-Pondéral) et de la dexfenfluramine (ex-Isoméride), deux anorexigènes amphétaminiques retirés du marché du fait d'effets indésirables graves : hypertensions artérielles pulmonaires et valvulopathies cardiaques. (ces effets secondaires sévères connus peuvent se manifester plus de 10 ans après la dernière prise)".

La note relève que le Mediator "classé par l'OMS parmi les anorexigènes" est "utilisé en France, hors AMM (hors indications diabète), comme traitement à visée amaigrissante".

"En Espagne, la survenue sous benfluorex de troubles cardiaques graves, semblables à ceux observés avec la fenfluramine et la dexfenfluramine, est à l'origine du retrait du marché des spécialités pharmaceutiques contenant du benfluorex en mars 2003. En juin 2005, l'agence espagnole du médicament a annoncé l'interdiction des préparations magistrales à base de divers produits amaigrissants, dont le benfluorex, suite à la survenue d'effets indésirables graves".

"La Commission Nationale de Pharmacovigilance (PV du 29 novembre 2005 ci joint) a souhaité une réévaluation du rapport bénéfice/risque du produit", conclut cette note en forme d'encadré.

Le document préparatoire conclut que le Médiator "ne présente pas d'intérêt en termes de santé publique".

BC/jca/ct

Annexe 4-40

Ministère des affaires sociales,
du travail et de la solidarité

Ministère de la santé, de la famille
et des personnes handicapées

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RÉPUBLIQUE FRANÇAISE

DIRECTION DE LA SÉCURITÉ SOCIALE
Sous-direction du financement du système de soins
Bureau des produits de santé
Personne chargée du dossier
Mes documents/textes TC/deremboSMRinsuf.doc

13 DEC 2002

Note pour le Ministre
(A l'attention de M. de TOURNEMIRE)

Objet : Fiches juridiques sur les différentes étapes de la procédure de radiation des spécialités à SMR insuffisant.
P.J : 7 fiches

Je vous prie de trouver ci-joint 7 fiches attirant votre attention sur les difficultés juridiques pouvant surgir à l'occasion des différentes étapes de la procédure contradictoire à engager avec les laboratoires en application de l'article R. 163-13 du code de la sécurité sociale.

Ces risques sont tirés de la connaissance que nous avons des arguments le plus souvent soulevés par les laboratoires à l'occasion des contentieux sur la baisse du taux des vasodilatateurs. Ces risques ne sont pas tous de nature à entraîner une annulation en cas de contentieux. Toutefois, il ne semble pas inutile de les prendre en compte.

S'agissant des contentieux sur les vasodilatateurs, les requêtes seront jugées par le CE probablement avant la fin de l'année. Nous ne savons donc pas à ce jour si les griefs utilisés par les requérants et repris dans la présente note entraîneront ou pas l'annulation de l'arrêté du 14 septembre 2001.

Il pourrait être utile que l'ensemble des intervenants de la procédure côté pouvoirs publics, et tout particulièrement l'AFSSAPS et le président de la commission de la transparence, aient conscience de ces différents aspects. Les fiches ci-jointes pourraient leur être transmises ou communiquées à l'occasion d'une prochaine réunion

Le Directeur de la Sécurité Sociale

Dominique LIBAULT

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Procédure : faire-apparaître ces questions comme des informations complémentaires et non

Annexe 4-40

Fiche n°1 : Elaboration des listes de médicaments à SMR insuffisant dont le déremboursement est envisagé

[redacted]

- La première phase doit intéresser les médicaments à SMR insuffisant qui n'ont plus leur place dans la stratégie thérapeutique. L'idée serait que la procédure débute en décembre 2002 pour aboutir à un déremboursement en juillet 2003.
- La deuxième phase concernerait les médicaments à SMR insuffisant susceptibles de trouver leur place sur le marché de l'automédication : début de la procédure en juillet 2003 avec un arrêté en janvier 2004.
- Enfin, la dernière phase concernerait les autres médicaments à SMR insuffisant : début de la procédure en juillet 2004 avec un arrêté en janvier 2005.

1/ la succession dans le temps des déremboursements suppose d'être très vigilant sur le champ de chaque liste afin d'éviter toute inégalité de traitement. Ainsi, s'agissant de la première liste :

- il faudra veiller à ce que tous les médicaments à SMR insuffisant n'ayant plus de place dans la stratégie thérapeutique **d'une même classe thérapeutique (même visée thérapeutique)** fassent l'objet d'un déremboursement en même temps sauf à générer des atteintes à la concurrence ;
- dans la même logique, veiller à exclure du remboursement les indications des médicaments qui ont, par ailleurs, un SMR qui n'est pas insuffisant mais dont ces indications correspondent à celles des médicaments, qui n'ont pas d'autres indications et dont le déremboursement est envisagé.

2/ Pour les médicaments à SMR insuffisant mais ayant plusieurs indications : il faudra faire une analyse indications par indications car le décret précise que les spécialités pharmaceutiques sont inscrites indications par indications (Voir fiche 2) et adapter, le cas échéant, la rédaction des arrêtés de déremboursement en conséquence (Voir fiche 7) ;

3/ définir clairement si le déremboursement vise la seule liste ville ou les deux listes (ville et collectivités). L'article R. 163-13 autorise les ministres à radier des spécialités sur l'une et/ou l'autre. En revanche, la mission confiée à la commission de la transparence sur la réévaluation ne concernait que les médicaments sur la liste ville. Toutefois, s'agissant de la première phase de déremboursement, la radiation sur la liste ville doit entraîner d'office la radiation sur la liste des collectivités car ces médicaments n'ont plus de place dans la stratégie thérapeutique. Pour les deux autres phases la réponse est moins évidente.

4/ enfin, dans l'hypothèse où les textes réglementaires définissant les critères du SMR seraient modifiés entre les différentes phases, il faut garder à l'esprit que les laboratoires redemanderont une évaluation selon les nouveaux critères. Tant que l'on reste avec les mêmes critères, le ministre peut prendre une décision se fondant sur les avis de 1999 concernant la réévaluation. Après changement, il sera plus difficile au ministre de prendre une décision sur la base d'un avis de 1999. Si la composition de la commission venait à être modifiée de manière importante, on s'expose à des demandes similaires de la part des entreprises, mais le risque est moindre.

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Fiche n° 2 : Cas des médicaments à plusieurs indications

Dans ce cas, il convient :

- de veiller à ce que toutes les indications soient évaluées dans l'avis de la CT ;
- si toutes les indications ont un SMR insuffisant : faire attention à ne pas dérembourser des indications qui ne devraient faire l'objet d'un déremboursement que dans la deuxième ou troisième phase sauf, bien sûr, en cas d'accord du laboratoire. En l'absence d'accord, les laboratoires pourraient également invoquer une rupture d'égalité de traitement ;
- si les indications n'ont pas toutes le même niveau de SMR :

La pratique actuelle veut que la spécialité soit prise en charge pour l'ensemble des indications dans le SMR le plus élevé à condition que cette indication représente une part substantielle des indications (lettre de l'afssaps du 16 septembre 1999). Les textes ne précisent pas ce point, l'article R. 163-3 précise simplement que la spécialité est inscrite au vu de son SMR indication par indication. Il n'est pas possible d'inscrire une spécialité avec plusieurs taux de remboursement car il n'est pas possible pour les caisses de connaître exactement l'indication dans laquelle la spécialité a été prescrite. D'où la pratique de retenir l'indication où le SMR est le plus élevé. Pour la DSS, la part substantielle est la part prépondérante[1]. Les laboratoires contestent cette position aujourd'hui[2], car ils estiment que même en présence d'une indication orpheline pour laquelle le SMR est supérieur mais qui représente une part de prescription non négligeable (mais non forcément majoritaire) on devrait retenir le SMR le plus important. Il conviendra donc d'avoir une position claire et transposable à tous les laboratoires sur l'indication qui est retenue pour l'admission au remboursement.

Mais lorsque l'on parle de déremboursement, on n'est plus tenu par la divergence de taux soulevé précédemment, il semble possible de dérembourser la spécialité dans une ou plusieurs indications et en revanche de garder au remboursement une indication remboursable. Mais attention dans ce cas, en principe, les médecins doivent inscrire NR sur l'ordonnance lorsqu'ils prescrivent le médicament en dehors de l'indication remboursable. En réalité les médecins ne remplissent pas cette obligation et les caisses n'ont pas les moyens de contrôler, ce qui rend le système largement inefficace. En termes d'efficacité, il est préférable de soutenir la position soutenue jusqu'à maintenant par la DSS. Le cas échéant, s'agissant d'indications « orphelines » dont le SMR justifierait le maintien au remboursement, on pourrait, à la limite, recourir à la procédure du médicament d'exception.

En tout état de cause, ces médicaments méritent qu'on s'interroge sur leur traitement dés le tout début de la procédure.

[1] C'est à dire la part pour laquelle les prescriptions sont le plus importantes en volume (ex : Pour Trivastal, afin de déterminer la part prépondérante, l'administration s'est référée aux statistiques du Doréma qui précisent que 22,2% des prescriptions concernent l'indication dans la maladie de Parkinson où le SMR est important et le reste des prescriptions se font dans des indications pour lesquelles le SMR est insuffisant.).

[2] Ils ne l'ont pas contesté après le courrier du 19 juin 1999, et n'ont commencé à contester cette interprétation qu'au moment des contentieux sur les vasodilatateurs.

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Fiche n°3 : Engagement de la procédure contradictoire ;

L'article R. 163-15 précise : « Le ministre chargé de la sécurité sociale et le ministre chargé de la santé informent l'entreprise qui exploite le médicament de leur intention soit de modifier le classement d'un médicament inscrit sur la liste prévue à l'article L. 162-17 au regard de la participation des assurés aux frais d'acquisition des médicaments, soit de radier un médicament des listes prévues aux articles L. 162-17 du présent code et L. 5123-2 du code de la santé publique.

L'entreprise qui exploite le médicament peut présenter des observations écrites ou demander à être entendue par la commission prévue à l'article R. 163-15, dans le mois suivant réception de cette information ».

L'absence de consultation préalable des entreprises préalablement à une baisse de taux ou de déremboursement entraîne inévitablement l'annulation de l'arrêté pris : **cette consultation est un préalable obligatoire.**

1/ La notification doit comporter les motifs de la décision des ministres. En l'espèce, il s'agit de l'avis de la CT qui conclut à un SMR insuffisant.

2/ Indiquer le délai laissé au laboratoire pour faire valoir ses observations. En l'espèce, un mois.

3/ Indiquer le lieu de centralisation de ses observations (en principe le ministère avec copie au secrétariat de la commission à l'AFSSAPS) ;

4/ La notification par les ministres doit avoir une date certaine car elle fait partir le délai de réponse d'un mois de l'entreprise. Le moyen le plus sûr est d'envoyer ce courrier avec un AR car en retour on a ainsi de façon incontestable, la preuve que le laboratoire a bien été informé et ce à une date précise.

L'administration serait fondée à refuser des observations qui parviennent au-delà du délai d'un mois mais en revanche, elle peut décider de les accepter si le mois est dépassé dans un délai qu'elle estime acceptable.

5/ Il faut une coordination parfaite entre les services du ministère qui centralisent les observations des laboratoires et l'AFSSAPS afin que toutes les observations fassent l'objet d'un traitement dont l'issue sera soit une audition par la CT à la demande de l'entreprise (art R. 163-13) où à la demande des ministres si le laboratoire n'a pas sollicité d'audition (6° de l'article R. 163-19) soit un traitement en interne au service du ministère ;

6/ Toutes les demandes d'audition ne sont pas forcément suivies d'une audition effective. En effet, le texte précise « le laboratoire peut demander à être entendu par la commission ». Ainsi, rien n'empêche la commission de refuser une nouvelle audition si par exemple elle considère que le dossier transmis par le laboratoire est complètement vide ou n'apporte aucun élément nouveau par rapport à l'audition précédente.

7/ le temps que prend l'administration et l'AFSSAPS pour répondre aux observations des laboratoires n'est pas prévu par les textes. Dès lors, la règle de droit commun pourrait trouver à s'appliquer, à savoir l'absence de réponse de l'administration dans un délai de deux mois vaut décision implicite de rejet (mais en l'espèce cette règle n'a qu'un intérêt relatif) ;

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Fiche n° 4 : Audition par la Commission de la transparence ou examen des observations écrites des entreprises

[redacted]

Dans les précédents contentieux sur la baisse de taux des vasodilatateurs, les requérants ont tous évoqués des vices dans la procédure de consultation de la commission

1/ veiller à un strict respect des règles de convocation, cf article R. 163-17 du CSS ; envoi de l'ordre du jour et des documents aux membres au plus tard 8 jours avant la date de la réunion (article 1-1-6 du règlement intérieur plus favorable que l'art 11 du décret du 28 novembre 1983 qui prévoyait 5 jours) ;

2/ **veiller au respect du quorum, à l'occasion de chaque vote.** La règle est fixée à l'article R. 163-16 I et II : les délibérations de la commission ne sont valables que si au moins douze membres de la commission sont présents. Les avis sont pris à la majorité des suffrages, le président ayant voix prépondérante en cas de partage égal des voix.

- Douze membres de la commission doivent être présents c'est à dire douze membres ayant le droit de vote. Si le membre titulaire et son suppléant sont tous deux présents, seul le membre titulaire a le droit de voter et cela compte pour 1 personne dans le quorum ;

- A l'occasion de chaque vote, les membres qui ont un droit de vote mais qui pourraient avoir un conflit d'intérêt avec le dossier étudié doivent sortir de la salle ou, en tout état de cause, ne pas prendre part au vote et ne pas être comptés dans le quorum (cf. dernière phrase de l'article R. 163-17) ;

- Les membres de droit de la commission peuvent se faire accompagner d'une personne de leurs services mais cette personne doit au préalable adresser au secrétariat de la commission de la transparence une déclaration mentionnant les liens directs ou indirects qu'elle peut avoir avec les titulaires d'autorisation de mise sur le marché et les entreprises dont les produits sont susceptibles de faire l'objet d'un examen par la commission (cf. 3) ;

- Le nombre de personnes de l'AFSSAPS assistant à la séance au titre du sécrétariat de la commission doit être raisonnable. En effet, dans les contentieux en cours la forte représentation des services de l'afssaps est fortement critiquée par les requérants. Ainsi, on a pu constater la présence de 12 ou 13 personnes[3] de l'AFSSAPS pour un quorum de 12 personnes. C'est manifestement disproportionné, il serait sans doute souhaitable de restreindre à 2 ou 3 le nombre de personnes assistant aux réunions de la commission de la tranparence au titre du secrétariat administratif.

[3] On ne sait pas très bien parmi ces personnes, quelles sont celles qui sont présentes au titre du secrétariat de la commission et qui en conséquence ne prennent pas la parole et n'ont pas à fournir de déclarations d'intérêt et celles qui sont là en qualité d'évaluateur interne qui elles peuvent prendre la parole et devraient être soumises à DI (cf. point 3).

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3/ Clarifier le rôle des évaluateurs internes :

L'article R. 163-15 du CSS précise que le président de la commission peut faire appel à des rapporteurs extérieurs à la commission. Ces derniers sont soumis à diverses obligations : un rapporteur ne peut intervenir pour un médicament comme expert devant la commission d'AMM et comme rapporteur de l'entreprise devant la CT ; il doit déposer une déclaration d'intérêt et il ne peut pas prendre part aux délibérations ni aux votes (CT I-3 du règlement intérieur).

Le CSS ne parle pas des évaluateurs internes. Ces derniers apparaissent dans le règlement intérieur de la commission (§ 1-2). Le rôle de ces évaluateurs internes est important : ils effectuent une synthèse du dossier et des données disponibles sur le dossier, ils présentent le dossier à la commission en réalisant une analyse critique du dossier, les membres de la commission peuvent attirer leur attention sur un point précis à tout moment, ils instruisent l'intégralité du dossier (pas de rapporteur externe) dans le cas des procédures simplifiées, ils assistent aux délibérations[4] puisqu'ils sont chargés de rédiger l'avis.

Ce rôle fondamental excède manifestement le simple secrétariat qui suppose une non participation aux débats. Certes ces évaluateurs internes, comme tous les membres de l'Agence conformément aux dispositions de l'article L. 1323-9 du CSP, sont tenus au secret et à la discrétion professionnelle et ne peuvent avoir, par eux-mêmes ou par personne interposée, aucun intérêt de nature à compromettre leur indépendance, mais il n'en reste pas moins que l'absence de conflits d'intérêt n'est pas vérifiée pour chaque dossier. On constate donc une plus grande rigueur vis à vis des rapporteurs externes que des évaluateurs internes. Peut-être faudrait-il assurer une plus grande transparence sur ce point et en tout cas faire apparaître les évaluateurs internes en tant que tel sur le P.V.

A noter que ce point n'a jamais été soulevé dans un contentieux jusqu'à aujourd'hui. Mais devant le caractère de plus en plus procédurier des laboratoires, il est probable qu'un jour ils contestent la présence de l'évaluateur interne et surtout le fait qu'il n'est pas soumis aux mêmes obligations que le rapporteur externe alors même que son rôle est tout aussi important. Il semble donc prudent d'essayer de clarifier la pratique sur ce point.

4/ veiller à la publication des déclarations mentionnant les liens directs ou indirects des personnes participant aux travaux de la commission de la transparence (membres de la commission, personnes des services accompagnant les membres de droit, rapporteurs ou experts externes et évaluateurs internes) au bulletin officiel du ministère chargé de la sécurité sociale. Aujourd'hui, seules les déclarations d'intérêt des membres de la commission ont été publiées au BO. La publication des déclarations d'intérêt des rapporteurs va être faite très prochainement dans un BOMES hebdomadaire. La jurisprudence accepte que la publication se fasse postérieurement à la réunion de la commission de la transparence mais elle doit se faire en tout état de cause dans un délai raisonnable.

4/ veiller à établir un procès verbal en bonne et due forme à chaque séance : **article 14 du décret du 28 novembre 1983 qui précise que le PV indique le nom et la qualité des membres présents, les questions traitées au cours de la séance et le sens de chacune des délibérations. Tout membre de l'organisme consultatif peut demander qu'il soit fait mention de son désaccord. Le PV doit être transmis à l'autorité compétente pour prendre la décision. Lorsque la décision doit être motivée, la notification de la décision doit être accompagnée des mentions du PV se rapportant à la question sur laquelle il est statué par cette décision.** Ce document n'a pas à être transmis au laboratoire sauf si ce dernier en fait la demande. Les PV sont des documents administratifs communicables sur demande (art 7 de la loi du 12 avril 2000).

[4] Contrairement aux rapporteurs externes qui ne participent ni aux délibérations ni aux votes (§ 1.3.1 du règlement intérieur de la CT)

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La loi du 12 avril nous autorise à ne communiquer ces PV que dés lors que la décision des ministres est prise soit postérieurement à l'arrêté (en l'espèce donc la règle est la même que pour les avis de recevabilité qui n'ont pas été publiés sur internet sauf l'AFSSAPS – voir fiche 6).

Lorsque le PV n'existe pas, cela peut constituer un vice de procédure substantiel car alors on n'a pas d'indication sur le nom des membres présents. En pratique, on constate que l'AFSSAPS est pour toutes les commissions en mesure de fournir la liste des membres présents avec les votes. En revanche, aucune précision supplémentaire n'existe dans le PV par rapport à la motivation qui existe dans l'avis. Cela n'est pas en soi critiquable, surtout si on considère que les avis sont correctement motivés. Mais lorsque l'avis est motivé succinctement, le fait de ne rien trouver dans le PV affaiblit la position des ministres qui prennent la décision vis à vis de l'inscription car ils ne peuvent puiser dans les PV la motivation qui ne figurent pas toujours dans les avis (Voir fiche 5 sur la motivation). En outre, en cas de contentieux, le PV est un outil précieux car il facilite la rédaction du mémoire environ 6 mois après les faits et donc à un moment où les personnes présentes lors de la séance de la commission n'ont plus un souvenir très précis de ce qui s'est réellement passé.

[5] Seules les conclusions ont été diffusées sur le site de l'AFSSAPS mais pas les avis proprement dits.

[6] De plus en plus, les laboratoires demandent communication du PV car ils savent avoir droit à la communication de ce document. Toutefois, très souvent en pratique le PV se résume à la feuille de présence et au sens des votes plus les avis de la CT. Ainsi, l'aspect «questions traitées au cours de la séance » ne fait pas l'objet de précisions supplémentaire par rapport à l'avis lui-même.

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Fiche n° 5 : Motivation des avis de la Commission de la transparence

[redacted]

L'a motivation doit exister :

[redacted]

- les requérants estiment qu'une motivation stéréotypée ne répond pas à l'exigence de motivation imposée par les textes car elle ne permet pas au laboratoire d'avoir la certitude que la commission s'est réellement prononcée sur chacun des critères dans le cas particulier de la spécialité qui lui était soumise ;

- les requérants estiment que l'exigence de motivation ne peut être remplie que si dans l'avis on retrouve la position de la CT sur tous les critères visés à l'article R. 163-18. Cet article précise que l'avis de la CT doit comporter notamment l'appréciation du SMR dans chaque indication, une comparaison du médicament avec ceux de la classe pharmaco-thérapeutique de référence, l'ASMR, l'estimation du nombre de patients relevant des indications thérapeutiques pour lesquelles la commission estime fondée l'inscription..... La rédaction des avis de réévaluation de la CT ne répond pas aux exigences du R. 163-18[7]. Notre défense consiste donc à soutenir que l'article R. 163-18 ne s'applique pas aux avis de réévaluation. **Que concernant ces avis, seul l'article R. 163-3 s'applique**, faisant uniquement obligation à la commission d'apprécier le service médical rendu. De toute façon, certains critères du R. 163-18 sont inapplicables comme par exemple l'appréciation de l'ASMR et les populations cibles qui sont clairement hors du champ de la réévaluation du SMR. Notre défense semble solide mais il faut attendre la position du CE pour savoir vraiment si cet argument est valable ou pas. **Si le CE nous donne tort, cela signifie que tous les avis de la CT sur la réévaluation ne sont pas suffisamment motivés.**

2/ L'avis de la CT doit porter sur toutes les indications thérapeutiques. Ainsi, si certaines indications n'ont pas été réévaluées par la CT et que le laboratoire demande une nouvelle audition, sans doute serait-il opportun d'évaluer les indications manquantes.

3/ La motivation doit permettre au laboratoire de comprendre les éléments justifiant l'appréciation par la commission. La rédaction actuelle de certaines rubriques ne semble pas correspondre à cette exigence. Ainsi,

- La mention « sans objet pour l'évaluation du SMR » sous la rubrique « intérêt en santé publique » doit être proscrite. L'intérêt en santé publique est l'un des critères du SMR visé à l'article R. 163-3 et la commission doit l'évaluer. Dans les contentieux en cours, nous avons expliqué cette mention en précisant au CE qu'il convenait d'interpréter la mention « sans objet » comme l'indication que le médicament en cause n'avait pas d'effets en termes de santé publique distincts de ceux, appréciés à partir d'autres critères du SMR, qui caractérisent son SMR auprès

[7] Article R. 163-18 du CSS : l'avis mentionné au premier alinéa de l'article R. 163-4 (avis pour inscription, renouvellement et modification des conditions d'inscription)...comporte notamment 1° : l'appréciation du SMR sur chacune des indications thérapeutiques, 2° une comparaison du médicament, en termes de SMR, avec ceux de la classe pharmaco-thérapeutique de référence...3° lors du renouvellement, la réévaluation du SMR, 4° une appréciation sur les modalités d'utilisation du médicament et notamment durées de traitement et posologie, 5° estimation du nombre de patients relevant des indications pour lesquelles la commission estime fondée l'inscription, 6° pour la liste ville, leur classement au regard de la participation de l'assuré en fonction de l'importance de leur SMR, 7° l'appréciation du conditionnement approprié au regard des indications thérapeutiques.

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des patients effectivement traités. En tout état de cause, si de nouvelles auditions ont lieu mais que l'avis précédemment émis n'est pas modifié il faudra trouver une autre rédaction ;

Par suite, sous la rubrique « place dans la stratégie thérapeutique » est précisé « il existe des alternatives thérapeutiques médicamenteuses ou non médicamenteuses à cette spécialité » les requérants font valoir que l'absence de précision sur les alternatives existantes ne lui permet pas de savoir quelles sont ces alternatives et surtout ne lui permet pas de contester ces références.

La motivation utilisée pour les autres critères semble moins contestable.

4/ l'élaboration d'un procès verbal complet peut être utile ici car dans le PV peuvent figurer des explications plus longues que dans le corps même de l'avis, reprenant, le cas échéant, des échanges avec le laboratoire dans lesquels la commission lui a expliqué les raisons pour lesquelles elle prenait cette position. En l'absence de PV nous sommes (AFSSAPS et DSS) assez démunis pour expliquer dans le cadre d'un contentieux les éléments pris en compte par la commission et les raisons pour lesquelles elle les a écartés.

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Fiche n°6 : Fin de la procédure contradictoire devant la commission de la transparence et devenir des avis définitifs

1/ A l'issue de l'audition demandée par le laboratoire, ou de l'examen par la CT de ses observations écrites, délai dans lequel l'avis devient définitif

- Si la commission confirme sans aucune modification son avis précédent, nous considérons que **l'avis est définitif immédiatement**. En effet, dans ce cas, l'avis de la commission est une simple confirmation de l'avis définitif précédent. Le laboratoire a eu un mois pour faire valoir ses observations et si la commission n'a pas modifié son avis c'est qu'elle considère que les éléments fournis par le laboratoire ne sont pas de nature à modifier son appréciation précédente du SMR.

Dans les contentieux sur les vasodilatateurs, les requérants ont fait valoir que l'administration n'avait pas respecté la procédure contradictoire en ne donnant pas les 8 jours supplémentaires au laboratoire alors même que l'avis définitif de la CT n'avait pas été modifié. Nous avons défendu devant le juge la position logique qui est de considérer que lorsque le laboratoire a été entendu à plusieurs reprises et que l'avis de la CT n'a jamais été modifié, il faut stopper la procédure car sinon le laboratoire pourrait par des manœuvres dilatoires demander indéfiniment une audition devant la CT et ce, même en l'absence de tout élément nouveau dans le seul but de retarder la décision qu'il sait par ailleurs inévitable. Ce moyen a peu de chance de prospérer mais il reste que la rédaction des textes est ambiguë.

- Si la commission prend un nouvel avis : la procédure prévue au III de l'article R. 163-16 doit trouver à s'appliquer. Cet article précise que lorsque l'avis **porte sur l'inscription, la modification des conditions d'inscription ou le renouvellement de l'inscription d'un médicament** sur la liste du L. 162-17 du CSS ou du L. 5123-2 du CSP, l'avis est immédiatement communiqué à l'entreprise qui a 8 jours à compter de la réception de l'avis pour présenter des observations écrites ou demander à être entendue par la commission. Nous considérons que s'agissant d'avis de réévaluation, ils ne sont pas expressément visés par cet article et que par conséquent, leur régime est indépendant. Toutefois, force est de reconnaître que ces avis de réévaluation conduisent les ministres à modifier les conditions d'inscription. Dès lors, il nous semble que lorsque la commission, à la suite de l'audition de l'entreprise, est amenée à modifier ou à prendre un nouvel avis, et afin d'éviter toute contestation ultérieure, il est préférable d'envoyer le nouvel avis à l'entreprise en lui laissant 8 jours pour réagir.

2/ Les droits de l'entreprise pendant ces 8 jours : l'article R. 163-16 précise que l'entreprise a 8 jours pour demander à être entendue par la commission de la transparence ou pour présenter des observations écrites. L'intention des pouvoirs publics dans cet article était clairement de cantonner les observations de l'entreprise à des observations purement formelles ou alors à des erreurs manifestes mais ne devait pas être l'occasion de contester à nouveau l'appréciation de chaque critère par la commission sauf bien sûr en cas d'apparition d'un élément nouveau absolument fondamental qui modifierait complètement l'appréciation du SMR. Mais en pratique, la procédure contradictoire de fond se déroule préalablement à l'envoi de cet avis par la CT et ce délai n'a d'autre ambition que de demander à l'entreprise une dernière relecture. Cette logique semble d'ailleurs confirmée par les dispositions de l'article R. 163-13 qui laissent 1 mois à l'entreprise pour demander une audition ou présenter des observations écrites mais c'est clairement pour laisser le temps à l'entreprise de trouver des arguments pour contester l'appréciation précédente portée par la CT sur le SMR de la spécialité.

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En tout état de cause, si nous laissons 8 jours au laboratoire pour relire l'avis, il faut clairement lui signifier qu'il s'agit d'une relecture « formelle » ne pouvant donner lieu à des observations de fond ou à une nouvelle demande d'audition, en l'absence d'éléments nouveaux portant sur l'appréciation du SMR.

Cette mention, ainsi que la mention du délai de 8 jours, doivent sans doute être mentionnées en clair dans le courrier qui adresse l'AFSSAPS aux laboratoires pour leur transmettre l'avis de la CT.

3/ Lorsque l'avis est sollicité par les pouvoirs publics (6° de l'article R. 163-19), l'avis ne devrait pas être transmis à l'entreprise mais seulement aux pouvoirs publics. Dans cette hypothèse, ce n'est pas cet avis qui servira de base à un éventuel arrêté de déremboursement mais bien l'avis définitif antérieur qui a été soumis à l'entreprise.

4/ L'obligation de publier les avis de la commission de la transparence ne porte que sur les avis relatifs à l'inscription, la modification des conditions d'inscription ou le renouvellement de l'inscription. Il n'y a aucune obligation de publier les avis de réévaluation.

En outre, les avis de la CT étant des actes préparatoires nous aurions pu ne les publier qu'une fois la décision des ministres prise et publiée. Toutefois, dans un souci de plus grande transparence la décision de publier non pas l'avis in extenso mais seulement le niveau de SMR a été prise et donc figurent sur le site de l'AFSSAPS les résultats de la réévaluation.

5/ Une publication de l'avis de la commission préalablement à la décision des ministres ne change pas les règles juridiques de ce document qui reste un acte préparatoire insusceptible de recours pour excès de pouvoir. Cet avis ne pourra être contesté qu'à l'occasion de la contestation de la décision finale des ministres.

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Fiche n°7 : Publication de l'arrêté et notification des déremboursements

L'article R. 163-14 du CSS précise les décisions portant refus d'inscription sur les listes prévues à l'article L. 162-17 et L. 162-22 refus de renouvellement d'inscription, radiation de ces listes ou refus de modification du prix doivent dans la notification à l'entreprise exploitant le médicament être motivées et mentionner les voies et délais de recours qui leur sont applicables.

1/ L'arrêté qui portera à la connaissance des tiers et des caisses le déremboursement des médicaments à SMR insuffisant devra être doublé d'une procédure de notification individuelle à chaque laboratoire concerné.

2/ Pour les spécialités dont certaines indications seront exclues des indications ouvrant droit à prise en charge ou remboursement, l'arrêté sera plus complexe à rédiger dans la mesure où il devra mentionner les indications « déremboursées ».

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HAUTE AUTORITÉ DE SANTÉ

Direction de l'Evaluation Médicale, Economique et de Santé Publique

Service Evaluation des Médicaments

Le chef de service

Madame, Monsieur le Pharmacien Responsable
Laboratoires SERVIER
22, rue Garnier
92578 NEUILLY-SUR-SEINE CEDEX

Lettre recommandée A/R

Saint-Denis, le

19 OCT. 2009

Objet : MEDIATOR 150 mg, comprimé enrobé

N/Réf : AA/SD

Madame, Monsieur le Pharmacien Responsable,

En application de l'article R.163-21 du code de la sécurité sociale, la Commission de la transparence souhaite réexaminer le service médical rendu par la spécialité MEDIATOR dont votre laboratoire est l'exploitant.

La Commission de la transparence a eu connaissance de nouvelles données relatives notamment à la tolérance cardiovasculaire du benfluorex (risque de survenue d'hypertension artérielle pulmonaire et de valvulopathies).

A ce titre, vous voudrez bien nous faire parvenir, dans un délai de 3 mois à dater de la réception de ce courrier, l'ensemble des données cliniques permettant de réévaluer le service médical rendu par la spécialité mentionnée en objet en 50 exemplaires (10 exemplaires papier et 40 CDRom).

Je vous prie d'agréer, Madame, Monsieur le pharmacien responsable, l'expression de ma considération distinguée.

Docteur Anne D'ANDON

Copie CEPS

Annexe 4-42

REUNION GROUPE DEUG N°24 DU 22 OCTOBRE 2009

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoire SERVIER

Demande déposée le

Principe actif: **Benfluorex**

Caractère d'originalité **Analyse des données d'efficacité de l'étude REGULATE (en vue de la réévaluation des données de Bénéfice et de Risque du benfluorex)**

Classe ATC: **Système cardio-vasculaire/Hypolipémiants (Code ATC à mettre)**

Cellule Transversale :

☐ IAM	☐ GROSSESSE	☐ PV
N° groupe/date	N° groupe/date	N°groupe/date
☐ PRECLINIQUE	☐ PMF	☐ AUTRES
N° groupe/date	N° groupe/date	N°groupe/date

☒ AUCUNE

CONTEXTE/TYPE DE DEMANDE

MEDIATOR a été une nouvelle fois présenté en Commission Nationale de Pharmacovigilance (CNPV) ; en effet, un signal relatif aux anomalies des valves cardiaques soupçonné depuis plusieurs mois par les données de pharmacovigilance se trouve confirmé par :

1. les données d'une étude cas /témoins brestoise rétrospective menée par le CHU de Brest.

2. les résultats d'une étude clinique (Etude REGULATE) dans laquelle en parallèle de l'analyse des données d'efficacité du benfluorex en association à un sulphonylurée (SU), une exploration de la tolérance cardiaque/impact du traitement sur les valves cardiaques a été explorée.

Les données de l'étude cas /témoins, ainsi que les résultats préliminaires de l'étude REGULATE ont été présentés en CNPV le 09 09 2009.

A l'issu de cette présentation, les membres de la CNPV ont considéré (25 voix pour et 1 abstention), que les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex, ceci malgré certaines limites méthodologiques soulevées par l'étude Cas/témoins. De même, ils considèrent (25 voix pour et 1 abstention) que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

La CNPV souhaite que l'ensemble des données soient transmises à la Commission d'AMM afin qu'elle se qu'elle puisse se prononcer – au vu de l'ensemble des données de bénéfice et

de risque dans les conditions d'utilisation actuelles du produit - sur la balance bénéfice-risque du produit.

La programmation en COM d'AMM est prévue le 23 10 2009. A cet effet, il a été demandé à la firme de déposer l'ensemble des données cliniques en vue de cette Commission, notamment les **résultats de l'étude REGULATE.**

Le Groupe DEUG est de ce fait sollicité avant cette Commission afin d'évaluer :i) les données d'efficacité de cette étude REGULATE et ii) plus généralement la place de cette molécule dans la prise en charge thérapeutique du diabète à partir des données existantes (bénéfice).

Historique/Rappel des données de Pharmacovigilance (mise à jour lors de la CNPV du 09 09 2009)

Données de la pharmacovigilance :

Une mise à jour des données de pharmacovigilance a été effectuée par le CRPV de Besançon. 11 nouveaux cas de valvulopathie associés au benfluorex sont rapportés dont 3 issus de la notification spontanée et 8 de des notifications sollicitées et provenant d'Amiens. L'analyse de ces 11 nouveaux cas montre une prédominance féminine, une durée moyenne de traitement de 3 ans et un âge de survenue le plus fréquemment identifié de 55 ans. Dans 9/11 cas une association à une hypertension artérielle pulmonaire est rapportée, une atteinte de type insuffisance mitrale et aortique dans 6 cas et une atteinte mitrale+aortique+tricuspide dans 2 cas. Malgré des échocardiographies documentées, les données anatomopathologiques restent peu informatives.

Certains membres ont souligné qu'en cas de notification sollicitée dans d'autres bassins de population, de nombreux autres cas de valvulopathie associés au benfluorex pourraient être mis en évidence.

Données de l'étude Brestoise :

L'étude cas-témoin rétrospective menée par le CHU de Brest, a pour objectif la recherche d'une association entre l'exposition au benfluorex et la survenue de cas d'insuffisance mitrale (IM) inexpliquée. La population source est constituée de tous les patients hospitalisés entre 2003 et 2009 dans le département de cardiologie ou le service de chirurgie cardiaque au CHU de Brest, et ayant un diagnostic d'IM. Les patients ayant une IM inexpliquée constituent les cas (n=27) et les patients ayant une IM expliquée constituent les témoins (n=54). Deux témoins ont été appariés à chaque cas sur les critères d'âge et de genre. L'appariement ne concernait le diagnostic de diabète ou l'Index de Masse Corporelle (IMC). L'exposition au benfluorex est recherchée auprès du patient, de sa famille et de ses médecins, par téléphone, sur la base d'un questionnaire semi-structuré et à l'aveugle du statut cas ou témoin.

Sur les 27 cas, 19 avaient été exposés au benfluorex contre 3 témoins sur 54 ($p<0.001$ soit un odds-ratio = 40,4 (9,7 – 168,3, IC à 95%)). L'ajustement à différentes variables telles que le poids, le diabète ou l'exposition à la dexfenfluramine, ne modifie pas la significativité du résultat.

CONTENU DU DOSSIER

Le dossier soumis ne comporte que quelques éléments de l'étude REGULATE.

Cette étude s'est achevée en 15 janvier 2009. Des analyses complémentaires sont actuellement en cours. Seul **un projet de résumé du rapport final de cette étude est disponible**. A noter, il état prévu initialement que le rapport de cette étude soit soumis début/courant du 1er semestre 2010.

Seules les données d'efficacité de cette étude sont analysées/expertisées par le Groupe DEUG ; les données de sécurité d'emploi dont les données valvulaires sont examinées en parallèle par le Département de Pharmacovigilance de l'Afssaps.

Les conclusions du Groupe DEUG ainsi que celles sur la sécurité d'emploi de cette étude seront présentées le 23 10 2009 en Commission d'AMM.

Analyse des données d'efficacité de l'Etude REGULATE

Titre de l'étude :

A one-year multicentre, international, randomised, doubleblind study with comparison of benfluorex (150 mg bid or 150 mg tid) *versus* pioglitazone (30 mg od or 45 mg od) in combination with sulfonylurea administered orally for the treatment of type 2 diabetes.

Méthodologie :

Il s'agit d'une multicentrique, randomisées, en double aveugle, contrôlée *versus* pioglitazone, d'une durée de 52 semaines, comparant chez 847 patients diabétiques de type 2, insuffisamment contrôlés par sulfamides hypoglycémiants (SU) l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR à la dose maximale recommandée (450 mg /jour, 1 comprimé pendant le repas), à un traitement par pioglitazone à la dose maximale recommandée (45 mg/jour, 1 comprimé au petit déjeuner)

Objectifs :

Le but de cette nouvelle étude était de comparer l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR versus un traitement par pioglitazone, en association à un SU, sur le contrôle glycémique et le profil lipidique.

L'objectif principal est de démontrer la non-infériorité de la combinaison SU + Benfluorex comparé à la combinaison SU + Pioglitazone sur l'évolution de l'HbA1c.

L'objectif secondaire est de démontrer la supériorité du benfluorex combiné aux SU comparativement à la Pioglitazone combiné aux SU sur le taux de cholestérol.

Les autres objectifs secondaires sont d'évaluer et de comparer ces combinaisons après 1 an de traitement sur : glycémie à jeun, l'insulinémie à jeun, le risque cardiovasculaire, la sécurité d'emploi et le coût de ces deux traitements.

Critères d'évaluation :

Critère principal : HbA1c mesuré à chaque visite (inclusion, 4, 8, 16, 28, 40 et 52 semaines)

Critères secondaires :

Paramètres lipidiques : LDL-cholestérol, cholestérol total, HDL-cholestérol, triglycérides à chaque visite.

Autres paramètres : glycémie à jeun (FPG), insulinémie à jeun (HOMA-IR), C-réactive protéine, mesure du tour de taille, poids.

Paramètres de sécurité d'emploi : événements indésirables, hypoglycémies, paramètres biologiques, examen cardiaque (ECG, échographie cardiaque à l'inclusion et à 12 mois)

Analyse statistique :

La borne de non-infériorité entre les deux traitements a été fixée à 0.4% d'HbA1c.

Résultats :

1. Caractéristiques de la population

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Tableau 7 REGULATE Caractéristiques de la population randomisée

	benfluorex (n = 423)	pioglitazone (n = 423)
Âge (années)	59.6 ± 10.3	58.6 ± 10.6
>=65 ans	30.5%	27.7%
Hommes	53.2%	56.5%
Caucasien/Asiatiques	75.4%/19.6%	77.3%/17.5%
Durée du diabète (années)	7.4 ± 6.0	6.7 ± 5.9
Indice de Masse Corporelle (kg/m²)	29.4 ± 4.0	29.7 ± 4.1
Présence d'un syndrome métabolique (%)	79.7	81.3
HTA (%)	59.8	59.8
Présence de complications		
Macrovasculaires(%)	11.8	8.5
Clearance créatinine<=60mL /min(%)	8.5	5.7
Neuropathie (%)	8	5.7
Rétinopathie (%)	2.8	1.7
HbA1c (%)	8.3 ± 0.8	8.3 ± 0.8
>=8%	57	56
Glycémie à jeun (mmol/L)	9.89±2.71	9.84 ± 2.52

2. Critère principal

A 52 semaines, la réduction de l'HbA1c est de -0.54% sous benfluorex versus -0.88% sous pioglitazone.

Change in HbA1c (%) from baseline to last post-baseline value in the FAS (N = 830)

HbA1c (%)		**Benfluorex (N= 413)**	**Pioglitazone (N = 417)**
Baseline	Mean ± SD	8.31 ± 0.82	8.33 ± 0.83
END	ean ± SD	7.77 ± 1.31	7.45 ± 1.30
Change (END-baseline)	Mean ± SD	-0.54 ± 1.12	-0.88 ± 1.24
Statistical analysis			
	E (SE) (1)	0.33 (0.08)	
	95% CI (2)	[0.17; 0.49]	
	p-value (3)	0.19	

END = last value; (1): Estimate (Standard Error) of the difference (benfluorex minus pioglitazone)between adjusted group means (2): 95% Confidence Interval of the estimate (3): For a non-inferiority one-sided test (alpha = 2.5%) obtained from an analysis of covariance with baseline and country (fixed effects) as covariates and a 0.4% margin of clinical relevance

Au total, **la non-infériorité de benfluorex par rapport à la pioglitazone n'a pas été démontrée** (limite supérieure de l'intervalle de confiance à 0.49 pour une limite de non infériorité fixée à 0.40 (E (SE) = 0,33 (0,08) %, 95 % CI = [0,17; 0,49], p = 0,19).

3. Critères secondaires

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Tableau 8 -REGULATE Evolution des principaux paramètres biologiques dans la population FAS

	Benfluorex			Pioglitazone			différence entre les groupes
	N	valeur initiale moyenne (SD)	différence pré-post (SD)	n	valeur initiale moyenne (SD)	différence pré-post (SD)	Δ (ES) IC 95%
Glycémie à jeun mmol/L	392	*9.9 (± 2.71)*	-1.20 (0.15)	396	*9.9 (± 2.51)*	-1.73 (0.23)	**0.56**** (0.18) [0.21;0.90]
HOMA- IR Index	332	*6.36 (± 5.30)*	-1.23 (0.38)	315	*6.83 (±7.34°*	-2.52 (0.35)	1.04 (0.41) [0.23;1.85]
Total Cholestérol mmol/L	396	*5.01 (± 0.99)*	-0.16 (0.04)	396	*5.02 (± 0.92)*	0.08 (0.05)	**-0.25**** (0.057) [-0.357;-0.134]
LDL cholestérol mmol/L	396	*3.11 0.83)*	-0.24 (0.03)	396	*3.15 (0.81)*	-0.12 (0.04)	**-0.13**** (0.05) **[-0.22;-0.04]**
Triglycérides mmol/L	397	*1.92 (± 0.97)*	-0.14 (0.05)	397	*1.96 (± 0.90)*	-0.21 (0.05)	0.058 (0.06) [-0.07 ;0.18]

****p < 0.001 **p< 0.01 *p< 0.05 °test non paramétrique*

On observe :

- une diminution du LDL-cholestérol moyen (-0,24) dans le groupe benfluorex plus importante que celle observée dans le groupe pioglitazone (-0.12).

- une diminution du cholestérol total moyen (-0.16) dans le groupe benfluorex comparativement à une augmentation dans le groupe pioglitazone (+0.08)

- une stabilité du HDL-cholestérol (0.01) dans le groupe benfluorex et une légère augmentation sous pioglitazone (+0.06)

- une diminution des concentrations de triglycérides comparable dans les 2 groupes.

Enfin, il y a une diminution du poids sous benfluorex (-1.6 kg) et une augmentation sous pioglitazone (3.3 kg).

Sécurité

La fréquence des effets indésirables est comparable entre les deux groupes (63,7% dans le groupe benfluorex versus 62,9% dans le groupe pioglitazone). Les effets indésirables les plus fréquents sont les infections et infestations (24,9% versus 28,6%), les troubles gastro-digestifs (14,7% versus 11,8%), et les troubles musculosqueletiques (13,1% versus 15,6%).

Les effets indésirables émergents dans le groupe benfluorex sont les hypoglycémies (9% versus 13,2% dans le groupe pioglitazone) et les diarrhées (4.3% versus 1,9%).

Au niveau cardiaque, 2 patients du groupe benfluorex versus 3 dans le groupe pioglitazone ont fait un infarctus du myocarde, 0 versus 1 pour les angines de poitrine, 1 versus 0 pour l'insuffisance cardiaque congestive, 0 versus 1 pour l'ischémie, 0 versus 1 pour le syndrome coronarien aigu et 1 versus 0 pour la cardiomyopathie congestive.

Enfin, il y a eu deux décès dans le groupe benfluorex contre 4 dans le groupe pioglitazone, ces décès n'étant pas reliés aux traitements.

CONCLUSIONS PRELIMINAIRES DE LA FIRME :

En conclusion, chez des patients diabétiques de type 2 insuffisamment contrôlés par SU, l'ajout d'un traitement par benfluorex pendant 12 mois permet/entraîne une diminution statistiquement significative de l'HbA1c.

L'effet antidiabétique du benfluorex est confirmé dans cette étude (diminution de -0,54% de l'HbA1c), bien que la non infériorité du benfluorex versus la pioglitazone ne soit pas démontrée.

La supériorité du benflurorex versus la pioglitazone sur la diminution du LDL-cholestérol est démontrée.

De plus, le benfluorex diminue significativement le cholestérol total contrairement à la pioglitazone.

Les deux traitements diminuent significativement les taux de triglycérides, la glycémie à jeun et améliore l'insulinorésistance.

Après un an de traitement, le poids ainsi que le tour de taille ont augmenté sous pioglitazone mais pas sous benfluorex.

Le profile de sécurité d'emploi est en ligne avec ce qui figure déjà dans le RCP

En ce qui concerne le profile de sécurité cardiaque (échographies cardiaques), aucune modification de la fraction d'éjection du ventricule gauche (FEGP) n'a été détectée dans les deux groupes de traitement.

Des régurgitations des valves cardiaques ont été observées plus fréquemment sous benfluorex que sous pioglitazone, mais sans retentissement clinique délétère (significatif).

La différence morphologique en termes d'anomalies des valves cardiaques dont les régurgitations (au dessus d'un grade 1) ne sont pas significatives.

Les anomalies émergentes (nouvelles) des valves cardiaques dans cette étude n'étaient pas associées à des signes ou symptômes cliniques.

Des analyses complémentaires visant à expliciter les anomalies valvulaires observées sont en cours.

Note d'évaluation :

Le Groupe DEUG est sollicité avant la Commission d'AMM afin d'évaluer :i) les données d'efficacité de cette étude REGULATE et ii) plus généralement la place de cette molécule dans la prise en charge thérapeutique du diabète à partir des données existantes (bénéfice).

Les points suivants ont été discutés au cours du groupe DEUG:

Au niveau efficacité :

- La non-infériorité du benfluorex versus la pioglitazone n'est pas démontrée sur le critère principal de jugement, l'HbA1c. On observe néanmoins une diminution de -0.54% sous benfluorex et de -0.88% sous pioglitazone. Les valeurs de la glycémie à jeun évoluent en cohérence avec celles de l'HbA1c (baisse de -1.2 ±2.9 mmol/L sous benfluorex et de – 1.7 ±2.9 mmol/L sous pioglitazone. Cette efficacité, même modeste, est à souligner et permet de confirmer les résultats de l'étude Moulin dans laquelle une diminution de -0.8% d'HbA1c était observée chez les patients sous benfluorex en add-on des sulphonylurées.

- une diminution de poids est observée dans le groupe benfluorex (- 1.6 kg) alors qu'une augmentation de poids est observée dans le groupe pioglitazone (+ 3.3 kg).

- Au niveau lipidique : un effet peu important est observé sur le cholestérol total (-0.16 mmol/L), sur le LDL cholestérol (-0.24 mmol/L) et encore plus faible sur les triglycérides (-0.14 mmol/L). Cet effet mimine du benfluorex sur les triglycérides confirme le bien-fondé du retrait de l'indication « adjuvant du régime adapté dans les hypertriglycéridémies » en 2007, d'autant que d'autres hypolipidémiants très supérieurs existent actuellement sur le marché.

Au niveau de la sécurité d'emploi :

La fréquence des effets indésirables est comparable entre les deux groupes : 63.7% sous benfluorex versus 62.9% sous pioglitazone. Il s'agit essentiellement de :

- Troubles gastro-intestinaux : 14.7% versus 11.8% dont les diarrhées (4.3% versus 1.9%)

- Troubles musculo-squelettiques : 11.4% versus 15.6%

- Hypoglycémies : 9% versus 13.2%

Au niveau des valvulopathies, 614 patients, 309 dans le groupe benfluorex et 305 dans le groupe pioglitazone ont eu une échocardiographie à l'inclusion et à 52 semaines, après une exposition aux traitements d'une durée moyenne de 328 jours.

Cette étude a mis en évidence dans le groupe traité par benfluorex versus le groupe pioglitazone :

- l'émergence d'anomalies valvulaires fonctionnelles statistiquement significatives, 26,5% versus 10,9%, (p<0,0001),

- des anomalies valvulaires morphologiques non statistiquement significatives (2,6% versus 1,3% respectivement, p=0,264).

Il est à noter que i) la durée d'exposition moyenne au benfluorex est limitée à 328 jours, ii) les anomalies émergentes fonctionnelles sont estimées "triviales" (selon les critères cardiologiques), sans traduction clinique et iii) la lecture des échocardiographies s'est faite par couple mais avec connaissance des dates des échographies.

Conclusion du groupe DEUG :

Le benfluorex a une efficacité modérée sur les paramètres glucidiques (baisse 0.5-0.8% sur l'HbA1c). Il présente l'avantage de ne pas entraîner de prise de poids voire d'entraîner une légère baisse, ce qui peut être intéressant dans le cadre de patients obèses. D'autre part, peu d'hypoglycémies sont constatées sous benfluorex, ce qui est pourrait avoir un éventuel intérêt dans le cadre d'une prescription sur le sujet âgé, bien qu'aucune étude spécifique n'ait été menée. Il semble avoir une efficacité similaire aux gliptines et à l'acarbose bien qu'aucune étude comparative de non-infériorité n'ait été réalisée.

Il n'a pour l'instant aucune place dans la stratégie de prise en charge du diabète, dans la mesure où le benfluorex ne fait pas partie des recommandations françaises et internationales de la prise en charge du diabète de type 2 car il est considéré uniquement comme un adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Le benfluorex est essentiellement prescrit par des médecins généralistes, les diabétologues ne le prescrivant très peu voire pas du tout. Il est bien souvent prescrit hors AMM, chez des patients obèses non diabétiques mais également chez des patients présentant une dyslipidémie.
Dans l'état actuel du dossier, les données préliminaires de l'étude REGULATE ne permettent pas de modifier le RCP comme demandé par la firme car :
- la non-infériorité de benfluorex n'est pas établie versus pioglitazone. Des alternatives thérapeutiques sont disponibles en add-on des SU et ont montré un profil de sécurité très supérieur au benfluorex.
- les données de l'étude REGULATE sont préliminaires et nécessitent une expertise approfondie. Une modification de l'indication doit d'autre part tenir compte des résultats de sécurité, très défavorables au regard des dysfonctionnements valvulaires apparues au cours de l'étude.
- Le groupe DEUG s'interroge sur la proposition de la firme de suivi échographique des patients avant et pendant un traitement par benfluorex, ainsi que sur la pertinence et la faisabilité d'une telle démarche.

AVIS DU GROUPE DEUG N°24 DU 22 OCTOBRE 2009:

Le Groupe DEUG a été sollicité avant la Commission d'AMM du 23 octobre afin d'évaluer :

i) les données d'efficacité de l'étude REGULATE et

ii) plus généralement la place de cette molécule dans la prise en charge thérapeutique du diabète à partir des données existantes (bénéfice).

L'analyse des données préliminaires d'efficacité de l'étude REGULATE

PERMET :

- de confirmer l'efficacité modérée du benfluorex sur l'HbA1c en association aux sulphonylurées : de – 0.5% (dans l'étude REGULATE) à – 0.8% (Etude MOULIN)

- de confirmer l'effet peu important du benfluorex sur le métabolisme lipidique.

NE PERMET PAS :

- de recommander le benfluorex en association aux SU ; dans cette étude, la non–infériorité versus pioglitazone n'est pas établie (limite supérieure de l'intervalle de confiance à 0.49 pour une limite de non infériorité fixée à 0.40 (E (SE) = 0,33 (0,08) %, 95 % CI = [0,17; 0,49], p = 0,19).

De plus, des alternatives thérapeutiques en association sont par ailleurs disponibles pour lesquelles le rapport bénéfice risque est favorable.

- de modifier l'indication du benfluorex comme proposé par la firme. En effet, seule une expertise partielle des résultats a été effectuée en l'absence de rapport final. D'autre part, une modification de l'indication doit tenir compte des données de sécurité d'emploi, notamment des cas de valvulopathies observées dans l'étude.

- tel que proposé par la firme, de positionner le benfluorex dans la stratégie thérapeutique de prise en charge du diabète de type 2 ; en effet, le benfluorex est actuellement uniquement considéré comme un adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Les conclusions du Groupe DEUG sur l'évaluation des données de l'étude REGULATE ainsi que l'ensemble des données d'efficacité dans les indications actuelles de l'AMM seront présentées à la Commission d'AMM du 23 octobre pour discussion et décision finale sur le rapport Bénéfice/Risque de cette molécule. En parallèle, et en vue de cette discussion seront

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présentées par le Département de Pharmacovigilance et les experts mandatés les conclusions sur les données relatives à la sécurité d'emploi du benfluorex

COMMISSION D'AMM N° 469 DU 23 OCTOBRE 2009

PROCEDURE NATIONALE

- MEDIATOR 150, comprimé

Dossier n° VNL 10008

Laboratoire SERVIER

Demande déposée le

Principe actif:	Benfluorex
Caractère d'originalité	Réévaluation des données de Bénéfice et de Risque
Classe ATC:	Système cardio-vasculaire/Hypolipémiants (Code ATC à mettre)

CONTEXTE DE LA PRESENTATION en COM D'AMM

MEDIATOR a été une nouvelle fois présenté en Commission Nationale de Pharmacovigilance (CNPV) ; en effet, un signal relatif aux anomalies des valves cardiaques soupçonné depuis plusieurs mois par les données de pharmacovigilance se trouve confirmé par :
1. les données d'une étude cas /témoins brestoise rétrospective menée par le CHU de Brest.
2. les résultats d'une étude clinique (Etude REGULATE) dans laquelle en parallèle de l'analyse des données d'efficacité du benfluorex en association à un sulphonylurée (SU), une exploration de la tolérance cardiaque/impact du traitement sur les valves cardiaques a été explorée.
Les données de l'étude cas /témoins, ainsi que les résultats préliminaires de l'étude REGULATE ont été présentés en CNPV le 09 09 2009.

A l'issue de cette présentation, les membres de la CNPV ont considéré (25 voix pour et 1 abstention), que les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex, ceci malgré certaines limites méthodologiques soulevées par l'étude Cas/témoins. De même, ils considèrent (25 voix pour et 1 abstention) que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

La CNPV souhaite que l'ensemble des données soient transmises à la Commission d'AMM afin qu'elle se qu'elle puisse se prononcer – au vu de l'ensemble des données de bénéfice et de risque dans les conditions d'utilisation actuelles du produit - sur la balance bénéfice- risque du produit.
Il a été demandé à la firme de déposer l'ensemble des données cliniques en vue de cette Commission, notamment les résultats de l'étude REGULATE.

Annexe 4-43

RESUME DES DONNEES DE BENEFICE

Historique de l'évaluation des données d'efficacité : de 2000 à 2009-10-13

- **Date d'AMM** : 16-07-1976 avec une indication en tant qu'hypolipidémiant

- **1995. Inscription sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes.** Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables de ces produits et étant donné les restrictions de leur délivrance, le CTPV a craint une dérive de l'utilisation du benfluorex comme anorexigène.

- **1987**: validation de la 1ère tranche dans l'indication « hypertriglycéridémies »

- **1990** : dépôt du dossier de la 8ème tranche de validation dans l'indication en « diabétologie » ; nombreux échanges entre l'Afssaps et la firme entre 1990 et 1995 sur la nature des données à soumettre afin de valider cette indication (type d'étude, population cible, etc.), aboutissant finalement en 1998 au dépôt de l'étude Del Prato (étude de l'efficacité du benfluorex versus placebo et metformine sur les paramètres glucidiques (voir ci-dessous données cliniques). En attente de cette étude, l'indication telle que libellée lors de l'octroi de l'AMM a été maintenue.

- **Septembre 2000:** demande d'extension d'indication au «*Diabète de type II insulino-dépendant, en association au régime adapté, lorsque ce régime n'est pas suffisamment suffisant pour rétablir à lui seul l'équilibre glycémique* ». Une seule étude de phase III **(Etude Del Prato)**, randomisée, en double insu, benfluorex versus placebo et metformine a été soumise à l'appui de cette demande (A noter, cette étude a été réalisée à la demande de l'Afssaps; protocole revu en concertation avec l'Afssaps). Un avis défavorable a été émis par le Groupe de Travail PTC2 ainsi que par la COM d'AMM. Après recours de la firme de cette décision, cet avis a été maintenu par la COM d'AMM. En effet, compte tenu des défauts de la qualité méthodologique de cet essai (ayant l'objet par ailleurs d'une inspection), aucune conclusion n'a pu être formulée sur la taille de l'effet: i) du benfluorex versus placebo; ii) du benfluorex versus metformine (non-infériorité non démontrée : déséquilibre des taux d'HbA1c entre les groupes à l'inclusion, 68% seulement inclus dans l'analyse per protocole, 25% de patients inclus à tort). A noter également, aucune efficacité sur les paramètres lipidiques n'a été mise en évidence dans cette étude. En conclusion, la COM d'AMM (20-09-2002) a demandé qu'une étude évaluant l'efficacité du benfluorex en monothérapie et en association avec d'autres antidiabétiques oraux soit effectuée; l'association devant être également étudiée chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisants rénaux, sujets âgés)

- 2007=> Réévaluation du rapport bénéfice Risque / Modification du code ATC

Conclusions de la réévaluation du bénéfice /risque demandé par la CNPV (AVIS DE LA COM d'AMM 419 DU 5 AVRIL 2007) (Extrait) faisant suite au Groupe de Travail DEUG N°6 du 21 10 2006 :

Après présentation et discussion des conclusions du Groupe de Travail DEUG sur les données d'efficacité et des conclusions de la CNPV sur les données de sécurité d'emploi, les conclusions suivantes ont été émises :

1. La COM d'AMM suit l'avis DEFAVORABLE émis par le Groupe DEUG au maintien de l'indication : « *Adjuvant au régime adapté dans les hypertriglycéridémies. L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée*», les données soumises ne montrant en effet qu'une efficacité très modeste et inconstante dans les études soumises sur les triglycérides et une absence d'efficacité sur les autres paramètres lipidiques tels que le LDL-cholestérol.

2. La COM d'AMM suit également l'avis du Groupe DEUG pour le maintien de l'indication : « *Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* » dans son libellé actuel. En l'attente de données plus complètes sur l'efficacité du benfluorex en association aux autres antidiabétiques oraux, la COM d'AMM n'a pas souhaité modifier le libellé actuel. A ce jour, seule l'étude MOULIN a permis de montrer une efficacité du benfluorex sur l'HbA1c en association à un sulfamide

L'étude Moulin (publiée dans Diabetes Care en 2006) est une étude multicentrique, internationale, randomisée en double aveugle, d'une durée de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par SU et intolérants ou ayant une contre indication à la metformine. Le critère principal était l'HbA1c ; les critères secondaires : insulinémie, glycémie à jeun, paramètres lipidiques, index d'insulino résistance HOMA. Trois sous-groupes ont été analysés : HbA1c > 8%, âge > 65 ans et clairance de la créatininémie < 80ml/mn. Etude de supériorité avec un différence de 06% entre les groupes sur l'HbA1c.

Résultats :

Après 18 semaines de traitement, les résultats d'efficacité sur les paramètres glucidiques de cette étude montrent que :

- l'HbA1c est diminuée de -0.82% dans le groupe benfluorex (versus baseline) et de 1% versus le groupe placebo. 34.2% et 19% arrivent à une HbA1c ≤ 7% et > 6.5% contre 11% et 5% respectivement sous placebo. Baisse de l'HbA1c significative dès la 4ème semaine ; d'après la firme, l'effet est du même ordre entre les trois sous groupes pré définis ;
- l'insulinorésistance s'améliore significativement sous benfluorex ; la glycémie à jeun baisse significativement dès la 4ème semaine sous benfluorex.

La perte de poids était de 1.3 kg sous benfluorex et de 0.7kg sous placebo

3. La COM d'AMM souhaite que les modifications d'ajout d'effets indésirables suivants tels que décidés par la CNPV soient mentionnées au sein de la rubrique 4.8. du RCP : « *troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations)* » et de la rubrique correspondante de la Notice.

4. Une inspection de l'étude MOULIN, seule étude à ce jour ayant montré une efficacité sur les paramètres glucidiques a été proposée et acceptée par les membres de la COM d'AMM. Une saisine sera adressée en ce sens à la DIE (Direction de l'Inspection des Etablissements).

5. Enfin, les membres de la COM d'AMM souhaitent qu'une communication soit faite sur l'usage hors AMM de cette spécialité ainsi que sur la seule indication retenue après réévaluation des bénéfice/risque de cette spécialité.

Au total, le libellé de l'indication retenu est le suivant : «Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ».

Code ATC

1) Avis Afssaps (Groupe DEUG du 13 09 2009

AVIS FAVORABLE à la modification du Code ATC ; le Code ATC retenu est le suivant : **DIVERS MEDICAMENTS DES VOIES DIGESTIVES ET DU METABOLISME/Code ATC A16X**

En effet, compte-tenu de la modification de l'indication avec suppression de l'indication : « *Adjuvant au régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours nécessaire* », le code ATC actuel : HYPOCHOLESTEROLEMIANT ET HYPOTRIGLYCERIDEMIANT/Code ATC : C10AX04 n'est donc plus d'actualité.

Dans l'attente du reclassement du benfluorex selon la classification ATC par l'Organisation Mondiale de la Santé (OMS), sur proposition des laboratoires SERVIER auprès de l'OMS, le code ATC proposé par la firme soit : AUTRES MEDICAMENTS DU DIABETE/Code ATC : A10X n'est pas acceptable. En effet, selon les experts ce code ne peut être accepté compte tenu du fait que cette spécialité n'a pas à ce jour d'indication reconnue dans le diabète de type 2.

2) Code ATC octroyé par l'OMS => Code ATC : A10X : AUTRES MEDICAMENTS DU DIABETE

Année 2009 => Nouvelles données d'efficacité : Etude REGULATE

Analyse des données d'efficacité de l'Etude REGULATE

Titre de l'étude :

A one-year multicentre, international, randomised, doubleblind study with comparison of benfluorex (150 mg bid or 150 mg tid) *versus* pioglitazone (30 mg od or 45 mg od) in combination with sulfonylurea administered orally for the treatment of type 2 diabetes.

Méthodologie :

Il s'agit d'une multicentrique, randomisées, en double aveugle, contrôlée *versus* pioglitazone, d'une durée de 52 semaines, comparant chez 847 patients diabétiques de type 2, insuffisamment contrôlés par sulfamides hypoglycémiants (SU) l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR à la dose maximale recommandée (450 mg /jour, 1 comprimé pendant le repas), à un traitement par pioglitazone à la dose maximale recommandée (45 mg/jour, 1 comprimé au petit déjeuner)

Objectifs :

Le but de cette nouvelle étude était de comparer l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR versus un traitement par pioglitazone, en association à un SU, sur le contrôle glycémique et le profil lipidique.

L'objectif principal est de démontrer la non-infériorité de la combinaison SU + Benfluorex comparé à la combinaison SU + Pioglitazone sur l'évolution de l'HbA1c.

L'objectif secondaire est de démontrer la supériorité du benfluorex combiné aux SU comparativement à la Pioglitazone combiné aux SU sur le taux de cholestérol.

Les autres objectifs secondaires sont d'évaluer et de comparer ces combinaisons après 1 an de traitement sur : glycémie à jeun, l'insulinémie à jeun, le risque cardiovasculaire, la sécurité d'emploi et le coût de ces deux traitements.

Critères d'évaluation :

Critère principal : HbA1c mesuré à chaque visite (inclusion, 4, 8, 16, 28, 40 et 52 semaines)

Critères secondaires :

Paramètres lipidiques : LDL-cholestérol, cholestérol total, HDL-cholestérol, triglycérides à chaque visite.

Autres paramètres : glycémie à jeun (FPG), insulinémie à jeun (HOMA-IR), C-réactive protéine, mesure du tour de taille, poids.

Paramètres de sécurité d'emploi : événements indésirables, hypoglycémies, paramètres biologiques, examen cardiaque (ECG, échographie cardiaque à l'inclusion et à 12 mois)

Analyse statistique :

La borne de non-infériorité entre les deux traitements a été fixée à 0.4% d'HbA1c.

Résultats :

1. Caractéristiques de la population

Tableau 7 REGULATE Caractéristiques de la population randomisée

	benfluorex (n = 423)	pioglitazone (n = 423)
Âge (années)	59.6 ± 10.3	58.6 ± 10.6
>65 ans	30.5%	27.7%
Hommes	53.2%	56.5%
Caucasien/Asiatiques	75.4%/19.6%	77.3%/17.5%
Durée du diabète (années)	7.4 ± 6.0	6.7 ± 5.9
Indice de Masse Corporelle (kg/m²)	29.4 ± 4.0	29.7 ± 4.1
Présence d'un syndrome metabolique (%)	79.7	81.3
HTA (%)	59.8	59.8
Présence de complications		
Macrovasculaires(%)	11.8	8.5
Clearance créatinine <60mL/min(%)	8.5	5.7
Neuropathie (%)	8	5.7
Rétinopathie (%)	2.8	1.7
HbA1c (%)	8.3 ± 0.8	8.3 ± 0.8
>8%	57	56
Glycémie à jeun (mmol/L)	9.89±2.71	9.84 ± 2.52

2. Critère principal

A 52 semaines, la réduction de l'HbA1c est de -0.54% sous benfluorex versus -0.88% sous pioglitazone.

Change in HbA1c (%) from baseline to last post-baseline value in the FAS (N = 830)

HbA1c (%)		**Benfluorex (N= 413)**	**Pioglitazone (N = 417)**
Baseline	Mean ± SD	8.31 ± 0.82	8.33 ± 0.83
END	ean ± SD	7.77 ± 1.31	7.45 ± 1.30
Change (END-baseline)	Mean ± SD	-0.54 ± 1.12	-0.88 ± 1.24
Statistical analysis			
	E (SE) (1)	0.33 (0.08)	
	95% CI (2)	[0.17; 0.49]	
	p-value (3)	0.19	

END = last value; (1): Estimate (Standard Error) of the difference (benfluorex minus pioglitazone)between adjusted group means (2) 95% Confidence Interval of the estimate (3): For a non-inferiority one-sided test (alpha = 2.5%) obtained from an analysis of covariance with baseline and country (fixed effects) as covariates and a 0.4% margin of clinical relevance

Au total, **la non-infériorité de benfluorex par rapport à la pioglitazone n'a pas été démontrée** (limite supérieure de l'intervalle de confiance à 0.49 pour une limite de non infériorité fixée à 0.40 (E (SE) = 0,33 (0,08) %, 95 % CI = [0,17; 0,49], p = 0,19).

3. Critères secondaires

Tableau 8 -REGULATE Evolution des principaux paramètres biologiques dans la population FAS

	Benfluorex			Pioglitazone			différence entre les groupes
	N	valeur initiale moyenne (SD)	différence pré-post (SD)	n	valeur initiale moyenne (SD)	différence pré-post (SD)	Δ (ES) IC 95%
Glycémie à jeun mmol/L	392	9.9 (± 2.71)	-1.20 (0.15)	396	9.9 (± 2.51)	-1.73 (0.23)	0.56** (0.18) [0.21;0.90]
HOMA- IR Index	332	9.36 (± 5.30)	-1.23 (0.38)	315	9.83 (±5.34*)	-2.52 (0.35)	1.04 (0.41) [0.23;1.85]
Total Cholestérol mmol/L	396	5.01 (± 0.99)	-0.16 (0.04)	396	5.02 (± 0.92)	0.08 (0.05)	-0.25** (0.057) [-0.357;-0.134]
LDL cholestérol mmol/L	396	3.13 (0.83)	-0.24 (0.03)	396	3.15 (0.81)	-0.12 (0.04)	-0.13** (0.05) [-0.22;-0.04]
Triglycérides mmol/L	397	1.92 (± 0.97)	-0.14 (0.05)	397	1.96 (± 0.90)	-0.21 (0.05)	0.058 (0.06) [-0.07 ;0.18]

***p : 0.001 **p : 0.01 *p : 0.05 *test non paramétrique*

On observe :

- une diminution du LDL-cholestérol moyen (-0,24) dans le groupe benfluorex plus importante que celle observée dans le groupe pioglitazone (-0.12).

- une diminution du cholestérol total moyen (-0.16) dans le groupe benfluorex comparativement à une augmentation dans le groupe pioglitazone (+0.08)

- une stabilité du HDL-cholestérol (0.01) dans le groupe benfluorex et une légère augmentation sous pioglitazone (+0.06)

- une diminution des concentrations de triglycérides comparable dans les 2 groupes.

Enfin, il y a une diminution du poids sous benfluorex (-1.6 kg) et une augmentation sous pioglitazone (3.3 kg).

Sécurité

La fréquence des effets indésirables est comparable entre les deux groupes (63,7% dans le groupe benfluorex versus 62,9% dans le groupe pioglitazone). Les effets indésirables les plus fréquents sont les infections et infestations (24,9% versus 28,6%), les troubles gastro-digestifs (14,7% versus 11,8%), et les troubles musculosqueletiques (13,1% versus 15,6%).

Les effets indésirables émergents dans le groupe benfluorex sont les hypoglycémies (9% versus 13,2% dans le groupe pioglitazone) et les diarrhées (4.3% versus 1,9%).

Au niveau cardiaque, 2 patients du groupe benfluorex versus 3 dans le groupe pioglitazone ont fait un infarctus du myocarde, 0 versus 1 pour les angines de poitrine, 1 versus 0 pour l'insuffisance cardiaque congestive, 0 versus 1 pour l'ischémie, 0 versus 1 pour le syndrome coronarien aigu et 1 versus 0 pour la cardiomyopathie congestive.

Enfin, il y a eu deux décès dans le groupe benfluorex contre 4 dans le groupe pioglitazone, ces décès n'étant pas reliés aux traitements.

CONCLUSIONS PRELIMINAIRES DE LA FIRME :

En conclusion, chez des patients diabétiques de type 2 insuffisamment contrôlés par SU, l'ajout d'un traitement par benfluorex pendant 12 mois permet/entraîne une diminution statistiquement significative de l'HbA1c.

L'effet antidiabétique du benfluorex est confirmé dans cette étude (diminution de -0,54% de l'HbA1c), bien que la non infériorité du benfluorex versus la pioglitazone ne soit pas démontrée.

La supériorité du benflurorex versus la pioglitazone sur la diminution du LDL-cholestérol est démontrée.

De plus, le benfluorex diminue significativement le cholestérol total contrairement à la pioglitazone.

Les deux traitements diminuent significativement les taux de triglycérides, la glycémie à jeun et améliore l'insulinorésistance.

Après un an de traitement, le poids ainsi que le tour de taille ont augmenté sous pioglitazone mais pas sous benfluorex.

Le profile de sécurité d'emploi est en ligne avec ce qui figure déjà dans le RCP

En ce qui concerne le profile de sécurité cardiaque (échographies cardiaques), aucune modification de la fraction d'éjection du ventricule gauche (FEGP) n'a été détectée dans les deux groupes de traitement.

Des régurgitations des valves cardiaques ont été observées plus fréquemment sous benfluorex que sous pioglitazone, mais sans retentissement clinique délétère (significatif).

La différence morphologique en termes d'anomalies des valves cardiaques dont les régurgitations (au dessus d'un grade 1) ne sont pas significatives.

Les anomalies émergentes (nouvelles) des valves cardiaques dans cette étude n'étaient pas associées à des signes ou symptômes cliniques.

Des analyses complémentaires visant à expliciter les anomalies valvulaires observées sont en cours.

Annexe 4-43

RESUME DES DONNEES DE SECURITE D'EMPLOI

- 1998: 1ère enquête de Pharmacovigilance. Présentation des effets indésirables en CTPV (plusieurs séances) en 1998 ainsi qu'au groupe Européen de PV le 30-11-2000, entraînant des modifications de la rubrique 4.8. du RCP (ajout de « confusion » comme effet indésirable».

- 2004-2005/Seconde enquête de Pharmacovigilance

Cette 2nd enquête fait suite à plusieurs notifications d'effets indésirables pouvant évoquer un effet de type amphétaminique, rapportés avec le benfluorex. De ce fait, une actualisation des données relatives aux troubles neuropsychiatriques observés avec cette spécialité a été décidée.

L'enquête a ensuite été étendue aux hypertensions artérielles pulmonaires du fait de la notification d'un cas d'HTAP associé à la prise de benfluorex. Les conclusions de la CNPV sont les suivantes:

1. en ce qui concerne les troubles neuropsychiatriques: « *cette enquête confirme la réalité du risque de survenue de « confusions » en présence de Médiator. Il est proposé que cet effet, déjà mentionné dans le RCP, soit détaillé comme suit :* ***« troubles des fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) ».***
2. en ce qui concerne l'HTAP: « *compte tenu de l'incidence des HTAP idiopathiques (1 à 2 par millions et par an), le nombre de cas d'HTAP idiopathique rapportés dans l'enquête ne constitue pas un signal significatif de toxicité du Médiator dans la classe organe cardio-vasculaire ».*

La discussion en CNPV (29-11-2005, adoptée le 16-06-2006) a par ailleurs, porté sur les éléments suivants (extrait):

- Les ventes de Médiator en Europe sont réalisées en quasi totalité en France. Les données DOREMA d'avril 2005 montrent une utilisation dans 46,3% dans les dyslipidémies et dans 8,3% dans d'autres indications. L'effet anorexigène du benfluorex n'a pas été démontré. Toutefois, les membres de la CNPV craignent un mésusage, en particulier dans l'obésité. Dans ce contexte, une étude d'utilisation de prescription serait utile.
Il est à noter que le renouvellement quinquennal du produit intervient dans 2 ans en France et que des données d'efficacité dans le diabète existent mais restent limitées et mériteraient d'être réévaluées.

- Le bilan de pharmacovigilance confirme les données de sécurité d'emploi du Médiator déjà connues. Les effets neuropsychiatriques décrits actuellement dans le RCP sous le terme « confusion » doivent être détaillés. Il n'y a pas actuellement assez de données pour affirmer l'existence de syndrome de sevrage. Le faible nombre de cas décrits d'HTAP idiopathique associés au Médiator doit être relativisé par rapport à la sous-notification habituelle en pharmacovigilance. Afin d'évaluer au mieux les risques potentiels de l'utilisation de Médiator, il conviendrait de réaliser:
i) une étude d'utilisation/prescription de Médiator;
ii) une étude expérimentale sur un modèle animal permettant d'évaluer le potentiel de Médiator à engendrer des HTAP;
iii) une étude au niveau des Centres d'Evaluation et d'Information sur la Pharmacodépendance (CEIP) afin d'évaluer un éventuel problème de pharmacodépendance. A ce titre, une saisine de la Commission Nationale des stupéfiants et psychotropes sera effectuée.

Enfin, il a été proposé d'étudier la possibilité d'interroger les registres d'HTAP existant dans 17 centres, afin de rechercher, dans une étude rétrospective cas-témoins, le rôle éventuel du benfluorex.

- Année 2009

En mai 2009, le Comité technique de Pharmacovigilance a examiné les résultats actualisés de l'enquête de PV, notamment les données relatives au risque d'HTAP et de valvulopathie cardiaque sous MEDIATOR® ainsi que les données d'une publication[1] récente sur ce sujet.

Annexe 4-43

Ce dossier a été successivement présenté :

- en CTPV le 05 05 2009
- en CNPV le 07 07 2009
- en CNPV le 29 09 2009
-

- CNPV du 7 juillet 2009

=> Point sur les données relatives à l'HTAP en CNPV du 07 07 2009

Depuis le dernier passage en Commission Nationale de Pharmacovigilance du 27 mars 2007, 8 nouveaux cas d'HTAP ont été notifiés, soit un total de 28 cas, parmi lesquels le nombre d'HTAP d'allure idiopathique sous MEDIATOR® non associés à un autre anorexigène, est passé de 3 à 4. Le taux de notification des HTAP imputables au MEDIATOR® reste donc stable par rapport à 2007 (1 cas sur 34 954 169 boîtes vendues, soit 1 cas pour 14 372 602 mois de traitement). De même, la fréquence des cas d'HTAP idiopathiques sous MEDIATOR® est stable par rapport aux données présentées en mars 2007.

Compte tenu de l'incidence des HTAP d'allure idiopathique dans la population générale (1 à 2 cas par millions et par an), le Comité Technique a considéré que le nombre de cas d'HTAP d'allure idiopathique associés à l'utilisation de MEDIATOR® ne semblait pas constituer un signal significatif de la toxicité pulmonaire du Médiator®. Les membres du Comité Technique ont recommandé la poursuite d'une surveillance des notifications spontanées des cas d'HTAP dans la population générale.

=> Point sur les données relatives aux valvulopathies 07.07.2009

Actualisation de l'enquête sur les valvulopathies => CNPV du 07 07 2009

Concernant les valvulopathies, 30 cas sont observés entre 1998 et 2009 sous MEDIATOR® ce qui constitue un signal. L'ensemble de ces résultats a fait l'objet d'une présentation en groupe pharmaco-épidémiologie de l'Afssaps afin de définir un modèle d'étude permettant d'explorer le signal relatif aux valvulopathies. Une étude rétrospective cas-témoins des cas de valvulopathies issus du PMSI a été proposée.

En France, 30 cas de valvulopathies cardiaques sont rapportés entre 1998 et 2009 :

- 19 cas issus de la notification spontanée (NS) dont 3 cas concernant également les HTAP post-capillaires
- 11 cas identifiés par le CRPV de Brest à la suite de l'interrogation du PMSI (Programme de médicalisation des systèmes d'information).

Annexe 4-43

Caractéristiques des patients :

	NS : 19	PMSI : 11
Sexe	Femmes : 24, hommes : 6	
Age moyen de survenue (ans)		
Femmes : 54,6	53,7	56,4
Hommes : 62,2	54,6	69,7
BMI (kg/m²)		
18,5 à 24,9 : 5 cas	3	3-2
25 à 29,9 : 7 cas	5	2
≥ 30 : 8 cas	4	4
Durée moyenne de traitement (ans)		
5,3	5,6	4,6
Antécédents / Terrain (nombre)		
Tabac : 13	10	3
Hypothyroïdie : 9	7	2
Diabète : 9	5	4
Dyslipidémie : 12	10	2
Polyarthrite rhumatoïde : 2	1	1
Antécédent/Terrain cardiaque (nombre)	15	
Médicaments associés (nombre)		
Levothyroxine	9	
Antidépresseur IRS	7	

Type et localisation des valvulopathies :

Les 30 valvulopathie rapportées sont monovalvulaires dans 6 cas, bivalvulaires dans 16 cas et trivalvulaires dans 8 cas. Concernant la localisation de ces valvulopathies, 28 cas sont des insuffisances mitrales (sévères dans 17 cas), 24 cas sont des insuffisances aortiques et 11 cas sont des insuffisances tricuspides (sévères dans 4 cas).

Aspects anatomo-pathologiques des valvulopathies opérées

Des diagnostics anatomo-pathologiques sont effectués chez 6 patients opérés : 5 patients français et un cas espagnol rapporté dans une publication (Rafel Ribera J.).

a) **4 cas dont l'aspect anatomo-pathologique serait compatible avec celui décrit sous anorexigène :**

TO060355 (Noize[1] 2006) : une femme de 48 ans, avec un BMI=25 kg/m², sous MEDIATOR® pendant 7 ans pour intolérance aux glucides.

BR20080051 (Boutet[2], cas n°6) : une femme de 50 ans ayant un diabète de type 2, avec un BMI=34 kg/m², sous MEDIATOR® de 2001 à 2007 et sous ISOMERIDE® pendant 1 à 3 mois 20 ans auparavant.

BR20090080 (Brest PMSI) : une femme de 54 ans, avec un BMI=30 kg/m², sous MEDIATOR® de septembre 2007 à décembre 2008, ayant pris des amphétamines 7 à 8 ans jusqu'en 1986.

S03000422 (R. Riber[3] J. 2003) : une femme de 50 ans, sous MEDIATOR® pendant 12 mois par intermittence.

b) **Autres cas**

Dans 2 cas, l'anatomopathologie n'est pas spécifique.

Dans les autres cas, seules les données échographiques sont disponibles.

Annexe 4-43

Conclusions du rapporteur (CRPV de Besançon) :

Le CRPV de Besançon, rapporteur de cette enquête, a conclu à l'existence d'un signal de cardiotoxicité détecté par la notification spontanée et les données du PMSI. Il convient alors de confirmer ce signal par une étude épidémiologique (cas-témoin).

Le rapporteur souligne que la pharmacologie du benfluorex et de son métabolite, la norfenfluramine, devra être prise en compte dans l'analyse du mécanisme de la cardiotoxicité.

Compte tenu de ces nouvelles données de sécurité, le rapporteur propose une réévaluation du bénéfice/risque de benfluorex.

Présentation du Dr. Frachon (praticien, CHU de Brest):

Lors de cette réunion, le Docteur Frachon, du groupe HTAP de Bretagne Occidentale (CHU de Brest) a présenté la méthodologie appliquée à Brest pour l'identification des cas de valvulopathies associées au benfluorex.

L'identification des cas de valvulopathies a reposé sur :

i) le signalement spontané de 4 cas par des médecins brestois,
ii) l'interrogation du PMSI en utilisant le codage « valvulopathies et diabète » qui a mis en évidence 240 dossiers dont 3 cas compatibles et le codage « valvulopathies et Médiator® » qui a rapporté 23 dossiers dont 11 compatibles,
iii) une surveillance prospective avec 3 nouveaux cas.

Sur les 15 patients identifiés « compatibles » (dont 11 rapportés par le CRPV de Besançon et 4 très récents à l'étude), 12 étaient des femmes et 3 des hommes. L'âge moyen est de 58 ans (49-78). 6 patients sur 12 étaient diabétiques. La durée moyenne d'exposition est de 53 mois (12-144) avec un délai entre la première prise du médicament et le diagnostic de 97 mois (13-384). L'échographie cardiaque antérieure est normale dans 5 cas sur 7. L'exposition à d'autres anorexigènes concerne 5 patients sur 12, et à un antidépresseur de type inhibiteur de recapture de la sérotonine (IRSI) concerne 8 patients sur 10.
Les valves atteintes sont la valve mitrale et la valve aortique dans 100% des cas, avec une atteinte de la valve tricuspide dans 7 cas et de la valve pulmonaire dans un cas. Une chirurgie de remplacement valvulaire a été effectuée dans 8 cas.

Une analyse systématique de toutes les insuffisances mitrales (IM), isolées ou associées, examinées au CHU de Brest depuis 2003, est actuellement en cours. Plus de 600 dossiers d'IM sont classés en 3 groupes: 1) IM dans un contexte étiologique bien identifié 2) IM inexpliquées 3) IM non classables.
Une recherche de l'exposition au benfluorex sur un modèle de cas témoins est réalisée pour les cas identifiés par le PMSI et par une enquête téléphonique auprès du médecin et du patient.

Les résultats de cette étude sont attendus pour fin juillet 2009.

Présentation du laboratoire :

A l'issu de la présentation des données, les représentants des laboratoires Servier ont proposé deux modèles d'études :

i) une étude anatomopathologique sur un modèle exposé/non-exposé (ce modèle d'étude a été récusé par la commission),

ii) une étude cas-témoin ayant pour objectif de quantifier un éventuel sur-risque de valvulopathie associé au MEDIATOR® chez des patients atteints de valvulopathie idiopathique comparativement à des patients indemnes de valvulopathie. Cette étude se ferait sur une population de patients diabétiques ayant une échographie cardiaque.

Le protocole de cette étude serait disponible début Septembre2009 et permettrait dans le meilleur des cas d'avoir des résultats dans un an.

Par ailleurs, la firme a informé la CNPV que l'étude REGULATE, (MEDIATOR® + SU versus pioglitazone + SU) est actuellement en cours d'analyse. Cette étude incluant 840 patients dont 420 dans chaque bras, comporte une échographie cardiaque à T0 et à la 52ème semaine de traitement. Les résultats d'efficacité et de tolérance sont attendus pour la fin du 1er trimestre 2010.

Conclusions de la CNPV du 07 07 2009

Le responsable du CRPV de Brest, présent à la réunion de la CNPV, a informé les membres que les résultats de l'étude brestoise cas-témoin seront disponibles fin Juillet 2009. Les membres de la commission nationale avaient alors souhaité disposer des résultats de l'étude cas-témoin brestoise afin de se prononcer sur les mesures éventuelles à entreprendre.

Les membres de la CNPV ont également discuté de l'importance des utilisations hors AMM de ce produit, notamment dans la perte de poids, malgré la restriction d'indication.

La commission s'est prononcée en faveur (16 voix pour, 2 voix contre et 2 abstentions) de l'attente des résultats de l'ensemble des études en cours ou planifiées (laboratoires Servier et CRPV de Brest) avant de proposer d'éventuelles mesures.

Elle a toutefois souhaité qu'une communication soit effectuée auprès des professionnels de santé pour leur rappeler le bon usage du Benfluorex dans le cadre de l'AMM.

• CNPV du 29 septembre

=> Actualisation des données relatives aux valvulopathies présentées en CNPV du 07.07 2009 :

1- *Données de la pharmacovigilance :*

Une mise à jour des données de pharmacovigilance a été effectuée par le CRPV de Besançon. 11 nouveaux cas de valvulopathie associés au benfluorex sont rapportés dont 3 issus de la notification spontanée et 8 de des notifications sollicitées et provenant d'Amiens. L'analyse de ces 11 nouveaux cas montre une prédominance féminine, une durée moyenne de traitement de 3 ans et un âge de survenue le plus fréquemment identifié de 55 ans. Dans 9/11 cas une association à une hypertension artérielle pulmonaire est rapportée, une atteinte de type insuffisance mitrale et aortique dans 6 cas et une atteinte mitrale+aortique+tricuspide dans 2 cas. Malgré des échocardiographies documentées, les données anatomopathologiques restent peu informatives.

Certains membres ont souligné qu'en cas de notification sollicitée dans d'autres bassins de population, de nombreux autres cas de valvulopathie associés au benfluorex pourraient être mis en évidence.

2- Données de l'étude Brestoise :

L'étude cas-témoin rétrospective menée par le CHU de Brest, a pour objectif la recherche d'une association entre l'exposition au benfluorex et la survenue de cas d'insuffisance mitrale (IM) inexpliquée. La population source est constituée de tous les patients hospitalisés entre 2003 et 2009 dans le département de cardiologie ou le service de chirurgie cardiaque au CHU de Brest, et ayant un diagnostic d'IM. Les patients ayant une IM inexpliquée constituent les cas (n=27) et les patients ayant une IM expliquée constituent les témoins (n=54). Deux témoins ont été appariés à chaque cas sur les critères d'âge et de genre. L'appariement ne concernait le diagnostic de diabète ou l'Index de Masse Corporelle (IMC). L'exposition au benfluorex est recherchée auprès du patient, de sa famille et de ses médecins, par téléphone, sur la base d'un questionnaire semi-structuré et à l'aveugle du statut cas ou témoin.

Sur les 27 cas, 19 avaient été exposés au benfluorex contre 3 témoins sur 54 ($p<0.001$ soit un odds-ratio = 40,4 (9,7 – 168,3, IC à 95%)). L'ajustement à différentes variables telles que le poids, le diabète ou l'exposition à la dexfenfluramine, ne modifie pas la significativité du résultat.

Annexe 4-43

3- Données de l'étude « REGULATE » :

Les résultats préliminaires de l'étude REGULATE ont été présentés par le laboratoire Servier. Il s'agit d'une étude multicentrique, en double aveugle, comparant pendant 52 semaines chez 840 diabétiques l'efficacité et la sécurité de 2 traitements, benfluorex et SU versus pioglitazone et sulphonylurée (SU). Deux échographies cardiaques ont été réalisées : avant exposition (T0) et à la 52ème semaine. La non-infériorité de l'association benfluorex + SU par rapport à l'association pioglitazone + SU sur la réduction de l'hémoglobine glycosylée n'a pas été démontrée. L'effet a été plus important sur la baisse du LDL-cholestérol

Concernant le profil de tolérance, cette étude a mis en évidence dans le groupe traité par benfluorex, l'émergence d'anomalies valvulaires fonctionnelles statistiquement significatives (26,5% versus 10,9% respectivement, p<0,0001) ainsi que des anomalies valvulaires morphologiques non statistiquement significatives (2,6% versus 1,3% respectivement, p=0,264). Il est à souligner que les anomalies fonctionnelles apparues sous benfluorex n'ont pas de traduction clinique.

A l'issue de cette présentation, le laboratoire Servier a proposé des modifications du Résumé des Caractéristiques du Produit de Médiator®:

- rubrique 4.2 « Indication » : *Restriction aux diabétiques en échec de traitement après les anti-diabétiques oraux*

- conditions de prescription et de délivrance : *Prescription réservée aux spécialistes tels que diabétologues/endocrinologues.*

- *contre-indication aux patients présentant une anomalie valvulaire*

- *mise en place d'une surveillance échocardiographique.*

=> Discussion :

Les résultats de l'étude cas-témoin de Brest ont été largement débattus par les experts de l'Afssaps, les membres de la commission, les investigateurs et le laboratoire.

Les experts ont déploré ne pas disposer du protocole de l'étude. Plusieurs biais ont cependant été identifiés:

- le choix des témoins : si la question posée est de savoir si le benfluorex peut ou non être responsable de valvulopathies, les témoins ne devraient alors pas présenter de valvulopathie,
- le choix des valvulopathies inexpliquées : il est difficile d'être absolument sûr que le diagnostic ne soit pas biaisé,
- les cas et les témoins ont des caractéristiques très différentes. Une confusion par indication (lien entre caractéristiques des patients témoins et l'absence de traitement par benfluorex) ne peut être exclue. Les témoins ont très peu de chance d'être exposés au benfluorex,
- le faible nombre de patients exposés,
- le choix de l'anomalie valvulaire (limité à la valve mitrale).

Toutefois, malgré certaines limites méthodologiques de cette l'étude, les experts et les membres de la commission considèrent que le signal d'une relation entre l'exposition au benfluorex et la survenue de valvulopathies se confirme. Ce signal est d'autant plus préoccupant que l'étude « REGULATE » met en évidence une émergence d'anomalies morphologiques et fonctionnelles valvulaires à la suite d'une exposition d'environ un an au benfluorex (328 jours en moyenne). De plus, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne peut être exclue, notamment en raison des données d'utilisation du produit qui montrent une durée moyenne d'exposition d'environ 3 ans.

Annexe 4-43

=> Conclusions de la CNPV du 29 septembre 2009 :

Les membres de la CNPV considèrent (25 voix pour et 1 abstention), que les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex, et ce malgré certaines limites méthodologiques. De même, ils considèrent (25 voix pour et 1 abstention) que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

Il est à noter que le dépôt par le laboratoire du protocole de l'étude cas-témoin, prévu initialement pour début septembre 2009 n'a pas encore été effectué.

La CNPV a été informée de la transmission de ces données à la Commission d'AMM au plus tard le 23 octobre 2009, afin qu'elle puisse se prononcer sur la balance bénéfice- risque du produit.

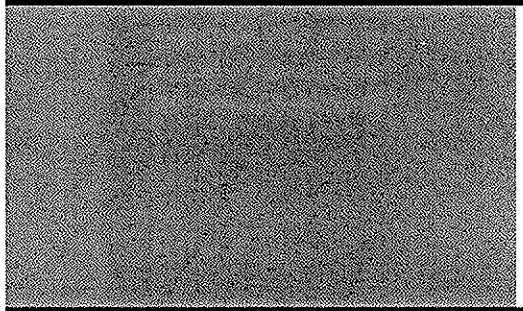
NOTE D'EVALUATION => DISCUSSIONS EN COMMISSION D'AMM

MEDIATOR 150 mg, comprimé enrobé

(Benfluorex)

Revue des données d'efficacité

Conclusions du Groupe DEUG



Agence française de sécurité sanitaire des produits de santé

afssaps

C. REY-QUINIO

D. BOUCAUD-MAITRE

COM d'AMM du 23/10/09

MEDIATOR
Mécanisme d'action

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Plusieurs mécanismes d'action évoqués :

- Action sur le **métabolisme du glycogène** (rat): augmentation de la synthèse du glycogène, **diminution de la glycogénolyse** stimulée par le glucagon (Melin)
- Diminution de la **production hépatique de glucose** et **effets sur la néoglocogenèse** (Tielens, Zorzano)
- Amélioration de la **sensibilité à l'insuline** (4 études: Brindley, Portha, Serrasas et Storlien)
- **Amélioration de l'insulino-résistance musculaire** avec **effet de majoration du transporteur GLUT-4** (Sevilla, Storlien, Zorzano er l'oxydation du glucose(Bailey)
- **Pas d'effet sur la sécrétion basale d'insuline** (rat normal ou diabétique)

=> **Effet insulino- sensibilisateurs chez l'Homme** avec **effet sur les transporteurs de glucose, effet direct sur le foie** et enfin **réduction du contenu musculaire en TG.**

MEDIATOR / Historique

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AMM octroyée en 1976

1987 => Validation indication "hypertriglycéridémies" en 1987

1990 => Validation indication "diabète" en 1990 (1er dépôt Etude Del Prato)

2000 => demande d'extension (2nd dépôt Etude Del Prato) => *"diabète de type 2 insulinodépendant, en association au régime adapté, lorsque ce regime n'est pas suffisant pour rétablir à lui seul l'équilibre glycémique"*

Jusqu'en 2007, deux indications:

- ***Adjuvant au régime adapté dans les hypertriglycéridémies.***
- ***Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.***

2007 => Réévaluation du bénéfice-risque (COM AMM 05-04-07)

=> Retrait indication "*adjuvant au régime adapté dans les hypertriglycéridémies*"

Réévaluation du Bénéfice Risque (2007)

afssaps

Conclusions de la COM d'AMM 5 avril 2007:

1. Suppression de l'indication "*Adjuvant du régime adapté dans les hypertriglycéridémies*"

   Les données soumises ne montrent qu'une efficacité très modeste sur les triglycérides et non démontrée sur les autres paramètres lipidiques

2. Maintien de l'indication "*Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale*"

   Les données soumises, en particulier celles de l'étude Moulin, semblent montrer une efficacité sur les paramètres glucidiques.

=> Demande de la COM de dépôt rapide d'une étude clinique évaluant l'efficacité du benfluorex en association aux autres antidiabétiques oraux (Etude REGULATE démarrée)

Etude DEL PRATO (1998)

Efficacité du benfluorex vs placebo et metformine

afssaps

Méthodologie:

Etude multicentrique, randomisée en double aveugle de 6 mois évaluant l'efficacité et la sécurité d'emploi de benfluorex vs placebo et vs metformine, chez 438 patients diabétiques de type 2 non équilibrés par régime seul (7,5% < HbA1c < 10%).

Etude déposée dans le cadre de la validation de l'AMM (en 1990) + extension d'indication (2000)

Résultats:

Taulle de l'effet difficile à estimer : i) vs placebo; ii) vs metformine (non infériorité non démontrée : déséquilibre del'HbA1c entre les groupes à l'inclusion; 68% seulement des patients inclus dans l'analyse PP. A noter : absence d'efficacité sur les paarmètres lipidiques.

Au total, seul le bras versus placebo avait été in fine retenu

INSPECTION DE L'ESSAI

Conclusions de la COM d'AMM du 09/12/99 (reprises en 2002)

"Il est noté une efficacité du benfluorex vs placebo **(-0,86% d'HbA1c),** néanmoins aucune conclusion ne peut être formulée sur la taille de l'effet compte tenu des défauts de la qualité méthodologique de cet essai."

Modification de l'indication rejetée (COM AMM 20-09-2002) => Indication *"Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale"* maintenue

afssaps

METHODOLOGIE:

Etude multicentrique, randomisée en double aveugle de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex vs placebo, chez 325 patients diabétiques de type 2 mal équilibrés (7% < HbA1c < 10%) **par SU, ou intolérants ou ayant une CI à la metformine.**

Deux phases :

- **Phase I de 18 semaines en double aveugle : supériorité du benfluorex vs placebo sur l'HbA1c** (différence attendue de 0.6%)

- **Phase II de 16 semaines en ouvert :** données de **sécurité d'emploi à long-terme** en association à un SU ou à l'acarbose

Critère principal: HbA1c

Critères secondaires: glycémie à jeun, insulinémie à jeun, paramètres lipidiques, sécurité d'emploi

Etude MOULIN (2006)

Résultats sur l'HbA1c à 18 semaines (phase I en DA)

afssaps

variable		benfluorex n	benfluorex HbA1c valeur initiale moyenne (DS)	benfluorex différence pré-post traitement (ES)	Placebo N	Placebo HbA1c valeur initiale moyenne (DS)	Placebo différence pré-post traitement (ES)	différence entre les groupes Δ (SE)
Population complète		161	*8.34 (± 0.83)*	-0.82 (0.08)	156	*8.33 (± 0.87)*	+ 0.19 (0.11)	**-1.01***** (0.13)
Sous-groupes	**HbA1c> 8%**	93	*8.9 (± 0.53)*	-1.15 (0.11)	89	*8.96 (± 0.56)*	-0.06 (0.15)	**-1.10***** (0.18)
	Âge > 65 ans	70	*8.28 (± 0.80)*	-0.86 (0.10)	82	*8.31 (± 0.87)*	-0.03 (0.13)	**-0.81***** (0.17)
	Clairance créat ≤ 80 mL/min	62	*8.17 (± 0.76)*	-0.78 (0.12)	78	*8.32 (± 0.87)*	+ 0.27 (0.15)	**-1.16***** (0.20)

*** p <0.001

Etude MOULIN (2006)

Résultats sur l'HbA1c à 18 semaines (phase I en DA)

afssaps

	benfluorex			Placebo			différence entre les groupes
	N	valeur initiale moyenne (DS)	différence pré-post (ES)	n	valeur initiale moyenne (DS)	différence pré-post (ES)	Δ (ES)
Glycémie à jeun mmol/L	159	*9.89 (± 2.57)*	-1.22 (0.20)	156	*9.71 (± 2.39)*	0.51 (0.23)	**-1.65*** (0.27)**
HOMA- IR Index	157	*6.62 (± 7.99)*	-1.75 (0.50)	150	*6.35 (± 7.95)*	-0.42 (0.65)	**-0.81**†**
LDL cholestérol mmol/L	149	*3.60 (± 0.80)*	-0.27 (0.06)	152	*3.52 (± 0.89)*	0.04 (0.05)	**-0.28*** (0.07)**
Triglycérides mmol/L	151	*2.26 (± 1.62)*	-0.11†	152	*2.11 (± 1.32)*	0.05†	**-0.16* (0.07)**

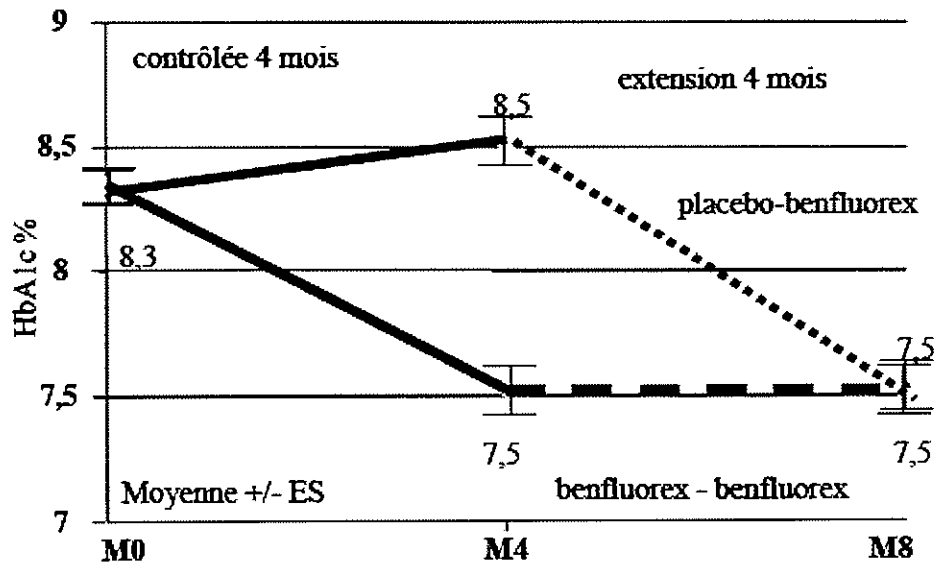
***p < 0.001 **p< 0.01 *p< 0.05 †test non paramétrique

Etude MOULIN (2006)

Résultats globaux sur l'HbA1c (Phase I et II)

afssaps

Figure 2 - Evolution de l'HbA1c pendant la période en double aveugle suivie de la période d'extension de l'étude Moulin 2006



COM DU 23/10/09

2723

Annexe 4-43

Etude MOULIN (2006)

Conclusions

afssaps

Bénéfice sur le métabolisme glucidique:

- **Sur l'HbA1c => supériorité du benfluorex vs placebo démontrée à 4 mois;** maintien de l'efficacité obtenue à 8 mois.
- Efficacité très modeste voire inexistante sur les TG (- 7%). Efficacité sur les autres paramètres lipidiques dont LDL-cholestérol (-6%) non démontrée.
- Variation du poids: - 1.3 kg sous benfluorex et - 0.7 kg sous placebo

Sécurité d'emploi => tolérance acceptable

- Troubles digestifs mineurs (diarrhée) : 15.2% vs 15.3%
- Pas de modification significative de la PA, FC, à l'ECG et des autres paramètres biologiques
- Troubles neurologiques plus fréquents sous benfluorex (9% vs 6.3%)
- Hypoglycémies: 20 patients rapportent 37 épisodes => fréquence plus importante sous sous benfluorex (> 65 and, ClCr < 80 ml/mn)

L'efficacité en seconde intention en association à un SU semble démontrée MAIS réserves méthodologiques soulevées par les experts => Nécessité d'une étude complémentaire pour confirmer cette efficacité pour les paramètres glucidiques

Etude REGULATE (2009)
Méthodologie – Objectifs

afssaps

Objectifs: comparaison de l'efficacité et de la sécurité d'emploi à un an d'un traitement par MEDIATOR vs pioglitazone, chez les patients insuffisamment contrôlés par un sulphonylurée (SU)

Objectif principal: **non-infériorité de la combinaison SU + benfluorex vs SU + pioglitazone sur l'évolution de l'HbA1c à un an** (borne fixée à 0,4%).

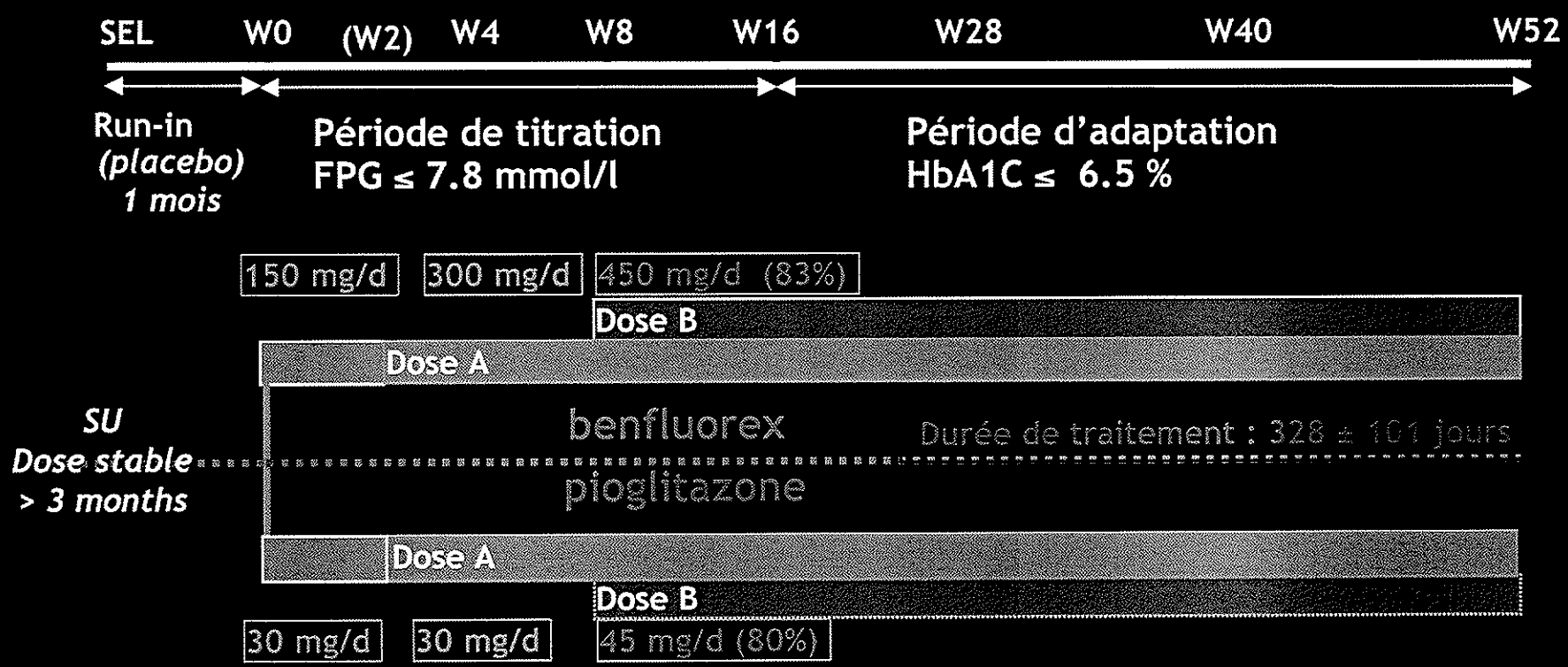
Objectifs secondaires:

Supériorité du benfluorex + SU vs pioglitazone + SU sur le taux de cholestérol.

Autres objectifs secondaires: glycémie à jeun, insulinémie à jeun, **risque cardiovasculaire (Echographie ++)**, sécurité d'emploi et coût de ces deux traitements.

Etude REGULATE (2009)
Méthodologie

afssaps



8 pays - 245 centres - 847 patients inclus

Etude REGULATE (2009)

Résultats sur l'HbA1c

afssaps

HbA1c (%)	Benfluorex	Pioglitazone
Inclusion	8.31 ± 0.82	8.33 ± 0.83
Finale	7.77 ± 1.31	7.45 ± 1.30
Différence	-0.54 ± 1.12	-0.88 ± 1.24

0.33 (0.08)

[0.17; 0.49]

=> Non-infériorité non démontrée entre le benfluorex et la pioglitazone (borne fixée à 0.40%)

Etude REGULATE (2009)

RESULTATS sur les critères secondaires

afssaps

	Benfluorex			Pioglitazone			différence entre les groupes
	N	valeur initiale moyenne (SD)	différence pré-post (SD)	n	valeur initiale moyenne (SD)	différence pré-post (SD)	Δ (ES) IC 95%
Glycémie à jeun mmol/L	392	*9.9 (± 2.71)*	-1.20 (0.15)	396	*9.9 (± 2..51)*	-1.73 (0.23)	**0.56**** (0.18) [0.21;0.90]
HOMA- IR Index	332	*6.36 (± 5.30)*	-1.23 (0.38)	315	*6.83 (±7.34°*	-2.52 (0.35)	1.04 (0.41) [0.23;1.85]
Total Cholestérol mmol/L	396	*5.01 (± 0.99)*	-0.16 (0.04)	396	*5.02 (± 0.92)*	0.08 (0.05)	**-0.25**** (0.057) [-0.357;-0.134]
LDL cholestérol mmol/L	396	*3.11 0.83)*	-0.24 (0.03)	396	*3.15 (0.81)*	-0.12 (0.04)	**-0.13**** (0.05) **[-0.22;-0.04]**
Triglycérides mmol/L	397	*1.92 (± 0.97)*	-0.14 (0.05)	397	*1.96 (± 0.90)*	-0.21 (0.05)	0.058 (0.06) [-0.07 ;0.18]

****p < 0.001 **p< 0.01 *p< 0.05 ftest non paramétrique*

Etude REGULATE (2009)

RESULTATS sur la sécurité d'emploi (hors Echo Coeur)

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	benfluorex	pioglitazone
Fréquence des EI	63,7%	62.9%
Infections	24,9%	28,6%
Troubles GI	14,7%	11,8%
Hypoglycémies	9%	13,2%

Etude REGULATE (2009)

CONCLUSIONS sur les données d'efficacité

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Bénéfice sur le métabolisme glucidique:

- **Sur l'HbA1c => non infériorité vs pioglitazone non établie. Diminution de l'HbA1C de – 0.54% sous benfluorex vs - 0.88% sous pioglitazone à 12 mois**
- **Evolution des autres paramètres glucidiques dans le même sens.**
- **Evolution des paramètres lipidiques similaire à celle observée dans l'étude Moulin: cholestérol total (-0.16 mmol/l).**
- **Variation du poids: - 1.6 kg sous benfluorex et + 3.3 mg sous pioglitazone**

Sécurité d'emploi => fréquence des effets indésirables comparable dans les 2 groupes : 63.7% vs 62.9%

- **Troubles gastro-intestinaux : 14.7 % vs 11.8% dont diarrhées (4.3% vs 1.9%)**
- **Pas de modification significative de la PA, FC et des autres paramètres biologiques**
- **Troubles musculosquelettiques (11.4 vs 15.6%)**
- **Hypoglycémies plus fréquentes sous benfluorex : 9% vs 13.2%**

=> NON INFERIORITE du BENFLUOREX versus la PIOGLITAZONE non démontrée (en seconde intention)

Modifications du RCP demandées par la firme suite aux Etudes MOULIN et REGULATE

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Modification de l'Indication (rubrique 4.1.) avec ajout d'une Restriction des prescriptions aux spécialistes :

- **Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale, intolérants à la metformine et/ou insuffisamment contrôlés par un insulinosécréteur sulfamidé ou non.**
- **Le traitement doit être instauré par un médecin spécialiste en diabétologie, en endocrinologie ou en médecine interne**

Autres modifications demandées (rubriques 4.2., 4.3., 4.4. et 4.8.) intégrant les nouvelles données de sécurité d'emploi sur les valvulopathies (suivi échographique)

AVIS DU GROUPE DEUG DU 22 Octobre 2009

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L'analyse des données d'efficacité de l'étude REGULATE

PERMET :

- de confirmer l'efficacité modérée du benfluorex sur l'HbA1c en association aux SU : de -0.5 % (Regulate) à -0.8% (Moulin)

- de confirmer l'effet peu important sur les lipides (retrait de l'AMM en 2007)

NE PERMET PAS:

- de recommander le benfluorex en add-on d'un SU (NI non établie vs pioglitazone dans REGULATE, alternatives thérapeutiques en add-on établies)

- de modifier l'indication du MEDIATOR (proposition de la firme rejetée) : expertise partielle en l'absence de rapport final, modification devant tenir compte de la partie safety de l'étude Regulate (valvulopathies)

- de situer le benfluorex dans la stratégie thérapeutique de prise en charge du diabète de type 2 (voir Recos actuelles)

BENEFICE-RISQUE MEDIATOR

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Bénéfices :

Efficacité modérée sur les paramètres glucidiques mais absence de bénéfice sur les paramètres lipidiques – effet sur l'HbA1c +/- similaire à celle des gliptines/acarbose mais doutes méthodologiques (Etude Moulin)

Absence d'hypoglycémies (intéressante chez le sujet âgé)

Pas de prise de poids voire légère baisse pondérale (intéressante chez les obèses)

Risques

HTPP signal

Emergence d'effet d'atteintes valvulaires = Signal ++

Utilisation hors AMM (obèses, dyslipidémiques)

Annexe 4-44

RÉPUBLIQUE FRANÇAISE

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Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation des Médicaments et des Produits Biologiques

Saint-Denis, le 24 NOV. 2009

Madame le Pharmacien responsable
Les Laboratoires SERVIER
22 rue Garnier
92200 NEUILLY-SUR-SEINE

Lettre recommandée avec avis de réception
1A 036 504 922 49

Dossier suivi par : BP/SO/DBM/CRQ/DR

Réf. : NL 10008 (CIS 6 242 648 7)
COM AMM 469 et 470

Madame,

Je vous prie de bien vouloir trouver ci-joint la décision de suspension de l'autorisation de mise sur le marché de la spécialité pharmaceutique :

MEDIATOR 150 mg, comprimé enrobé,

dont la date d'effet est fixée au 30 novembre 2009.

A cet égard, je vous indique que cette décision est prise dans le contexte procédural de l'article 107 paragraphe 2 de la directive 2001/83/CE du Parlement européen et du Conseil du 6 novembre 2001 instituant un code communautaire relatif aux médicaments à usage humain. Néanmoins, conformément aux dispositions du 1er paragraphe de ce même article, je vous informe que, au vu l'évaluation des données disponibles et en l'état actuel du dossier, je considère que le retrait de l'autorisation de votre spécialité apparaîtrait fondé.

La présente décision peut faire l'objet d'un recours contentieux devant le Conseil d'Etat dans un délai de deux mois à compter de la date de réception.

Par ailleurs, je vous indique que la procédure de rappel des lots de votre spécialité dans les pharmacies sera mise en œuvre à la date d'effet de la présente décision.

Je vous prie d'agréer, Madame, l'expression de ma considération distinguée.

Le Directeur Général

Jean MARIMBERT

Annexe 4-44

RÉPUBLIQUE FRANÇAISE

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Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation des Médicaments et des Produits Biologiques

Saint-Denis, le 24 NOV. 2009

Réf. : NL 10008 (CIS 6 242 648 7)
COM AMM 469 et 470

DECISION

du..... 24 NOV. 2009

portant suspension de l'autorisation de mise sur le marché du médicament :

MEDIATOR 150 mg, comprimé enrobé

LE DIRECTEUR GENERAL DE L'AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Vu la directive 2001/83/CE du Parlement européen et du Conseil du 6 novembre 2001 instituant un code communautaire relatif aux médicaments à usage humain, notamment l'article 107 ;

Vu le code de la santé publique, cinquième partie, notamment les articles L. 5121-9, L. 5121-20, R. 5121-21 et suivants, ainsi que l'article R.5121-158 ;

Vu l'avis de la Commission d'autorisation de mise sur le marché (AMM) prévu à l'article R. 5121-50 du code de la santé publique, en date du 12 novembre 2009, par lequel elle se prononce, suite à la réévaluation menée au vu de l'ensemble des données disponibles d'efficacité et de risque dans les conditions d'utilisation actuelles et ayant fait apparaître un rapport bénéfice-risque défavorable de la spécialité pharmaceutique MEDIATOR 150 mg, comprimé enrobé, contre son maintien sur le marché ;

Vu la lettre du 13 novembre 2009 informant les Laboratoires SERVIER de l'intention de l'Agence française de sécurité sanitaire des produits de santé de suspendre l'AMM de la spécialité pharmaceutique MEDIATOR 150 mg, comprimé enrobé et l'invitant à présenter ses observations ;

Vu la réponse des Laboratoires SERVIER en date du 23 novembre 2009 par laquelle ils proposent la modification du résumé des caractéristiques du produit afin de restreindre le libellé de l'indication thérapeutique, de limiter la prescription du médicament à certains spécialistes et d'ajouter une contre-indication ainsi que des mises en gardes spéciales et des précautions d'emploi, compte tenu de leur analyse ayant conclu à un rapport bénéfice/risque favorable de la spécialité précitée dans les nouvelles conditions d'utilisation proposées ;

Considérant le principe général de prééminence de la protection de la santé publique énoncé par le second considérant de la directive 2001/83/CE précitée ;

Considérant la mise en œuvre de la procédure prévue à l'article 107 de la même directive, à l'issue de laquelle, après avis du Comité des médicaments à usage humain de l'Agence européenne des médicaments, une décision définitive sera prise par la Commission européenne en ce qui concerne le devenir de l'AMM de la spécialité MEDIATOR 150 mg, comprimé enrobé ;

Considérant que dans l'attente de la décision de la Commission européenne, les autorités sanitaires nationales peuvent, lorsqu'une action urgente apparaît nécessaire pour protéger la santé publique à la suite de l'évaluation de données de pharmacovigilance, suspendre l'AMM de la spécialité concernée ;

Considérant qu'aux termes des articles L.5121-9 et R.5121-47 du code de la santé publique, l'AMM peut être suspendue notamment lorsque l'évaluation des effets thérapeutiques positifs du médicament au regard des risques pour la santé du patient ou la santé publique liés à sa qualité, sa sécurité ou son efficacité n'est pas considérée comme favorable ou lorsque l'effet thérapeutique annoncé fait défaut ;

Considérant que les notions de nocivité et d'effet thérapeutique ne peuvent être examinées qu'en relation réciproque et n'ont de signification relative qu'appréciées en fonction de l'état d'avancement de la science et compte tenu de la destination du médicament ;
Considérant que l'exigence d'une évaluation du rapport bénéfice/risque présenté par un médicament ne vise pas exclusivement l'octroi de l'AMM, mais implique une évaluation continue, et notamment dans le cadre d'une procédure de suspension d'AMM ;

Considérant en l'espèce que des données nouvelles modifient le profil de sécurité de la spécialité pharmaceutique MEDIATOR ; plus précisément, alors qu'aucune étude n'établit un bénéfice attendu du médicament permettant de contrebalancer les risques d'emploi, ceux-ci sont majorés. En effet, la réévaluation fait apparaître les éléments suivants :

Données d'efficacité

Il résulte des trois études disponibles que l'efficacité des spécialités à base de benfluorex, dans l'indication thérapeutique à ce jour revendiquée (adjuvant du régime adapté chez les diabétiques avec surcharge pondérale), est modérée. En effet :

- Etude DEL PRATO (1997), déjà examinée dans le cadre de la validation en 1999 de l'indication thérapeutique précitée : Il s'agit d'une étude multicentrique, randomisée, en double aveugle, d'une durée de 6 mois et dont l'objectif est d'évaluer l'efficacité et la sécurité d'emploi de benfluorex versus placebo et versus metformine, chez 438 patients diabétiques de type 2 non équilibrés par régime seul. Du fait des réserves méthodologiques relevées dans cette étude, aucune conclusion définitive sur la taille de l'effet n'a pu être formulée, même si les résultats du bras benfluorex versus placebo ont pu faire apparaître une diminution de -0,86% de l'hémoglobine glyquée (HbA1c) qui est le paramètre de référence dans la surveillance de l'équilibre glycémique des patients diabétiques.

- Etude MOULIN (2006), déjà examinée dans le cadre de la modification de l'AMM de la spécialité MEDIATOR 150 mg, comprimé enrobé par décision du 25 juillet 2007 : Il s'agit d'une étude multicentrique, internationale, randomisée, en double aveugle, d'une durée de 18 semaines et dont l'objectif est d'évaluer l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par sulphonylurées (SU) et intolérants ou ayant une contre-indication à la metformine. Les résultats de cette étude en termes d'efficacité du benfluorex en association aux sulphonylurées ont été une diminution de l'HbA1c de -0,82% par rapport à sa valeur de base dans le groupe benfluorex et de -1% versus le groupe placebo. Néanmoins, du fait de réserves méthodologiques concernant notamment les méthodes d'ajustement utilisées, une étude d'efficacité clinique complémentaire versus un comparateur actif en seconde intention est apparue nécessaire afin de conforter les résultats obtenus sur l'HbA1c.

- Etude REGULATE (2009), dont seuls les résultats préliminaires ont à ce jour été fournis : Il s'agit d'une étude multicentrique, randomisée, en double aveugle, contrôlée versus pioglitazone, d'une durée de 52 semaines, dont l'objectif est de comparer chez 840 patients diabétiques de type 2 insuffisamment contrôlés par SU, l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR 150 mg, comprimé enrobé à la dose maximale recommandée (450 mg/jour), à un traitement par pioglitazone à la dose maximale recommandée (45 mg/jour). Au vu des résultats disponibles, cette étude de non-infériorité n'a pas permis de démontrer la non infériorité sur l'HbA1c (critère principal) du benfluorex par rapport à la pioglitazone. En effet, la diminution de l'HbA1c a été de -0,54% sous benfluorex versus -0,88% sous pioglitazone. Le traitement par benfluorex aurait été considéré comme non-inférieur au traitement par pioglitazone si la borne supérieure de l'intervalle de confiance de la différence d'HbA1c entre les deux traitements avait été inférieure à 0,40%. Dans la mesure où la borne supérieure de l'intervalle de confiance est de 0,49%, le traitement par benfluorex n'est pas considéré comme au moins équivalent au traitement par pioglitazone (différence entre les deux traitements = 0,33 (0,08) %, intervalle de confiance à 98% = [0,17; 0,49], p=0,19).

Enfin, il est rappelé que le benfluorex n'est pas mentionné dans les recommandations françaises et internationales relatives à la prise en charge du diabète de type 2 car il est considéré uniquement comme un adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

Données de sécurité

Depuis 1995, le benfluorex a fait l'objet de plusieurs mises au point en ce qui concerne les effets indésirables, ainsi que de deux enquêtes de pharmacovigilance, l'une en 1999 portant sur les troubles neuro-psychiques et la deuxième en 2004 suite à la notification d'effets de type amphétaminiques. Cette deuxième enquête a été étendue en 2005 aux hypertensions artérielles pulmonaires (HTAP), puis aux valvulopathies. La notification par les centres régionaux de pharmacovigilance (CRPV) de cas de valvulopathies cardiaques sous benfluorex et la publication de Boutet en 2009 (*Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 20098 :33 :684-688. Boutet K*) rapportant 5 cas d'HTAP et 1 cas de valvulopathie cardiaque associé, après exposition au benfluorex, ont conduit à une actualisation

des données de pharmacovigilance, en vu d'un examen lors des séances de la Commission nationale de pharmacovigilance du 7 juillet et du 29 septembre 2009.

Données actualisées de l'enquête de pharmacovigilance en juillet 2009

Entre 1998 et juillet 2009, en France, 30 cas de valvulopathies cardiaques ont été rapportés :
- 19 cas issus de la notification spontanée (NS) dont 3 cas concernent également des HTAP post-capillaires ;
- 11 cas identifiés par le CRPV de Brest à la suite de l'interrogation du PMSI.

Les 30 valvulopathies rapportées sont monovalvulaires dans 6 cas, bivalvulaires dans 16 cas et trivalvulaires dans 8 cas. Concernant la localisation de ces valvulopathies, 28 cas sont des insuffisances mitrales (grade 2-3 dans 17 cas), 24 cas sont des insuffisances aortiques (grade 1-2 dans 17 cas) et 11 cas sont des insuffisances tricuspides (sévères, de grade 3 dans 4 cas).
L'évolution de ces atteintes a été marquée par une chirurgie valvulaire dans 10 cas (plus 2 prévues), une stabilité dans 4 cas, une stabilité sous traitement dans 5 cas. Elle est inconnue dans 4 cas et en cours dans 5.
Parmi les valvulopathies opérées, 4 cas ont un aspect anatomo-pathologique des valves compatible avec celui décrit sous anorexigène. Dans les 2 autres cas opérés, l'anatomopathologie n'est pas spécifique.
A cet égard, il peut être rappelé que la cardio-toxicité des anorexigènes a une plausibilité biologique : la stimulation des récepteurs 5-HT2B, exprimés au niveau des valves cardiaques, peut induire une mitogénèse fibroblastique. Or le benfluorex est métabolisé en deux produits dont le N-benzoyloxy-2-ethyl-norfenfluramine.

Il ressort de l'évaluation de ces données d'une part qu'il existe un signal de cardiotoxicité (atteinte valvulaire) détecté par l'analyse de la notification spontanée et des données issues de l'exploitation du PMSI du CHU de Brest, d'autre part que la pharmacologie du benfluorex et de son métabolite la nor-fenfluramine doit être prise en considération dans l'analyse du mécanisme de la cardio-toxicité.

Données actualisées en septembre 2009 de l'enquête de pharmacovigilance par rapport à celles de juillet 2009

Une mise à jour des données de pharmacovigilance a été effectuée par le CRPV de Besançon entre juillet et septembre 2009. Onze nouveaux cas de valvulopathie ont été rapportés dont 3 issus de la notification spontanée et 8 des notifications sollicitées provenant d'Amiens.
L'analyse de ces 11 nouveaux cas montre : une prédominance féminine, une durée moyenne de traitement de 3 ans, un âge moyen de survenue de 55 ans, une association à une hypertension artérielle pulmonaire dans 9 cas sur 11 cas rapportés et une atteinte de type insuffisance mitrale, isolée ou associée à une insuffisance aortique et/ou tricuspide.

Par ailleurs, 4 cas supplémentaires de valvulopathie ont été identifiés à Brest, ce qui porte, à ce jour, le total des cas de valvulopathie spontanément notifiés, sollicités ou par le biais de l'exploitation du PMSI, à 45.

Etude cas-témoin rétrospective menée par le groupe HTAP de Bretagne Occidentale (CHU de Brest)

La méthodologie de cette étude pour l'identification des cas de valvulopathies associées au benfluorex repose sur l'interrogation du PMSI en utilisant les codages « valvulopathies et diabète » et « valvulopathies et Médiator ».
L'étude analyse toutes les insuffisances mitrales, isolées ou associées, examinées au CHU de Brest depuis 2003. L'objectif est la recherche d'une association entre l'exposition au benfluorex et la survenue de cas d'insuffisance mitrale (IM) inexpliquée. La population source est constituée de tous les patients hospitalisés entre 2003 et 2009 dans le département de cardiologie ou le service de chirurgie cardiaque au CHU de Brest, et ayant un diagnostic d'IM. Les patients ayant une IM inexpliquée constituent les cas (n=27) et les patients ayant une IM expliquée constituent les témoins (n=54). Deux témoins ont été appariés à chaque cas sur les critères d'âge et de genre. L'appariement ne concernait pas le diagnostic de diabète ni l'Index de Masse Corporelle (IMC). L'exposition au benfluorex a été recherchée auprès du patient, de sa famille et de ses médecins, sur la base d'un questionnaire semi-structuré et à l'aveugle du statut cas ou témoin.

Sur les 27 cas identifiés, 19 avaient été exposés au benfluorex contre 3 témoins sur 54 ($p<0.001$ soit un odds-ratio = 40,4 (9,7 – 168,3, IC à 95%)), soit un risque relatif très important d'IM en cas d'exposition au benfluorex.
L'ajustement à différentes variables telles que le poids, le diabète ou l'exposition à la dexfenfluramine, ne modifie pas le signal.

Malgré certaines limites méthodologiques, il apparaît que les résultats de cette étude confortent le signal de risque entre l'exposition au benfluorex et la survenue de valvulopathies.

Résultats préliminaires de l'étude REGULATE

Six cent quatorze patients, 309 dans le groupe benfluorex et 305 dans le groupe pioglitazone, ont eu une échocardiographie à l'inclusion et à 52 semaines après une exposition aux traitements d'une durée moyenne de 328 jours.

Concernant le profil de tolérance cardio-vasculaire, cette étude a mis en évidence dans le groupe traité par benfluorex versus le groupe pioglitazone :
- l'émergence d'anomalies valvulaires fonctionnelles statistiquement significatives (26,5% versus 10,9%, p<0,0001),
- des anomalies valvulaires morphologiques non statistiquement significatives (2,6% versus 1,3% respectivement, p=0,264).

En dépit de certaines limites méthodologiques de l'étude cas-témoin de Brest, elle est de nature à corroborer le signal d'une association entre l'exposition au benfluorex et la survenue de valvulopathie. Ce signal est considéré d'autant plus préoccupant que l'étude REGULATE met en évidence une émergence d'anomalies morphologiques et fonctionnelles valvulaires à la suite d'une exposition moyenne de seulement 328 jours. De plus, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne peut être exclue, notamment en raison des données d'utilisation du produit qui montrent une durée moyenne d'exposition d'environ 3 ans.
Par ailleurs, selon l'expertise présentée par les laboratoires SERVIER, parmi les 45 cas de valvulopathies notifiés (19 notifications spontanées, 16 notifications du CRPV de Brest, 10 notifications du CRPV d'Amiens), l'imputabilité d'une valvulopathie au benfluorex est forte pour 6 cas, possible dans 16 cas, la principale alternative étant une valvulopathie rhumatismale. L'imputabilité est faible dans 16 cas pour lesquels la présence de régurgitations valvulaires est difficile à interpréter en l'absence de tout détail concernant l'anatomie valvulaire. Enfin, l'imputabilité est très faible dans 7 cas pour lesquels une autre étiologie paraît plus probable. Toutefois, cette analyse ne remet pas en cause la mise en évidence du signal d'une association entre l'exposition au benfluorex et la survenue de valvulopathie.

Résultats préliminaires d'une étude de cohorte réalisée par la Caisse Nationale d'Assurance Maladie (CNAM) en octobre 2009

Il s'agit d'une étude de cohorte de type exposé-non exposé à partir des données du système national inter-régime de l'assurance maladie (SNIIRAM). Etaient éligibles les patients diabétiques traités (antidiabétiques oraux et/ou insuline) en 2006 et âgés de 40 à 69 ans. Les cas exposés ont été enregistrés de façon passive et définis par la délivrance et le remboursement en 2006 de médicament à base de benfluorex. Après chaînage des données, les évènements recherchés au cours de l'année n+1 et n+2 dans le PMSI 2007 et 2008 sont une hospitalisation pour une insuffisance valvulaire toutes causes confondues, une hospitalisation pour une insuffisance mitrale et chirurgie de remplacement valvulaire sous circulation extracorporelle pour une insuffisance valvulaire toutes causes confondues.
Les résultats portent sur 1 092 858 diabétiques dont 43 208 exposés au benfluorex en 2006. Le risque d'hospitalisation en 2007 pour insuffisance valvulaire cardiaque est de 81 pour 100 000 dans le groupe exposé versus 29 pour 100 000 dans le groupe non exposé (RR=2,77 IC 95[1,95 ; 3,93]). Le risque d'hospitalisation pour insuffisance mitrale est de 53 pour 100 000 dans le groupe exposé versus 20 pour 100 000 dans le groupe non exposé RR=2,66 IC 95[1,7 ; 4,1]. Le risque de chirurgie en 2007 avec un remplacement valvulaire sous circulation extracorporelle (CEC) pour une insuffisance valvulaire toutes causes confondues est de 30 pour 100 000 dans le groupe exposé au benfluorex versus 9 pour 100 000 dans le groupe non exposé (RR=3,4 [1,9 ; 6,1]). Parmi les 13 personnes diabétiques exposées et ayant subi un remplacement valvulaire sous CEC en 2007, une est décédée en milieu d'année 2008. Pour les personnes exposées au benfluorex en 2006, les risques absolus et les risques relatifs sont en 2008 très proches de ceux observés en 2007. Le risque relatif des exposés au benfluorex de chirurgie valvulaire sous CEC est identique (3,4).

Bien que préliminaires, ces résultats confortent le signal de pharmacovigilance d'augmentation du risque de valvulopathie clinique chez les diabétiques, qui est établi au vu des données précitées. En effet, les résultats montrent que l'usage du benfluorex chez les diabétiques âgés de 49 à 59 ans est associé significativement dans les deux années qui suivent à des valvulopathies de régurgitation mitrales, aortiques et tricuspidiennes et à des chirurgies de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.

Considérant, au vu de cette situation particulièrement préoccupante en termes de santé publique, d'une part que les arguments développés par les Laboratoires SERVIER notamment dans la lettre précitée du 23 novembre 2009 ne remettent pas en question l'évaluation négative du rapport bénéfice/risque de la spécialité, et d'autre part que la proposition formulée lors de la séance de la Commission d'AMM du 23 octobre 2009 et réitérée dans la lettre du 23 novembre 2009 visant à modifier le résumé des caractéristiques du produit apparaît insuffisante. Notamment, la surveillance échographique pendant le traitement n'est pas de nature à prévenir le risque de survenue de valvulopathie, laquelle par ailleurs pourrait continuer à évoluer même après l'arrêt de benfluorex ;

Considérant d'une part que les données issues d'une publication récente*, citées par les Laboratoires SERVIER dans la lettre précitée du 23 novembre 2009, démontrent une relation temps-dépendant de l'évolution de la pathologie valvulaire sous fenfluramine ; D'autre part, concernant l'évolution d'une valvulopathie après arrêt du traitement de fenfluramine, la publication précitée montre qu'après un suivi moyen de 30 mois, l'insuffisance aortique liée à la prise de fenfluramine s'aggrave dans 15,2 % des cas, se stabilise dans 63,1 % des cas et s'améliore dans 21,7 % des cas ; De même, l'insuffisance mitrale s'aggrave dans 24,8 % des cas, se stabilise dans 47,4 % des cas et s'améliore dans 27,9 % des

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** Dahl CM. BMC Med 2008;6 (34) :1-13.*

Annexe 4-44

cas. Une chirurgie valvulaire a été réalisée pour 38 (0,66 % de 5743) et 25 patients (0,44 %) souffrant respectivement d'insuffisance aortique d'insuffisance mitrale liées à l'exposition à la fenfluramine ;

Considérant que les cas de pharmacovigilance de stabilisation ou de régression de valvulopathie sous benfluorex constituent des données insuffisantes en nombre de cas et en termes de durée de suivi pour pouvoir être prédictifs de l'évolution de l'ensemble des valvulopathies observées avec le benfluorex ; En juillet 2009, un tiers des cas identifiés a dû subir une chirurgie valvulaire ;

Considérant, compte tenu de ce qui précède, que l'ensemble des nouvelles données susmentionnées (notifications spontanées et sollicitées, étude cas-témoins de Brest, PMSI, REGULATE) conforte le signal d'un risque de valvulopathie associé à l'exposition au benfluorex et que ce profil de toiérance du produit est inacceptable dans l'indication thérapeutique telle que définie par l'AMM ;

Considérant que l'évaluation des effets thérapeutiques positifs de la spécialité concernée au regard des risques pour la santé du patient ou la santé publique liés à sa qualité, sa sécurité ou son efficacité n'est donc pas considérée comme favorable dans l'indication d'adjuvant du régime adapté chez les diabétiques avec surcharge pondérale. Plus précisément, en l'état des données disponibles telles que présentées ci-dessus, tant en ce qu'elles concernent l'efficacité que la sécurité, il apparaît qu'alors que le bénéfice thérapeutique n'est pas fermement établi, il existe un risque d'effets indésirables graves pour les patients ;

Considérant que la sortie de l'arsenal thérapeutique de la spécialité MEDIATOR 150 mg, comprimé enrobé n'est pas de nature à occasionner de perte de chance pour les patients ;

D E C I D E :

ARTICLE 1er
L'autorisation de mise sur le marché octroyée le 16 juillet 1974 à la spécialité pharmaceutique dénommée :

MEDIATOR 150 mg, comprimé enrobé,

dont le titulaire est :
Les Laboratoires SERVIER,

est suspendue sous toutes ses présentations à compter du 30 novembre 2009, dans l'attente de la décision de la Commission européenne prise en application de l'article 107de la directive 2001/83/CE précitée.

ARTICLE 2
Le titulaire doit prendre toutes dispositions, notamment auprès des détenteurs de stocks, en vue de faire cesser la délivrance au public de la spécialité.

ARTICLE 3
Conformément au 3ème alinéa de l'article L. 5124-11 du code de la santé publique, l'exportation de la spécialité est interdite à compter du 30 novembre 2009.

ARTICLE 4
Le Directeur de l'Evaluation des Médicaments et des Produits Biologiques et le Directeur de l'Inspection et des Etablissements sont chargés, chacun en ce qui le concerne, de l'exécution de la présente décision qui sera publiée par extrait au journal officiel de la République Française.

Fait à Saint-Denis, le

24 NOV. 2009

Le Directeur Général

Jean MARIMBERT

COMMISSION EUROPÉENNE

Bruxelles, le 14.6.2010
C(2010)4127

DÉCISION DE LA COMMISSION

du 14.6.2010

concernant, dans le cadre de l'article 107 de la directive 2001/83/CE du Parlement européen et du Conseil, les autorisations de mise sur le marché des médicaments à usage humain contenant la substance active «benfluorex»

DÉCISION DE LA COMMISSION

du 14.6.2010

concernant, dans le cadre de l'article 107 de la directive 2001/83/CE du Parlement européen et du Conseil, les autorisations de mise sur le marché des médicaments à usage humain contenant la substance active «benfluorex»

(Texte présentant de l'intérêt pour l'EEE)

LA COMMISSION EUROPÉENNE,

vu le traité sur le fonctionnement de l'Union européenne,

vu la directive 2001/83/CE du Parlement européen et du Conseil du 6 novembre 2001 instituant un code communautaire relatif aux médicaments à usage humain[1], et notamment son article 107,

vu l'avis de l'Agence européenne des médicaments, formulé le 18 mars 2010 par le comité des médicaments à usage humain, saisi le 2 décembre 2009,

considérant ce qui suit:

(1) Les médicaments à usage humain autorisés par les États membres doivent répondre aux exigences de la directive 2001/83/CE.

(2) À la suite de l'évaluation des données de pharmacovigilance concernant les médicaments à usage humain qui contiennent la substance active «benfluorex», la République française a informé l'agence, conformément à l'article 107, paragraphe 1, de la directive 2001/83/CE, que l'autorisation ou les autorisations de mise sur le marché devaient être suspendues.

(3) Le comité a préparé un avis, dont les conclusions figurent à l'annexe II de la présente décision, recommandant qu'une décision soit prise pour retirer les autorisations de mise sur le marché des médicaments concernés.

(4) Les mesures prévues par la présente décision sont conformes à l'avis du comité permanent des médicaments à usage humain,

[1] JO L 311 du 28.11.2001, p. 67.

A ADOPTÉ LA PRÉSENTE DÉCISION:

Article premier

Les États membres concernés retirent les autorisations nationales de mise sur le marché des médicaments visés à l'annexe I, sur la base des conclusions scientifiques et des motifs de retrait des autorisations de mise sur le marché figurant à l'annexe II.

Article 2

Les États membres sont destinataires de la présente décision.

Fait à Bruxelles, le 14.6.2010

Par la Commission
Paola TESTORI COGGI
Directeur général

ANNEXE I

LISTE REPRENANT LES NOMS DE FANTAISIE, LES FORMES PHARMACEUTIQUES, LE DOSAGE DES MÉDICAMENTS, LA VOIE D'ADMINISTRATION ET LES TITULAIRES DES AUTORISATIONS DE MISE SUR LE MARCHÉ DANS LES ÉTATS MEMBRES (EEE)

Etat membre	Titulaire de l'autorisation de mise sur le marché	Nom de fantaisie	Dosage	Forme Pharmaceutique	Voie d'administration
Chypre	Les Laboratoires Servier 22, rue Garnier F- 92200 Neuilly-sur-Seine France	Lipophoral Tablets 150mg	150mg	Comprimé	Voie orale
France	Les laboratoires Servier 22 rue Garnier F-92200 Neuilly-sur-Seine France	Mediator	150 mg	Comprimé	Voie orale
France	Mylan SAS 117 allée des Parcs 69800 Saint-Priest France	Benfluorex Mylan	150 mg	Comprimé	Voie orale
France	Qualimed 117 allée des Parcs 69800 Saint-Priest France	Benfluorex Qualimed	150 mg	Comprimé	Voie orale
Luxembourg	Les Laboratoires Servier 22, rue Garnier F- 92200 Neuilly-sur-Seine France	Mediator	150mg	Comprimé	Voie orale
Portugal	Servier Portugal - Especialidades Farmacêuticas, Lda. Av. António Augusto de Aguiar 128, 1069-133 Lisboa Portugal	Mediator	150 mg	Comprimé enrobé	Voie orale

ANNEXE II

CONCLUSIONS SCIENTIFIQUES ET MOTIFS DU RETRAIT DES AUTORISATIONS DE MISE SUR LE MARCHÉ PRÉSENTÉS PAR L'AGENCE EUROPÉENNE DES MÉDICAMENTS

CONCLUSIONS SCIENTIFIQUES

RÉSUMÉ GÉNÉRAL DE L'ÉVALUATION SCIENTIFIQUE DES MÉDICAMENTS CONTENANT DU BENFLUOREX (voir annexe I)

Le benfluorex est utilisé comme adjuvant dans la prise en charge du diabète de type 2 chez les patients en surcharge pondérale. L'indication thérapeutique actuellement autorisée en France est l'utilisation comme «*Traitement adjuvant du régime adapté chez les diabétiques avec surcharge pondérale*». Le benfluorex agit sur le métabolisme des hydrates de carbone. Chez l'animal, on a pu observer les effets suivants:
- facilitation de la précipitation et de l'utilisation du glucose dans les cellules (rat);
- réduction de l'hyperglycémie chez le rat diabétique (privé ou non d'insuline), diminution de l'hyperglycémie (mesurée par l'aire de test de tolérance au glucose) chez le lapin.
Le benfluorex n'a aucune action sur la sécrétion d'insuline.

Les médicaments à base de benfluorex sont autorisés dans quatre États membres de l'UE sous une formulation en comprimés, le produit n'ayant été commercialisé que dans deux pays (la France et le Portugal) jusqu'au retrait des autorisations de mise sur le marché en novembre 2009 (voir annexe I pour la liste des médicaments à base de benfluorex autorisés dans l'UE). À Chypre et au Luxembourg, les médicaments contenant du benfluorex n'étaient plus commercialisés.

Le 25 novembre 2009, l'autorité compétente française (Afssaps) a émis une alerte rapide informant les États membres, l'Agence européenne des médicaments et la Commission européenne, conformément à l'article 107 de la directive 2001/83/CE, telle que modifiée, de sa décision de suspendre les autorisations de mise sur le marché pour tous les médicaments contenant du benfluorex en France, en raison d'une augmentation du risque de signal de cardiotoxicité (maladies valvulaires cardiaques) avec le benfluorex.

La décision de l'autorité compétente française était fondée sur les résultats actualisés d'une étude de pharmacovigilance, les données préliminaires de 3 études cliniques (l'étude rétrospective cas-témoin réalisée dans un hôpital de Brest, l'essai REGULATE et les données du fonds national d'assurance maladie française) et d'une publication récente (K. Boutet *Fenfluramine-like cardiovascular side-effects of Benfluorex,* Eur. Respir. J. 2009; 33: 684-688), qui ont décelé un risque de maladies des valves cardiaques et d'hypertension pulmonaire (HTP) chez les patients traités par le benfluorex.

Après réception de l'avis d'alerte rapide, l'autorité compétente portugaise a également décidé de suspendre l'autorisation de mise sur le marché de tous les médicaments à base de benfluorex au Portugal, le 30 novembre 2009.

Le CHMP a examiné la question conformément à l'article 107, paragraphe 2, de la directive 2001/83/CE, telle que modifiée, dans le cadre d'une procédure écrite lors des réunions plénières du CHMP de décembre 2009 et de mars 2010.

Sécurité

Les résultats actualisés de l'étude de pharmacovigilance concernant le risque de maladies des valves cardiaques avec le benfluorex et les données d'une publication récente sur ce sujet (K. Boutet *Fenfluramine-like cardiovascular side-effects of Benfluorex,* Eur. Respir. J. 2009; 33: 684-688) ont amené à conclure à l'existence d'une valvulopathie cardiaque et d'HTP dans la population générale des patients utilisant le benfluorex.

De plus, l'étude rétrospective cas-témoin réalisée à Brest afin de chercher un lien entre l'exposition au benfluorex et la survenue d'unc insuffisance mitrale inexpliquée établit une association entre l'exposition au benfluorex et l'apparition d'une valvulopathie.

Sur la base des données susmentionnées, le CHMP considère que le lien entre l'exposition au benfluorex et la survenue de maladies des valves cardiaques est confirmé. Le comité est d'avis que le lien est étayé par les résultats obtenus dans l'étude REGULATE, qui confirme le risque de valvulopathie avec le benfluorex et révèle l'apparition d'anomalies morphologiques et fonctionnelles des valves après seulement 328 jours d'exposition en moyenne.

En outre, les résultats d'une autre étude (étude de cohorte menée par le Fonds national de l'assurance maladie française) ont fait l'objet de commentaires de la part du TAMM dans son document de réponse à la liste de questions adoptée par le comité. Le manque de précision des informations relatives au diagnostic de maladie des valves cardiaques et le nombre limité de patients identifiés comme présentant une maladie des valves cardiaques et traités par le benfluorex (35 patients) ont été soulignés par le TAMM. Le CHMP maintient cependant son avis que ces données confirment elles aussi le signal de sécurité indiquant un risque de maladie des valves cardiaques lors de l'utilisation du benfluorex.

Enfin, se fondant sur les sources de données disponibles, le CHMP estime que le nombre de rapports spontanés de valvulopathies cardiaques associées au benfluorex est considérablement sous-estimé en raison du volume limité de données recueillies à partir des rapports spontanés dans cette situation, comme par exemple:
- le type d'effet du benfluorex (valvulopathie qui reste cliniquement asymptomatique pendant une longue période);
- le temps écoulé avant la survenue de l'événement (une très longue période d'exposition au benfluorex est nécessaire pour induire des modifications valvulaires).

Par conséquent, le CHMP considère que l'aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne pouvait pas être exclue, en particulier au vu de l'utilisation prolongée du produit sur la base de données d'utilisation qui ont fait apparaître un temps d'exposition moyen de 3 ans.

Comme le déclare le TAMM dans sa réponse par écrit, au moment de l'évaluation nationale de l'anomalie valvulaire cardiaque, il a proposé de maintenir le benfluorex sur le marché avec une restriction pour l'indication chez les patients ne présentant pas de signes d'anomalies valvulaires à l'échographie et la mise en œuvre d'une surveillance échocardiographique. Le TAMM a prévu d'interrompre le traitement en cas d'anomalies échocardiographiques.

Le CHMP n'a pas accepté cette proposition. Il estime que la surveillance échocardiographique additionnelle proposée par le TAMM ne pourrait pas apporter de solution à ce problème, du fait que la surveillance échocardiographique évite l'utilisation chez des patients présentant une valvulopathie antérieure, mais n'en évite pas le développement chez des patients qui ne présentent pas d'anomalies antérieures.

Rapport bénéfice/risque

Le benfluorex est utilisé comme «*Traitement adjuvant du régime adapté chez les diabétiques avec surcharge pondérale*». Dans sa réponse par écrit, le TAMM considère qu'il y a un effet clinique significatif consistant sur le contrôle de la glycémie dans toutes les études réalisées avec le benfluorex chez des patients en surcharge pondérale présentant un diabète de type 2. Toutefois, le CHMP constate que le benfluorex est approuvé uniquement en tant que traitement adjuvant dans le traitement du diabète de type 2 chez les patients en surcharge pondérale: sur la base d'une importance très limitée de l'efficacité chez les patients diabétiques, il n'a jamais été accordé une indication en tant que monothérapie pour le traitement du diabète pour le benfluorex. En conséquence, le CHMP, après examen des données fournies par le TAMM et l'État membre, considère que le bénéfice du benfluorex n'est que limité dans la prise en charge du diabète de type 2.

Les résultats actualisés de la seconde étude nationale de pharmacovigilance, les données préliminaires de 3 études cliniques (l'étude rétrospective cas-témoin réalisée dans un hôpital de Brest, l'essai

REGULATE et les données de l'étude du Fonds national de l'assurance maladie française), ainsi que la publication récente de K. Boutet, démontrent le risque grave de valvulopathies cardiaques morphologiques et fonctionnelles et d'hypertension pulmonaire, associé à l'utilisation du benfluorex.

Le comité a noté que des anomalies valvulaires cardiaques morphologiques et fonctionnelles peuvent s'observer après seulement 328 jours d'exposition en moyenne. En outre, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée n'est pas exclue; cela suscite une inquiétude particulière étant donnée l'utilisation prolongée du produit, avec une durée d'exposition moyenne de 3 ans (sur la base des données d'utilisation).

Compte tenu de tous ces éléments, le CHMP a conclu que les médicaments à base de benfluorex sont nocifs dans les conditions normales d'utilisation et que le rapport bénéfice/risque pour benfluorex n'est pas considéré comme étant favorable. En conséquence, le comité a recommandé le retrait des autorisations de mise sur le marché pour les médicaments mentionnés dans l'annexe I.

MOTIFS DU RETRAIT DES AUTORISATIONS DE MISE SUR LE MARCHÉ

Considérant que

- le comité a pris en considération la procédure au titre de l'article 107 de la directive 2001/83/CE, telle que modifiée, pour les médicaments à base de benfluorex;

- le comité a conclu, après avoir examiné les données disponibles, que l'utilisation du benfluorex est nocive dans les conditions normales d'utilisation et conduit à une hypertension pulmonaire et à des valvulopathies cardiaques. Ces valvulopathies peuvent induire un affaiblissement progressif de la fonction cardiaque et des symptômes cliniques associés nécessitant, dans les cas graves, une chirurgie cardiaque;

- le comité a noté que des anomalies valvulaires cardiaques morphologiques et fonctionnelles peuvent s'observer après seulement 328 jours d'exposition en moyenne. En outre, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée n'est pas exclue, ce qui suscite une inquiétude particulière étant donné l'utilisation prolongée du produit, avec une durée d'exposition moyenne de trois ans (sur la base de données d'utilisation);

- le comité a examiné le rapport bénéfice-risque du benfluorex dans les conditions normales d'utilisation et a estimé que le risque prouvé susmentionné de maladie des valves cardiaques n'est pas acceptable, compte tenu du fait que le bénéfice du benfluorex n'est que limité dans le traitement du diabète de type 2;

- le comité, à la lumière des résultats ci-dessus, a conclu que le rapport bénéfice/risque des médicaments à base de benfluorex n'est pas favorable dans les conditions normales d'utilisation.

En application des dispositions de l'article 107, paragraphe 2, de la directive 2001/83/CE, telle que modifiée, le comité des médicaments à usage humain (CHMP) de l'Agence recommande le retrait des autorisations de mise sur le marché pour tous les médicaments à base de benfluorex énumérés dans l'annexe I.

Annexe 4-46

REUNION COMMISSION D'AMM N° 484 DU 1er JUILLET 2010

PROCEDURE NATIONALE

Spécialités concernées	
MEDIATOR 150 mg, comprimé enrobé	**Laboratoires Servier**
BENFLUOREX MYLAN 150 mg, comprimé enrobé	**Laboratoires Mylan**
BENFLUOREX QUALIMED 150 mg, comprimé enrobé	**Laboratoires Qualimed**

Principe actif: **benfluorex**

Caractère d'originalité **Décision de la Commission européenne en date du 14/06/10 de retrait des AMM nationales des spécialités composées de benfluorex – Article 107 de la Directive 2001/83 modifiée**

Classe ATC: **Autres antidiabétiques sauf insuline (Code ATC : A10BX06)**

CONTEXTE DE LA PRESENTATION en COM D'AMM du 12 novembre 2009

Le benfluorex a été une nouvelle fois présenté en Commission Nationale de Pharmacovigilance (CNPV) ; le signal relatif aux anomalies des valves cardiaques, soupçonné depuis plusieurs mois par les données de pharmacovigilance se trouvant confirmé par :

1. les données d'une étude cas /témoins brestoise rétrospective menée par le CHU de Brest.

2. les résultats d'une étude clinique (Etude REGULATE) dans laquelle en parallèle de l'analyse des données d'efficacité du benfluorex en association à un sulphonylurée (SU), une exploration de la tolérance cardiaque/impact du traitement sur les valves cardiaques a été menée.

Les données de l'étude cas /témoins, ainsi que les résultats préliminaires de l'étude REGULATE ont été présentés en CNPV le 09.09.09.

A l'issu de cette présentation, les membres de la CNPV ont considéré (25 voix pour et 1 abstention), que les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex, ceci malgré certaines limites méthodologiques soulevées pour l'étude Cas/témoins. De même, ils considèrent (25 voix pour et 1 abstention) que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

L'ensemble des données a été transmis à la Commission d'AMM du 23.10.09 afin qu'elle puisse se prononcer – au vu de l'ensemble des données de bénéfice et de risque dans les conditions d'utilisation actuelles du produit - sur la balance bénéfice- risque du produit.

En l'absence de quorum à l'instant du vote, la commission d'AMM du 23.10.09 n'a pu rendre d'avis. En conséquence, le dossier est réexaminé par la commission d'AMM du 12 novembre 09.

RESUME DES DONNEES DE BENEFICE

Historique de l'évaluation des données d'efficacité : de 2000 à 2009-10-13

- Date d'AMM : 16-07-1976 avec une indication en tant qu'hypolipidémiant

- 1995. Inscription sur la liste des substances interdites dans l'exécution et la délivrance des préparations magistrales en même temps que les anorexigènes. Le benfluorex n'est pas classé parmi les anorexigènes, mais lors de l'enquête sur les effets indésirables de ces produits et étant donné les restrictions de leur délivrance, le CTPV a craint une dérive de l'utilisation du benfluorex comme anorexigène.

- 1987: validation de la 1ère tranche dans l'indication « hypertriglycéridémies »

- 1990 : dépôt du dossier de la 8ème tranche de validation dans l'indication en « diabétologie » ; nombreux échanges entre l'Afssaps et la firme entre 1990 et 1995 sur la nature des données à soumettre afin de valider cette indication (type d'étude, population cible, etc.), aboutissant finalement en 1998 au dépôt de l'étude Del Prato (étude de l'efficacité du benfluorex versus placebo et metformine sur les paramètres glucidiques (voir ci-dessous données cliniques). En attente de cette étude, l'indication telle que libellée lors de l'octroi de l'AMM a été maintenue.

- Septembre 2000: demande d'extension d'indication au «*Diabète de type II insulino-dépendant, en association au régime adapté, lorsque ce régime n'est pas suffisamment suffisant pour rétablir à lui seul l'équilibre glycémique* ». Une seule étude de phase III **(Etude Del Prato)**, randomisée, en double insu, benfluorex versus placebo et metformine a été soumise à l'appui de cette demande (A noter, cette étude a été réalisée à la demande de l'Afssaps; protocole revu en concertation avec l'Afssaps). Un avis défavorable a été émis par le Groupe de Travail PTC2 ainsi que par la COM d'AMM. Après recours de la firme de cette décision, cet avis a été maintenu par la COM d'AMM. En effet, compte tenu des défauts de la qualité méthodologique de cet essai (ayant l'objet par ailleurs d'une inspection), aucune conclusion n'a pu être formulée sur la taille de l'effet: i) du benfluorex versus placebo; ii) du benfluorex versus metformine (non-infériorité non démontrée : déséquilibre des taux d'HbA1c entre les groupes à l'inclusion, 68% seulement inclus dans l'analyse per protocole, 25% de patients inclus à tort). A noter également, aucune efficacité sur les paramètres lipidiques n'a été mise en évidence dans cette étude. En conclusion, la COM d'AMM (20-09-2002) a demandé qu'une étude évaluant l'efficacité du benfluorex en monothérapie et en association avec d'autres antidiabétiques oraux soit effectuée; l'association devant être également étudiée chez les patients chez qui d'autres antidiabétiques oraux sont contre-indiqués ou mal tolérés (insuffisants rénaux, sujets âgés)

- 2007=> Réévaluation du rapport bénéfice Risque / Modification du code ATC

Conclusions de la réévaluation du bénéfice /risque demandé par la CNPV (AVIS DE LA COM d'AMM 419 DU 5 AVRIL 2007) (Extrait) faisant suite au Groupe de Travail DEUG N°6 du 21 10 2006 :

Après présentation et discussion des conclusions du Groupe de Travail DEUG sur les données d'efficacité et des conclusions de la CNPV sur les données de sécurité d'emploi, les conclusions suivantes ont été émises :

1. La COM d'AMM suit l'avis DEFAVORABLE émis par le Groupe DEUG au maintien de l'indication : « *Adjuvant au régime adapté dans les hypertriglycéridémies. L'efficacité pour la prévention primaire et secondaire des complications de l'athérosclérose n'est pas prouvée*», les données soumises ne montrant en effet qu'une efficacité très modeste et inconstante dans les études soumises sur les triglycérides et une absence d'efficacité sur les autres paramètres lipidiques tels que le LDL-cholestérol.

2. La Commission d'AMM suit également l'avis du Groupe DEUG pour le maintien de l'indication : « *Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale* » dans son libellé actuel. En l'attente de données plus complètes sur l'efficacité du benfluorex en association aux autres antidiabétiques oraux, la COM d'AMM n'a pas souhaité modifier le libellé actuel. A ce jour, seule l'étude MOULIN a permis de montrer une efficacité du benfluorex sur l'HbA1c en association à un sulfamide

L'étude Moulin (publiée dans Diabetes Care en 2006) est une étude multicentrique, internationale, randomisée en double aveugle, d'une durée de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par SU et intolérants ou ayant une contre indication à la metformine. Le critère principal était l'HbA1c ; les critères secondaires : insulinémie, glycémie à jeun, paramètres lipidiques, index d'insulino résistance HOMA. Trois sous-groupes ont été analysés : HbA1c > 8%, âge > 65 ans et clairance de la créatininémie < 80ml/mn. Etude de supériorité avec un différence de 06% entre les groupes sur l'HbA1c.

Résultats :

Après 18 semaines de traitement, les résultats d'efficacité sur les paramètres glucidiques de cette étude montrent que :

- l'HbA1c est diminuée de -0.82% dans le groupe benfluorex (versus baseline) et de 1% versus le groupe placebo. 34.2% et 19% arrivent à une HbA1c ≤ 7% et > 6.5% contre 11% et 5% respectivement sous placebo. Baisse de l'HbA1c significative dès la 4ème semaine ; d'après la firme, l'effet est du même ordre entre les trois sous groupes pré définis ;
- l'insulinorésistance s'améliore significativement sous benfluorex ; la glycémie à jeun baisse significativement dès la 4ème semaine sous benfluorex.

La perte de poids était de 1.3 kg sous benfluorex et de 0.7kg sous placebo

3. La COM d'AMM souhaite que les modifications d'ajout d'effets indésirables suivants tels que décidés par la CNPV soient mentionnées au sein de la rubrique 4.8. du RCP *: « troubles de fonctions cognitives: désorientation temporo-spatiale, troubles du comportement : agitation, délire, troubles de la perception (hallucinations) »* et de la rubrique correspondante de la Notice.

4. Une inspection de l'étude MOULIN, seule étude à ce jour ayant montré une efficacité sur les paramètres glucidiques a été proposée et acceptée par les membres de la COM d'AMM. Une saisine sera adressée en ce sens à la DIE (Direction de l'Inspection des Etablissements).

5. Enfin, les membres de la COM d'AMM souhaitent qu'une communication soit faite sur l'usage hors AMM de cette spécialité ainsi que sur la seule indication retenue après réévaluation des bénéfice/risque de cette spécialité.

Au total, le libellé de l'indication retenu est le suivant : «Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale ».

Code ATC

1) Avis Afssaps (Groupe DEUG du 13 09 2009

AVIS FAVORABLE à la modification du Code ATC ; le Code ATC retenu est le suivant : **DIVERS MEDICAMENTS DES VOIES DIGESTIVES ET DU METABOLISME/Code ATC A16X**

En effet, compte-tenu de la modification de l'indication avec suppression de l'indication : « *Adjuvant au régime adapté dans les hypertriglycéridémies. La poursuite du traitement est toujours nécessaire* », le code ATC actuel : HYPOCHOLESTEROLEMIANT ET HYPOTRIGLYCERIDEMIANT/Code ATC : C10AX04 n'est donc plus d'actualité.

Dans l'attente du reclassement du benfluorex selon la classification ATC par l'Organisation Mondiale de la Santé (OMS), sur proposition des laboratoires SERVIER auprès de l'OMS, le code ATC proposé par la firme soit : AUTRES MEDICAMENTS DU DIABETE/Code ATC : A10X n'est pas acceptable. En effet, selon les experts ce code ne peut être accepté compte tenu du fait que cette spécialité n'a pas à ce jour d'indication reconnue dans le diabète de type 2.

2) Code ATC octroyé par l'OMS => **Code ATC : A10X : AUTRES MEDICAMENTS DU DIABETE**

Année 2009 => Nouvelles données d'efficacité : Etude REGULATE

Analyse des données d'efficacité de l'Etude REGULATE

Titre de l'étude :

A one-year multicentre, international, randomised, doubleblind study with comparison of benfluorex (150 mg bid or 150 mg tid) *versus* pioglitazone (30 mg od or 45 mg od) in combination with sulfonylurea administered orally for the treatment of type 2 diabetes.

Méthodologie :

Il s'agit d'une multicentrique, randomisées, en double aveugle, contrôlée *versus* pioglitazone, d'une durée de 52 semaines, comparant chez 847 patients diabétiques de type 2, insuffisamment contrôlés par sulfamides hypoglycémiants (SU) l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR à la dose maximale recommandée (450 mg /jour, 1 comprimé pendant le repas), à un traitement par pioglitazone à la dose maximale recommandée (45 mg/jour, 1 comprimé au petit déjeuner)

Objectifs :

Le but de cette nouvelle étude était de comparer l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR versus un traitement par pioglitazone, en association à un SU, sur le contrôle glycémique et le profil lipidique.

L'objectif principal est de démontrer la non-infériorité de la combinaison SU + Benfluorex comparé à la combinaison SU + Pioglitazone sur l'évolution de l'HbA1c.

L'objectif secondaire est de démontrer la supériorité du benfluorex combiné aux SU comparativement à la Pioglitazone combiné aux SU sur le taux de cholestérol.

Les autres objectifs secondaires sont d'évaluer et de comparer ces combinaisons après 1 an de traitement sur : glycémie à jeun, l'insulinémie à jeun, le risque cardiovasculaire, la sécurité d'emploi et le coût de ces deux traitements.

Critères d'évaluation :

Critère principal : HbA1c mesuré à chaque visite (inclusion, 4, 8, 16, 28, 40 et 52 semaines)

Critères secondaires :

Paramètres lipidiques : LDL-cholestérol, cholestérol total, HDL-cholestérol, triglycérides à chaque visite.

Autres paramètres : glycémie à jeun (FPG), insulinémie à jeun (HOMA-IR), C-réactive protéine, mesure du tour de taille, poids.

Paramètres de sécurité d'emploi : événements indésirables, hypoglycémies, paramètres biologiques, examen cardiaque (ECG, échographie cardiaque à l'inclusion et à 12 mois)

Analyse statistique :

La borne de non-infériorité entre les deux traitements a été fixée à 0.4% d'HbA1c.

Résultats :

1. Caractéristiques de la population

Tableau 7 REGULATE Caractéristiques de la population randomisée

	benfluorex (n = 423)	pioglitazone (n = 423)
Âge (années)	59.6. ± 10.3	58.6 ± 10.6
>65 ans	30.5%	27.7%
Hommes	53.2%	56.5%
Caucasien/Asiatiques	75.4%/19.6%	77.3%/17.5%
Durée du diabète (années)	7.4 ± 6.0	6.7 ± 5.9
Indice de Masse Corporelle (kg/m²)	29.4 ± 4.0	29.7 ± 4.1
Présence d'un syndrome métabolique (%)	79.7	81.3
HTA (%)	59.8	59.8
Présence de complications		
Macrovasculaires(%)	11.8	8.5
Clearance créatinine<60mL /min(%)	8.5	5.7
Neuropathie (%)	8	5.7
Rétinopathie (%)	2.8	1.7
HbA1c (%)	8.3 ± 0.8	8.3 ± 0.8
>8%	57	56
Glycémie à jeun (mmol/L)	9.89±2.71	9.84 ± 2.52

2. Critère principal

A 52 semaines, la réduction de l'HbA1c est de -0.54% sous benfluorex versus -0.88% sous pioglitazone.

Change in HbA1c (%) from baseline to last post-baseline value in the FAS (N = 830)

HbA1c (%)		**Benfluorex (N= 413)**	**Pioglitazone (N = 417)**
Baseline	Mean ± SD	8.31 ± 0.82	8.33 ± 0.83
END	ean ± SD	7.77 ± 1.31	7.45 ± 1.30
Change (END-baseline)	Mean ± SD	-0.54 ± 1.12	-0.88 ± 1.24
Statistical analysis			
	E (SE) (1)	0.33 (0.08)	
	95% CI (2)	[0.17; 0.49]	
	p-value (3)	0.19	

END = last value; (1): Estimate (Standard Error) of the difference (benfluorex minus pioglitazone)between adjusted group means (2): 95% Confidence Interval of the estimate (3): For a non-inferiority one-sided test (alpha = 2.5%) obtained from an analysis of covariance with baseline and country (fixed effects) as covariates and a 0.4% margin of clinical relevance

Au total, **la non-infériorité de benfluorex par rapport à la pioglitazone n'a pas été démontrée** (limite supérieure de l'intervalle de confiance à 0.49 pour une limite de non infériorité fixée à 0.40 (E (SE) = 0,33 (0,08) %, 95 % CI = [0,17; 0,49], p = 0,19).

3. Critères secondaires

Tableau 8 -REGULATE Evolution des principaux paramètres biologiques dans la population FAS

	Benfluorex			Pioglitazone			différence entre les groupes
	N	valeur initiale moyenne (SD)	différence pré-post (SD)	n	valeur initiale moyenne (SD)	différence pré-post (SD)	Δ (ES) IC 95%
Glycémie à jeun mmol/L	392	*9.9 (± 2.71)*	-1.20 (0.15)	396	*9.9 (± 2..51)*	-1.73 (0.23)	**0.56**** (0.18) [0.21;0.90]
HOMA- IR Index	332	*6.36 (± 5.30)*	-1.23 (0.38)	315	*6.83 (±7.34°*	-2.52 (0.35)	1.04 (0.41) [0.23;1.85]
Total Cholestérol mmol/L	396	*5.01 (± 0.99)*	-0.16 (0.04)	396	*5.02 (± 0.92)*	0.08 (0.05)	**-0.25**** (0.057) [-0.357;-0.134]
LDL cholestérol mmol/L	396	*3.11 0.83)*	-0.24 (0.03)	396	*3.15 (0.81)*	-0.12 (0.04)	**-0.13**** (0.05) **[-0.22;-0.04]**
Triglycérides mmol/L	397	*1.92 (± 0.97)*	-0.14 (0.05)	397	*1.96 (± 0.90)*	-0.21 (0.05)	0.058 (0.06) [-0.07 ;0.18]

****p < 0.001 **p< 0.01 *p< 0.05 †test non paramétrique*

On observe :

- une diminution du LDL-cholestérol moyen (-0,24) dans le groupe benfluorex plus importante que celle observée dans le groupe pioglitazone (-0.12).

- une diminution du cholestérol total moyen (-0.16) dans le groupe benfluorex comparativement à une augmentation dans le groupe pioglitazone (+0.08)

- une stabilité du HDL-cholestérol (0.01) dans le groupe benfluorex et une légère augmentation sous pioglitazone (+0.06)

- une diminution des concentrations de triglycérides comparable dans les 2 groupes.

Enfin, il y a une diminution du poids sous benfluorex (-1.6 kg) et une augmentation sous pioglitazone (3.3 kg).

Sécurité

La fréquence des effets indésirables est comparable entre les deux groupes (63,7% dans le groupe benfluorex versus 62,9% dans le groupe pioglitazone). Les effets indésirables les plus fréquents sont les infections et infestations (24,9% versus 28,6%), les troubles gastro-digestifs (14,7% versus 11,8%), et les troubles musculosqueletiques (13,1% versus 15,6%).

Les effets indésirables émergents dans le groupe benfluorex sont les hypoglycémies (9% versus 13,2% dans le groupe pioglitazone) et les diarrhées (4.3% versus 1,9%).

Au niveau cardiaque, 2 patients du groupe benfluorex versus 3 dans le groupe pioglitazone ont fait un infarctus du myocarde, 0 versus 1 pour les angines de poitrine, 1 versus 0 pour l'insuffisance cardiaque congestive, 0 versus 1 pour l'ischémie, 0 versus 1 pour le syndrome coronarien aigu et 1 versus 0 pour la cardiomyopathie congestive.

Enfin, il y a eu deux décès dans le groupe benfluorex contre 4 dans le groupe pioglitazone, ces décès n'étant pas reliés aux traitements.

CONCLUSIONS PRELIMINAIRES DE LA FIRME :

En conclusion, chez des patients diabétiques de type 2 insuffisamment contrôlés par SU, l'ajout d'un traitement par benfluorex pendant 12 mois permet/entraîne une diminution statistiquement significative de l'HbA1c.

L'effet antidiabétique du benfluorex est confirmé dans cette étude (diminution de -0,54% de l'HbA1c), bien que la non infériorité du benfluorex versus la pioglitazone ne soit pas démontrée.

La supériorité du benflurorex versus la pioglitazone sur la diminution du LDL-cholestérol est démontrée.

De plus, le benfluorex diminue significativement le cholestérol total contrairement à la pioglitazone.

Les deux traitements diminuent significativement les taux de triglycérides, la glycémie à jeun et améliore l'insulinorésistance.

Après un an de traitement, le poids ainsi que le tour de taille ont augmenté sous pioglitazone mais pas sous benfluorex.

Le profil de sécurité d'emploi est en ligne avec ce qui figure déjà dans le RCP

En ce qui concerne le profil de sécurité cardiaque (échographies cardiaques), aucune modification de la fraction d'éjection du ventricule gauche (FEGP) n'a été détectée dans les deux groupes de traitement.

Des régurgitations des valves cardiaques ont été observées plus fréquemment sous benfluorex que sous pioglitazone, mais sans retentissement clinique délétère (significatif).

La différence morphologique en termes d'anomalies des valves cardiaques dont les régurgitations (au dessus d'un grade 1) ne sont pas significatives.

Les anomalies émergentes (nouvelles) des valves cardiaques dans cette étude n'étaient pas associées à des signes ou symptômes cliniques.

Des analyses complémentaires visant à expliciter les anomalies valvulaires observées sont en cours.

Antécédent/Terrain cardiaque (nombre)	15
Médicaments associés (nombre) *Levothyroxine* *Antidépresseur IRS*	 9 7

Type et localisation des valvulopathies :

Les 30 valvulopathie rapportées sont monovalvulaires dans 6 cas, bivalvulaires dans 16 cas et trivalvulaires dans 8 cas. Concernant la localisation de ces valvulopathies, 28 cas sont des insuffisances mitrales (sévères dans 17 cas), 24 cas sont des insuffisances aortiques et 11 cas sont des insuffisances tricuspides (sévères dans 4 cas).

Aspects anatomo-pathologiques des valvulopathies opérées

Des diagnostics anatomo-pathologiques sont effectués chez 6 patients opérés : 5 patients français et un cas espagnol rapporté dans une publication (Rafel Ribera J.).

a) 4 cas dont l'aspect anatomo-pathologique serait compatible avec celui décrit sous anorexigène :

TO060355 (Noize[1] 2006) : une femme de 48 ans, avec un BMI=25 kg/m^2, sous MEDIATOR® pendant 7 ans pour intolérance aux glucides.

BR20080051 (Boutet[2], cas n°6) : une femme de 50 ans ayant un diabète de type 2, avec un BMI=34 kg/m^2, sous MEDIATOR® de 2001 à 2007 et sous ISOMERIDE® pendant 1 à 3 mois 20 ans auparavant.

BR20090080 (Brest PMSI) : une femme de 54 ans, avec un BMI=30 kg/m^2, sous MEDIATOR® de septembre 2007 à décembre 2008, ayant pris des amphétamines 7 à 8 ans jusqu'en 1986.

S03000422 (R. Riber[3] J. 2003) : une femme de 50 ans, sous MEDIATOR® pendant 12 mois par intermittence.

b) Autres cas

Dans 2 cas, l'anatomopathologie n'est pas spécifique.

Dans les autres cas, seules les données échographiques sont disponibles.

Conclusions du rapporteur (CRPV de Besançon) :

Le CRPV de Besançon, rapporteur de cette enquête, a conclu à l'existence d'un signal de cardiotoxicité détecté par la notification spontanée et les données du PMSI. Il convient alors de confirmer ce signal par une étude épidémiologique (cas-témoin).

Le rapporteur souligne que la pharmacologie du benfluorex et de son métabolite, la nor-fenfluramine, devra être prise en compte dans l'analyse du mécanisme de la cardiotoxicité.

Compte tenu de ces nouvelles données de sécurité, le rapporteur propose une réévaluation du bénéfice/risque de benfluorex.

Présentation du Dr. Frachon (praticien, CHU de Brest):

Lors de cette réunion, le Docteur Frachon, du groupe HTAP de Bretagne Occidentale (CHU de Brest) a présenté la méthodologie appliquée à Brest pour l'identification des cas de valvulopathies associées au benfluorex.

L'identification des cas de valvulopathies a reposé sur :

i) le signalement spontané de 4 cas par des médecins brestois,
ii) l'interrogation du PMSI en utilisant le codage « valvulopathies et diabète » qui a mis en évidence 240 dossiers dont 3 cas compatibles et le codage « valvulopathies et Médiator® » qui a rapporté 23 dossiers dont 11 compatibles,
iii) une surveillance prospective avec 3 nouveaux cas.

Sur les 15 patients identifiés « compatibles » (dont 11 rapportés par le CRPV de Besançon et 4 très récents à l'étude), 12 étaient des femmes et 3 des hommes. L'âge moyen est de 58 ans (49-78). 6 patients sur 12 étaient diabétiques. La durée moyenne d'exposition est de 53 mois (12-144) avec un délai entre la première prise du médicament et le diagnostic de 97 mois (13-384). L'échographie cardiaque antérieure est normale dans 5 cas sur 7. L'exposition à d'autres anorexigènes concerne 5 patients sur 12, et à un antidépresseur de type inhibiteur de recapture de la sérotonine (IRSI) concerne 8 patients sur 10.
Les valves atteintes sont la valve mitrale et la valve aortique dans 100% des cas, avec une atteinte de la valve tricuspide dans 7 cas et de la valve pulmonaire dans un cas. Une chirurgie de remplacement valvulaire a été effectuée dans 8 cas.

Une analyse systématique de toutes les insuffisances mitrales (IM), isolées ou associées, examinées au CHU de Brest depuis 2003, est actuellement en cours. Plus de 600 dossiers d'IM sont classés en 3 groupes: 1) IM dans un contexte étiologique bien identifié 2) IM inexpliquées 3) IM non classables.
Une recherche de l'exposition au benfluorex sur un modèle de cas témoins est réalisée pour les cas identifiés par le PMSI et par une enquête téléphonique auprès du médecin et du patient.

Les résultats de cette étude sont attendus pour fin juillet 2009.

Présentation du laboratoire :

A l'issu de la présentation des données, les représentants des laboratoires Servier ont proposé deux modèles d'études :

i) une étude anatomopathologique sur un modèle exposé/non-exposé (ce modèle d'étude a été récusé par la commission),

ii) une étude cas-témoin ayant pour objectif de quantifier un éventuel sur-risque de valvulopathie associé au MEDIATOR® chez des patients atteints de valvulopathie idiopathique comparativement à des patients indemnes de valvulopathie. Cette étude se ferait sur une population de patients diabétiques ayant une échographie cardiaque.

Le protocole de cette étude serait disponible début Septembre2009 et permettrait dans le meilleur des cas d'avoir des résultats dans un an.

Par ailleurs, la firme a informé la CNPV que l'étude REGULATE, (MEDIATOR® + SU versus pioglitazone + SU) est actuellement en cours d'analyse. Cette étude incluant 840 patients dont 420 dans chaque bras, comporte une échographie cardiaque à T0 et à la 52ème semaine de traitement. Les résultats d'efficacité et de tolérance sont attendus pour la fin du 1er trimestre 2010.

Conclusions de la CNPV du 07 07 2009

Le responsable du CRPV de Brest, présent à la réunion de la CNPV, a informé les membres que les résultats de l'étude brestoise cas-témoin seront disponibles fin Juillet 2009. Les membres de la commission nationale avaient alors souhaité disposer des résultats de l'étude cas-témoin brestoise afin de se prononcer sur les mesures éventuelles à entreprendre.

Les membres de la CNPV ont également discuté de l'importance des utilisations hors AMM de ce produit, notamment dans la perte de poids, malgré la restriction d'indication.

La commission s'est prononcée en faveur (16 voix pour, 2 voix contre et 2 abstentions) de l'attente des résultats de l'ensemble des études en cours ou planifiées (laboratoires Servier et CRPV de Brest) avant de proposer d'éventuelles mesures.

Elle a toutefois souhaité qu'une communication soit effectuée auprès des professionnels de santé pour leur rappeler le bon usage du Benfluorex dans le cadre de l'AMM.

• CNPV du 29 septembre

=> Actualisation des données relatives aux valvulopathies présentées en CNPV du 07.07 2009 :

1- *Données de la pharmacovigilance :*

Une mise à jour des données de pharmacovigilance a été effectuée par le CRPV de Besançon. 11 nouveaux cas de valvulopathie associés au benfluorex sont rapportés dont 3 issus de la notification spontanée et 8 de des notifications sollicitées et provenant d'Amiens. L'analyse de ces 11 nouveaux cas montre une prédominance féminine, une durée moyenne de traitement de 3 ans et un âge de survenue le plus fréquemment identifié de 55 ans. Dans 9/11 cas une association à une hypertension artérielle pulmonaire est rapportée, une atteinte de type insuffisance mitrale et aortique dans 6 cas et une atteinte mitrale+aortique+tricuspide dans 2 cas. Malgré des échocardiographies documentées, les données anatomopathologiques restent peu informatives.

Certains membres ont souligné qu'en cas de notification sollicitée dans d'autres bassins de population, de nombreux autres cas de valvulopathie associés au benfluorex pourraient être mis en évidence.

2- Données de l'étude Brestoise :

L'étude cas-témoin rétrospective menée par le CHU de Brest, a pour objectif la recherche d'une association entre l'exposition au benfluorex et la survenue de cas d'insuffisance mitrale (IM) inexpliquée. La population source est constituée de tous les patients hospitalisés entre 2003 et 2009 dans le département de cardiologie ou le service de chirurgie cardiaque au CHU de Brest, et ayant un diagnostic d'IM. Les patients ayant une IM inexpliquée constituent les cas (n=27) et les patients ayant une IM expliquée constituent les témoins (n=54). Deux témoins ont été appariés à chaque cas sur les critères d'âge et de genre. L'appariement ne concernait le diagnostic de diabète ou l'Index de Masse Corporelle (IMC). L'exposition au benfluorex est recherchée auprès du patient, de sa famille et de ses médecins, par téléphone, sur la base d'un questionnaire semi-structuré et à l'aveugle du statut cas ou témoin.

Sur les 27 cas, 19 avaient été exposés au benfluorex contre 3 témoins sur 54 ($p<0.001$ soit un odds-ratio = 40,4 (9,7 – 168,3, IC à 95%)). L'ajustement à différentes variables telles que le poids, le diabète ou l'exposition à la dexfenfluramine, ne modifie pas la significativité du résultat.

3- Données de l'étude « REGULATE » :

Les résultats préliminaires de l'étude REGULATE ont été présentés par le laboratoire Servier. Il s'agit d'une étude multicentrique, en double aveugle, comparant pendant 52 semaines chez 840 diabétiques l'efficacité et la sécurité de 2 traitements, benfluorex et SU versus pioglitazone et sulphonylurée (SU). Deux échographies cardiaques ont été réalisées : avant exposition (T0) et à la 52ème semaine. La non-infériorité de l'association benfluorex + SU par rapport à l'association pioglitazone + SU sur la réduction de l'hémoglobine glycosylée n'a pas été démontrée. L'effet a été plus important sur la baisse du LDL-cholestérol

Concernant le profil de tolérance, cette étude a mis en évidence dans le groupe traité par benfluorex, l'émergence d'anomalies valvulaires fonctionnelles statistiquement significatives (26,5% versus 10,9% respectivement, $p<0,0001$) ainsi que des anomalies valvulaires morphologiques non statistiquement significatives (2,6% versus 1,3% respectivement, $p=0,264$). Il est à souligner que les anomalies fonctionnelles apparues sous benfluorex n'ont pas de traduction clinique.

A l'issue de cette présentation, le laboratoire Servier a proposé des modifications du Résumé des Caractéristiques du Produit de Médiator®:

- rubrique 4.2 « Indication » : *Restriction aux diabétiques en échec de traitement après les anti-diabétiques oraux*

- conditions de prescription et de délivrance : *Prescription réservée aux spécialistes tels que diabétologues/endocrinologues.*

- *contre-indication aux patients présentant une anomalie valvulaire*

- *mise en place d'une surveillance échocardiographique.*

=> Discussion :

Les résultats de l'étude cas-témoin de Brest ont été largement débattus par les experts de l'Afssaps, les membres de la commission, les investigateurs et le laboratoire.

Les experts ont déploré ne pas disposer du protocole de l'étude. Plusieurs biais ont cependant été identifiés:

- le choix des témoins : si la question posée est de savoir si le benfluorex peut ou non être responsable de valvulopathies, les témoins ne devraient alors pas présenter de valvulopathie,
- le choix des valvulopathies inexpliquées : il est difficile d'être absolument sûr que le diagnostic ne soit pas biaisé,
- les cas et les témoins ont des caractéristiques très différentes. Une confusion par indication (lien entre caractéristiques des patients témoins et l'absence de traitement par benfluorex) ne peut être exclue. Les témoins ont très peu de chance d'être exposés au benfluorex,
- le faible nombre de patients exposés,
- le choix de l'anomalie valvulaire (limité à la valve mitrale).

Toutefois, malgré certaines limites méthodologiques de cette l'étude, les experts et les membres de la commission considèrent que le signal d'une relation entre l'exposition au benfluorex et la survenue de valvulopathies se confirme. Ce signal est d'autant plus préoccupant que l'étude « REGULATE » met en évidence une émergence d'anomalies morphologiques et fonctionnelles valvulaires à la suite d'une exposition d'environ un an au benfluorex (328 jours en moyenne). De plus, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne peut être exclue, notamment en raison des données d'utilisation du produit qui montrent une durée moyenne d'exposition d'environ 3 ans.

=> Conclusions de la CNPV du 29 septembre 2009 :

Les membres de la CNPV considèrent (25 voix pour et 1 abstention), que les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex, et ce malgré certaines limites méthodologiques. De même, ils considèrent (25 voix pour et 1 abstention) que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

Il est à noter que le dépôt par le laboratoire du protocole de l'étude cas-témoin, prévu initialement pour début septembre 2009 n'a pas encore été effectué.

La CNPV a été informée de la transmission de ces données à la Commission d'AMM au plus tard le 23 octobre 2009, afin qu'elle puisse se prononcer sur la balance bénéfice- risque du produit.

Rappel des données présentées au cours de la Commission du 23 octobre:

Présentation des données d'efficacité du benfluorex

Un résumé/Rappel des principales données d'efficacité du benfluorex a été effectué par le Docteur Catherine Rey-Quinio (Unité PTC2, DEMEB).

Les données d'efficacité soumises comportaient notamment les études suivantes :

- l'étude Del Prato (1997), déjà examinée dans le cadre de la validation de l'indication comme adjuvant du régime adapté chez les diabétiques avec surcharge pondérale en 1999. Il s'agissait d'une étude multicentrique, randomisée, en double aveugle de 6 mois qui évaluait l'efficacité et la sécurité d'emploi de benfluorex versus placebo et versus metformine, chez 438 patients diabétiques de type 2 non équilibrés par régime seul. Suite aux réserves méthodologiques relevées dans cette étude, seuls les résultats du bras benfluorex versus placebo avaient été retenus. Une diminution de -0,86% de l'HbA1c était observée dans le bras benfluorex versus placebo ; aucune conclusion définitive sur la taille de l'effet ne pouvant être cependant formulée compte tenu des réserves méthodologiques constatées dans cet essai.

- l'étude Moulin (2006), déjà examinée par la Commission d'AMM en 2007. Il s'agissait d'une étude multicentrique, internationale, randomisée en double aveugle, d'une durée de 18 semaines évaluant l'efficacité et la sécurité d'emploi de 450 mg/jour de benfluorex versus placebo chez 325 patients diabétiques de type 2 mal contrôlés par un traitement par sulphonylurées (SU) et intolérants ou ayant une contre indication à la metformine. L'efficacité du benfluorex en association aux sulphonylurées semblait démontrée (HbA1c diminuée de -0.82% dans le groupe benfluorex (versus baseline) et de -1% versus le groupe placebo). Néanmoins, des réserves méthodologiques ayant été soulevées par les experts, une étude d'efficacité clinique complémentaire versus un comparateur actif en seconde intention avait été demandée afin de conforter les résultats obtenus sur l'HbA1c.

- l'étude Regulate (2009), dont seuls les résultats préliminaires ont été fournis, a été examinée en groupe DEUG le 22 octobre 2009. Il s'agit d'une étude multicentrique, randomisée, en double aveugle, contrôlée *versus* pioglitazone, d'une durée de 52 semaines, comparant chez 847 patients diabétiques de type 2 insuffisamment contrôlés par SU, l'efficacité et la sécurité d'emploi d'un traitement par MEDIATOR à la dose maximale recommandée (450 mg /jour, 1 comprimé pendant le repas), à un traitement par pioglitazone à la dose maximale recommandée (45 mg/jour, 1 comprimé au petit déjeuner). Cette étude de non-infériorité n'a pas permis de démontrer la non infériorité sur l'HbA1c (critère principal de jugement) du benfluorex par rapport à la pioglitazone (limite supérieure de l'intervalle de confiance à 0.49 pour une limite de non infériorité fixée à 0.40 (différence entre les deux traitements = 0,33 (0,08) %, intervalle de confiance à 98% = [0,17; **0,49**], p = 0,19). La diminution de l'HbA1c a été de -0.54% sous benfluorex versus -0.88% sous pioglitazone.

Présentation des données de sécurité d'emploi du benfluorex examinées au cours des CNPV du 07 juillet et du 29 septembre 2009

Au niveau sécurité d'emploi, un rappel des données concernant les valvulopathies, examinées au cours des CNPV du 07 juillet et du 29 septembre 2009, a été présenté par le Docteur Carmen Kreft Jais (département de pharmacovigilance), ainsi que par l'équipe du CHU de Brest ayant réalisé l'étude cas / témoins :

Depuis 1995, le benfluorex a fait l'objet de plusieurs mises au point des effets indésirables, ainsi que de deux enquêtes de pharmacovigilance, l'une en 1999 sur les troubles neuro-psychiques et la deuxième en 2004 du fait de la notification d'effets de type amphétaminiques. Cette enquête a été étendue en 2005 aux hypertensions artérielles pulmonaires (HTAP), puis aux valvulopathies. La notification par les CRPV de cas de valvulopathies cardiaques sous benfluorex et la publication de Boutet en 2009 (Fenfluramine-like cardiovascular side-effects of benfluorex. Eur Respir J 20098 :33 :684-688. Boutet K) rapportant 5 cas d'HTAP et un cas de valvulopathie cardiaque associé, après exposition au benfluorex ont conduit à une actualisation des données de PV, successivement pour la CNPV du 7 juillet 09 et celle du 29 septembre 09.

CNPV DU 7 JUILLET 2009

Entre 1998 et juillet 2009, en France, 30 cas de valvulopathies cardiaques ont été rapportés :

- 19 cas issus de la notification spontanée (NS) dont 3 cas concernaient également des HTAP post-capillaires

- 11 cas identifiés par le CRPV de Brest à la suite de l'interrogation du PMSI (Programme de médicalisation des systèmes d'information).

Les 30 valvulopathies rapportées étaient monovalvulaires dans 6 cas, bivalvulaires dans 16 cas et trivalvulaires dans 8 cas. Concernant la localisation de ces valvulopathies, 28 cas étaient des insuffisances mitrales (grade 2-3 dans 17 cas), 24 cas étaient des insuffisances aortiques (grade 1-2 dans 17 cas) et 11 cas étaient des insuffisances tricuspides (sévères, de grade 3 dans 4 cas).

L'évolution de ces atteintes a été marquée par une chirurgie valvulaire dans 10 cas (+ 2 prévues), une stabilité dans 4 cas, une stabilité sous traitement dans 5 cas. Elle est inconnue dans 4 cas et en cours dans 5.

Parmi les valvulopathies opérées, 4 cas dont 2 ont fait l'objet d'une publication avaient un aspect anatomo-pathologique des valves compatible avec celui décrit sous anorexigène. Dans les 2 autres cas opérés, l'anatomopathologie n'était pas spécifique.

Pour mémoire, la cardio-toxicité des anorexigènes a une plausibilité biologique : la stimulation des récepteurs 5-HT2B, exprimés au niveau des valves cardiaques peut induire une mitogénèse fibroblastique. Or le benfluorex est métabolisé en deux produits dont le N-benzoyloxy-2-ethyl-norfenfluramine.

La conclusion de la CNPV de juillet 2009 a été i) qu'il existe un signal de cardiotoxicité (atteinte valvulaire) détecté par l'analyse de la notification spontanée et des données issues du PMSI du CHU de Brest, ii) qu'il est nécessaire de confirmer ce signal par une étude cas-témoins, iii) que la pharmacologie du benfluorex et de son métabolite la nor-fenfluramine doit être pris en considération dans l'analyse du mécanisme de la cardio-toxicité et iv) qu'une nouvelle réévaluation de la balance Bénéfice/Risque est à envisager, compte-tenu des nouvelles données de sécurité d'emploi.

CNPV DU 29 SEPTEMBRE 09

Une mise à jour des données de pharmacovigilance a été effectuée par le CRPV de Besançon entre juillet et septembre 09. Onze nouveaux cas de valvulopathie ont été rapportés dont 3 issus de la notification spontanée et 8 des notifications sollicitées provenant d'Amiens.

L'analyse de ces 11 nouveaux cas montre :

- une prédominance féminine,
- une durée moyenne de traitement de 3 ans
- un âge moyenne de survenue de 55 ans
- une association à une hypertension artérielle pulmonaire dans 9/11 cas rapportés
- une atteinte de type insuffisance mitrale, isolée ou associée à une insuffisance aortique et/ou tricuspide.

Les résultats des échocardiographies sont documentés, mais les données anatomopathologiques restent peu informatives. Il a été souligné qu'en cas de notification sollicitée dans d'autres bassins de population, de nombreux autres cas de valvulopathie associés au benfluorex pourraient être mis en évidence.

Le Docteur Frachon, du groupe HTAP de Bretagne Occidentale (CHU de Brest) a présenté la méthodologie de l'étude cas-témoin appliquée à Brest pour l'identification des cas de valvulopathies associées au benfluorex. Cette méthodologie repose sur l'interrogation du PMSI en utilisant les codages « valvulopathies et diabète » et le codage « valvulopathies et Médiator ».

L'équipe du CHU de Brest a présenté son étude cas-témoins, rétrospective, analysant toutes les insuffisances mitrales (IM), isolées ou associées, examinées au CHU de Brest depuis 2003. L'objectif est la recherche d'une association entre l'exposition au benfluorex et la survenue de cas d'insuffisance mitrale (IM) inexpliquée. La population source est constituée de tous les patients hospitalisés entre 2003 et 2009 dans le département de cardiologie ou le service de chirurgie cardiaque au CHU de Brest, et ayant un diagnostic d'IM. Les patients ayant une IM inexpliquée constituent les cas (n=27) et les patients ayant une IM expliquée constituent les témoins (n=54). Deux témoins ont été appariés à chaque cas sur les critères d'âge et de genre. L'appariement ne concernait pas le diagnostic de diabète ni l'Index de Masse Corporelle (IMC). L'exposition au benfluorex a été recherchée auprès du patient, de sa famille et de ses médecins, sur la base d'un questionnaire semi-structuré et à l'aveugle du statut cas ou témoin.

Sur les 27 cas identifiés, 19 avaient été exposés au benfluorex contre 3 témoins sur 54 ($p<0.001$ soit un odds-ratio = 40,4 (9,7 – 168,3, IC à 95%).

L'ajustement à différentes variables telles que le poids, le diabète ou l'exposition à la dexfenfluramine, ne modifie pas le signal.

Malgré certaines limites méthodologiques, les experts et les membres de la commission ont considéré que le signal de risque entre l'exposition au benfluorex et la survenue de valvulopathies était conforté.

Les résultats préliminaires de l'étude REGULATE ont été présentés par les laboratoires Servier lors de la CNPV du 29 septembre 09.

Concernant le profil de tolérance cardio-vasculaire, 614 patients, 309 dans le groupe benfluorex et 305 dans le groupe pioglitazone ont eu une échocardiographie à l'inclusion et à 52 semaines, après une exposition aux traitements d'une durée moyenne de 328 jours.

Cette étude a mis en évidence dans le groupe traité par benfluorex versus le groupe pioglitazone :

- l'émergence d'anomalies valvulaires fonctionnelles statistiquement significatives, 26,5% versus 10,9%, (p<0,0001),

- des anomalies valvulaires morphologiques non statistiquement significatives (2,6% versus 1,3% respectivement, p=0,264).

Il est à noter que i) la durée d'exposition moyenne au benfluorex est de 328 jours, ii) les anomalies émergentes fonctionnelles sont triviales, sans traduction clinique et iii) la lecture des échocardiographies s'est faite par couple mais avec connaissance des dates des échographies.

En dépit des certains limites méthodologiques de l'étude cas-témoin de Brest, les experts et les membres de la commission de PV ont considéré que le signal d'une association entre l'exposition au benfluorex et la survenue de valvulopathies se confirmait. Ce signal était considéré d'autant plus préoccupant que l'étude REGULATE mettait en évidence une émergence d'anomalies morphologiques et fonctionnelles valvulaires à la suite d'une exposition moyenne de seulement 328 jours. De plus, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne peut être exclue, notamment en raison des données d'utilisation du produit qui montrent une durée moyenne d'exposition d'environ 3 ans.

Les conclusions de la CNPV du 29 septembre 09 ont été que: les nouvelles données présentées confortent le signal d'un risque de valvulopathie associé à l'exposition au benfluorex. De même, ils ont considéré que le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, était inacceptable. En conséquence, les membres de la Commission Nationale de PV ont proposé un passage devant la Commission d'AMM afin que soit discutée une réévaluation de la balance Bénéfice/Risque des spécialités à base de benfluorex.

Audition de la firme

La firme (Servier) a été auditionnée au cours de la Commission d'AMM. Deux experts mandatés, M. Iung et M. Guillausseau, se sont exprimés sur respectivement l'analyse des anomalies valvulaires cardiaques et sur l'efficacité métabolique du benfluorex dans le diabète de type 2.

Selon l'expertise de M. Iung, parmi les 45 cas de valvulopathies notifiés (19 notifications spontanés, 16 notifications du CRPV de Brest, 10 notifications du CRPV d'Amiens), l'imputabilité d'une valvulopathie au benfluorex est forte pour 6 cas, possible dans 16 cas, la principale alternative étant une valvulopathie rhumatismale. L'imputabilité est faible dans 16 cas où la présence de regurgitations valvulaires est difficile à interpréter en l'absence de tout détail concernant l'anatomie valvulaire. Enfin, l'imputabilité est très faible dans 7 cas pour lesquels une autre étiologie paraît plus probable.

M. Guillausseau, diabétologue, a présenté un résumé des données d'efficacité de Mediator.

Au vu des données d'efficacité et de sécurité d'emploi du benfluorex exposées, des propositions de modifications de RCP de MEDIATOR ont été proposées par la firme afin de prendre en compte ce risque de valvulopathies.

- modification du libellé de l'indication (rubrique 4.1): *« Adjuvant du régime adapté chez les diabétiques avec surcharge pondérale, intolérants à la metformine et insuffisamment contrôlés par un insulinosécréteur sulfamidé ou non. »*

- restriction de l'indication aux spécialistes (rubrique 4.1) : *«Le traitement doit être instauré par un médecin spécialiste en diabétologie, en endocrinologie ou en médecine interne. »*

- ajout d'une contre-indication (rubrique 4.3) : *« Anomalie valvulaire à l'échographie »*

- ajout de mises en gardes spéciales et précautions d'emploi (rubrique 4.4) : *« Des valvulopathies aortique ou mitrale ont été observées lors d'un traitement par benfluorex.*

Pendant le traitement : Une échographie devra être réalisée environ 6 mois après l'instauration du traitement. Un suivi échographique doit être effectué régulièrement. Le traitement par benfluorex

Avant de débuter le traitement : Une échographie doit être réalisée, afin de détecter une éventuelle valvulopathie asymptomatique. Si une atteinte valvulaire est diagnostiquée, le traitement par benfluorex est contre-indiqué (voir rubrique 4.3) devra *être arrêté en cas d'anomalie valvulaire cardiaque (voir rubrique 4.3).*

- ajout d'effets indésirables (rubrique 4.8) : *« Valvulopathie cardiaque (fréquence inconnue) »*

Au cours de la commission d'AMM, il a été rappelé entre autres que:

- le benfluorex ne fait pas partie des recommandations françaises et internationales de la prise en charge du diabète de type 2 car il est considéré uniquement comme un adjuvant du régime adapté chez les diabétiques avec surcharge pondérale.

- le benfluorex est essentiellement prescrit par des médecins généralistes (88%), bien souvent hors AMM, chez des patients obèses non diabétiques mais également chez des patients présentant une dyslipidémie. Pour rappel, l'indication « Adjuvant du régime adapté dans les hypertriglycéridémies » a été retirée en 2007 pour insuffisance de données d'efficacité dans cette indication.

- la grande majorité des patients diabétiques présentent des valvulopathies.

Au vu des questions soulevées par l'ensemble de ces résultats, il est demandé à la Commission d'AMM du 12 novembre 2009 de se positionner sur le bénéfice/risque des spécialités dont la substance active est le benfluorex.

AVIS DE LA COMMISSION D'AMM du 12 novembre 2009 :

Le dossier benfluorex a été examiné lors de la commission d'AMM du 23 octobre 2009. La Commission devait se prononcer – au vu de l'ensemble des données de bénéfice et de risque dans les conditions d'utilisation actuelles - sur la balance bénéfice- risque du benfluorex.
En l'absence de quorum à l'instant du vote, la commission d'AMM n'avait pu rendre d'avis. En conséquence, le dossier a été réexaminé par la commission d'AMM du 12 novembre.
Un rappel des données d'efficacité et de sécurité d'emploi du benfluorex déjà examinées lors de la précédente commission d'AMM a été effectué par les docteurs Catherine Rey-Quinio et Carmen Kreft-Jaïs respectivement.

D'autre part, depuis la dernière Commission, les résultats préliminaires d'une nouvelle étude effectuée par la CNAM (Caisse Nationale d'Assurance Maladie) sur le benfluorex ont été transmis à l'Afssaps ainsi qu' à la Direction Générale de la Santé. Les résultats préliminaires de cette étude ont été examinés et présentés par un méthodologiste, M. Lièvre, au cours de la Commission d'AMM :
Il s'agit d'une étude de cohorte de type exposé-non exposé à partir des données du système national inter-régime de l'assurance maladie (SNIIRAM). Etaient éligibles les patients diabétiques traités (antidiabétiques oraux et/ou insuline) en 2006 et âgés de 40 à 69 ans. Les cas exposés étaient enregistrés de façon passive et définis par la délivrance et le remboursement en 2006 de benfluorex. Après chaînage des données, les évènements recherchés au cours de l'année n+1 et n+2 dans le PMSI 2007 et 2008 étaient une hospitalisation pour une insuffisance valvulaire toutes causes confondues, une hospitalisation pour une insuffisance mitrale et chirurgie de remplacement valvulaire sous circulation extracorporelle pour une insuffisance valvulaire toutes causes confondues.

Les résultats ont porté sur 1 092 858 diabétiques dont 43 208 exposés au benfluorex en 2006. Le risque d'hospitalisation en 2007 pour insuffisance valvulaire cardiaque était de 81 pour 100 000 dans le groupe exposé versus 29 pour 100 000 dans le groupe non exposé (RR=2,77 IC 95[1,95 ; 3,93]).. Le risque d'hospitalisation pour insuffisance mitrale est de 53 pour 100 000 dans le groupe exposé versus 20 pour 100 000 dans le groupe non exposé RR=2,66 IC 95[1,7 ; 4,1]. Le risque de chirurgie en 2007 avec un remplacement valvulaire sous circulation extracorporelle (CEC) pour une insuffisance valvulaire toutes causes confondues était de 30 pour 100 000 dans le groupe exposé au benfluorex versus 9 pour 100 000 dans le groupe non exposé (RR=3,4 [1,9 ; 6,1]). Parmi les 13 personnes diabétiques exposées et ayant subi un remplacement valvulaire sous CEC en 2007, une était décédée en milieu d'année 2008. Pour les exposés au benfluorex en 2006, les risques absolus et les risques relatifs étaient en 2008 très proches de ceux observés en 2007. Pour les exposés au benfluorex ; le risque relatif de chirurgie valvulaire sous CEC était identique (3,4) pour 2007 et 2008..
Si l'étude présente certaines limites, notamment le manque de détails de l'analyse et de ses ajustements, ces résultats confortent le signal de pharmacovigilance, de risque de valvulopathies chez les diabétiques traités par benfluorex. En effet, les résultats montrent que l'usage du benfluorex chez les diabétiques âgés de 49 à 59 ans est associé significativement dans les deux années qui suivent l'exposition, à des valvulopathies de régurgitation mitrales, aortiques et tricuspidiennes et à des chirurgies de remplacement valvulaire sous circulation extracorporelle pour des valvulopathies de régurgitation.

La firme a été auditionnée au cours de la Commission d'AMM. Un rapport complémentaire du Pr B. Bauduceau sur l'efficacité métabolique du benfluorex dans le diabète de type 2 a été fourni.
La firme n'a pas contesté les résultats de l'étude de la CNAM, mais a émis quelques réserves méthodologiques.
Elle a proposé une modification supplémentaire du RCP par rapport à la version proposée lors de la Commission d'AMM du 23 octobre 09 : Ajout d' une surveillance échographique en rubrique 4.2 : « En association à un régime adapté, MEDIATOR constitue un traitement adjuvant : une surveillance régulière clinique, biologique et **échographique** de chaque patient sera instauré **(voir rubrique 4.4).** »
De plus, la firme a proposé la mise en place d'un plan de gestion des risques comprenant une communication renforcée auprès des médecins prescripteurs et des pharmaciens, ainsi que la définition de modalités de suivi des patients en cours de traitement et après l'arrêt du traitement.

Avis de la commission d'AMM

Il apparaît que l'ensemble des nouvelles données susmentionnées (notifications spontanées et sollicitées, PMSI, REGULATE) confortent le signal de risque de valvulopathies associé à l'exposition au benfluorex. Les membres de la Commission estiment que la surveillance échographique pendant le traitement n'est pas de nature à prévenir le risque de survenue de valvulopathie, laquelle par ailleurs pourrait continuer à évoluer même après l'arrêt de benfluorex.
Après débat, un vote a été sollicité pour la question suivante : Etes-vous pour ou contre le maintien du médicament (benfluorex) sur le marché ? Le résultat du vote a été le suivant : 1 voix pour, 18 voix contre, et 3 abstentions.

CONTEXTE DE LA COM D'AMM DU 1er juillet 2010

Rappel des conclusions et mesures prises suite à la réévaluation du rapport bénéfice-risque du benfluorex

Après examen des données actualisées relatives aux valvulopathies associées à la prise de benfluorex, issues des données de pharmacovigilance, de l'étude cas-témoin rétrospective du CHU de Brest ainsi que de l'étude REGULATE (étude multicentrique, en double aveugle, comparant pendant 52 semaines chez 840 diabétiques l'efficacité et la sécurité des deux traitements, benfluorex et sulphonylurée (SU) versus pioglitazone et SU), la Commission nationale de pharmacovigilance lors de sa séance du 29/09/09 a considéré que :

- les nouvelles données présentées confortent, malgré certaines limites méthodologiques, le

signal d'un risque de valvulopathie associé à l'exposition au benfluorex,
- le profil de tolérance du produit dans les conditions actuelles d'utilisation telles que définies dans l'AMM, est inacceptable.

Lors de ses séances du 23 octobre puis du 12 novembre 2009, après avoir étudié et discuté le rapport bénéfice-risque du benfluorex au vu des données disponibles, la Commission d'AMM s'est prononcée en défaveur du maintien sur le marché des spécialités composées de benfluorex.

Par conséquent, le directeur général de l'Afssaps a décidé en date du 24 novembre 2009 la suspension des AMM de ces spécialités, avec une prise d'effet le 30 novembre 2009, date à laquelle a été procédé au rappel des lots des spécialités commercialisées.

Décision de la Commission européenne en date du 14/06/10 :

Conformément aux dispositions de l'article 107 de la directive 2001/83/CE telle que modifiée, l'Afssaps a averti l'EMA, la Commission européenne et l'ensemble des Etats membres des décisions de suspension, ce qui a conduit à une évaluation européenne du rapport bénéfice-risque du benfluorex. Dans ce cadre, le CHMP a recommandé le retrait des AMM des spécialités composées de benfluorex.
Par décision du 14 juin 2010, la Commission européenne a enjoint les Etats membres concernés (Chypre, France, Luxembourg et Portugal) à retirer les AMM nationales.

Aussi, l'avis de la Commission d'AMM est aujourd'hui sollicité, conformément aux dispositions de l'article R. 5121-50 du code de la santé publique, quant au retrait des AMM des spécialités composées de benfluorex, suspendues en novembre 2009 dans l'attente de l'issue de la procédure d'évaluation européenne selon l'article 107 précité.

AVIS DE LA COMMISSION D'AMM n°484 du 1er JUILLET 2010 : AVIS FAVORABLE au retrait des AMM des spécialités contenant du benfluorex et ce,

- considérant qu'au terme de l'évaluation qu'il a menée et ayant concerné l'ensemble des médicaments contenant du benfluorex autorisés dans l'Union européenne, le CHMP de l'EMA a conclu que l'utilisation du benfluorex est nocive dans les conditions normales d'utilisation et conduit à des valvulopathies cardiaques. Ces valvulopathies peuvent induire une altération progressive de la fonction cardiaque et des symptômes cliniques associés nécessitant, dans les cas graves, une chirurgie cardiaque de remplacement des valves. Il a également noté que des anomalies valvulaires cardiaques morphologiques et fonctionnelles peuvent s'observer après seulement 328 jours d'exposition en moyenne. En outre, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée n'est pas exclue, ce qui suscite une inquiétude particulière étant donné l'utilisation prolongée du produit, avec une durée moyenne d'exposition de trois ans (sur la base de données d'utilisation) ;

- considérant qu'après avoir examiné le rapport bénéfice/risque du benfluorex dans les conditions normales d'utilisation, il a estimé que le risque prouvé susmentionné de maladie des valves cardiaques n'est pas acceptable, compte tenu du fait que le bénéfice du benfluorex n'est que limité dans le traitement du diabète de type 2 ;

- considérant que, au vu de ces éléments, le CHMP a adopté le 18 mars 2010 un avis recommandant à la Commission européenne d'enjoindre aux Etats membres de retirer les AMM de tous les médicaments à base de benfluorex ;

- considérant que suite à cet avis, la Commission européenne a, par décision du 14 juin 2010, demandé aux Etats membres concernés de retirer les AMM délivrées au niveau national des médicaments contenant du benfluorex et ce, en application des dispositions de l'article 107, paragraphe 2 de la directive 2001/83/CE précitée, au motif que l'évaluation des effets thérapeutiques positifs de ces produits au regard des risques pour la santé du patient liés à leur sécurité n'est pas favorable dans les conditions normales d'emploi.

Annexe 4-46

European Medicines Agency

London, 18 March 2010
EMA/CHMP/771880/2009

CHMP ASSESSMENT REPORT FOR BENFLUOREX-CONTAINING MEDICINAL PRODUCTS

PROCEDURE No: EMEA/H/A-107/1257

Procedure under Article 107 of Directive 2001/83/EC, as amended

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Referral of the matter to the CHMP

A Rapid Alert was circulated to CHMP, EMEA and Commission (see attachment 1) by France on 25 November 2009, following the suspension of the Marketing Authorisations of Benfluorex on 26 November 2009, triggering a review under Article 107 of Directive 2001/83/EC, as amended and referring the concerns to the CHMP for its opinion on whether the marketing authorisations for Benfluorex (Mediaxal, Mediator, Lipophoral) should be maintained, varied, suspended or revoked.

The CHMP agreed that the procedure described in Article 107 of Directive 2001/83/EC, as amended, was applicable.

The scope of the review was to review the benefit-risk ratio of medicinal products containing Benfluorex due to detection of cardiac valvulopathy excess risk.

1.2 Steps taken for the review procedure

- During the December Written Procedure, the following was agreed by CHMP:
  - Professor Philippe Lechat was appointed Rapporteur.
  - Professor Cristina Sampaio was appointed Co-Rapporteur.
  - The procedure under Article 107 started on 2 December 2009.
  - A consolidated list of questions (EMEA/CHMP/776192/2009) was adopted (see attachment 3).
- On 2 December 2009, a letter was sent to the MAHs for benfluorex-containing medicinal products informing them about the start of the procedure including the list of consolidated questions, the official notification from France to the CHMP/EMEA on the procedure under Article 107 of Directive 2001/83/EC, as amended, the assessment report of France, and the list of all MAHs involved in the review procedure.
- The CHMP and the EMEA received a MAH's response to the list of questions by 7 December 2009.
- On 11 December 2009, the Rapporteur's and the Co-Rapporteur's Assessment Reports were forwarded to the CHMP (see attachments 4 and 5).
- On 11 and 14 December 2009, the Rapporteur's and Co-Rapporteur's Assessment Reports were forwarded to the MAHs.
- On 17 December 2009, the CHMP adopted an opinion recommending the revocation of the Marketing Authorisations for medicinal products containing benfluorex.
- The Opinion is being forwarded to the European Commission, to Member States, to Iceland and to Norway and to the Marketing Authorisation Holders together with its annexes and appendices.
- On 18 March 2010, at the request of the European Commission, the CHMP adopted a revised opinion recommending the revocation of the Marketing Authorisations for medicinal products containing benfluorex.

- The Opinion is being forwarded to the European Commission, to Member States, to Iceland and to Norway and to the Marketing Authorisation Holders together with its annexes and appendices.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Benfluorex is used as an adjunct in the management of type 2 diabetes mellitus in overweight patients. The currently authorised therapeutic indication in France is as « *Adjuvant therapy of overweight diabetics, in combination with an appropriate diet*». Benfluorex has an action on carbohydrate metabolism. In animals, the following effects have been observed:

- Facilitation of precipitation and use of glucose in cells (rats)

- Reduction in hyperglycaemia in diabetic rats (insulin deprived or not), decrease in hyperglycaemia (measured by the glucose tolerance test area) in rabbits

Benfluorex has no action on insulino-secretion.

Medicinal products containing benfluorex are authorised in four EU Member States under a tablet formulation, with only 2 countries (France and Portugal) in which the product was marketed up to the suspension of the Marketing Authorisations in November 2009. In Cyprus and Luxembourg, medicinal products containing benfluorex were not marketed any longer.

On 25 November 2009, the French Competent Authority (Afssaps) issued a Rapid Alert informing the Members States, the EMEA and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of its decision to suspend the marketing authorisations of all benfluorex containing medicinal products in France due to an increased risk of a cardiotoxicity signal (valvular heart diseases) with benfluorex. The decision of the French Competent Authority was based on:
- updated results of a Pharmacovigilance (PV) survey,
- preliminary data from 3 clinical studies (the retrospective case-control study performed in a Brest hospital, the REGULATE trial and the data from the French National Insurance Fund);
- and from a recent publication (K. Boutet *Fenfluramine-like cardiovascular side-effects of benfluorex*, Eur Respir. J. 2009; 33: 684-688) that have shown a risk of cardiac valve diseases and of pulmonary hypertension (PHT) for patients treated with benfluorex.

On 30 November 2009, the Portuguese Competent Authority decided as well to suspend the marketing authorisation of all benfluorex containing medicinal products in Portugal.

On 2 December 2009, on the starting day of the Article 107 for medicinal products containing Benfluorex started, the CHMP adopted a list of consolidated questions to be addressed to the MAHs. The MAHs were invited to comment on this List of questions which could have an impact on the conclusions of the Competent Authorities and the regulatory action described above, and to justify by additional data, as appropriate.

On 7 December 2009, the CHMP and the EMEA received only the brand leader's response (Laboratoires Servier) to the list of questions confirming in their cover page that *"no additional data were available since the conclusions of the French Competent Authority"*'s report. The Committee reviewed the MAH's response along with the data provided by the Member State (French assessment) and issued an opinion according to the Rapporteur and Co-Rapporteur's assessment reports at the December 2009 plenary meeting.

2.2 Clinical Safety

Since its marketing authorisation, several pharmacovigilance surveys have been performed on benfluorex, leading, among others, to the removal of its indication for hypertriglyceridemia.

The detection of a cardiotoxicity signal (valvular heart diseases) led to the current review by the CHMP. Updated results of a Pharmacovigilance survey, preliminary data 3 clinical studies (the retrospective case-control study performed in a Brest hospital, the REGULATE trial and the data from the French National Insurance Fund), and a recent publication (K. Boutet. *Fenfluramine-like cardiovascular side-effects of benfluorex*, Eur Respir. J. 2009; 33: 684-688) showed a risk of cardiac valve diseases and of pulmonary hypertension (PHT) for patients treated with benfluorex.

In this context, old study data such as the Del PRATO and MOULIN studies (including the MOULIN open-label extension) were also reviewed and taken into consideration into the conclusions reached by the CHMP.

2.2.1 Del PRATO study

Presentation of the study

The purpose of this study was the granting of the approval of the indication in treating diabetes. Only the results of the *versus placebo* arm were adopted and enabled the approval of the current indication.

The objective of this study was to assess the long-term efficacy (6 months) of benfluorex in improving the glycaemic control of type-2 diabetic patients poorly balanced by diet alone.

This international multi-centre, double-blind, parallel-group study involved 438 type-2 diabetic patients insufficiently controlled by diet alone. The study included a 2-month pre-inclusion period during which the patients received a placebo (single-blind) and dietary advice.

The principle efficacy criterion was HbA1c (centralised dosage, HPLC method). The secondary efficacy criteria were fasting blood glucose, insulinemia and lipid profile.

The tolerance criteria were the physical examination data (weight, heart rate, BP), creatininaemia and the recording of spontaneously-reported adverse events.

Discussion and conclusion on safety in the Del PRATO study

The reported events involved the gastro-digestive system: 13% with benfluorex and 10% with the placebo. Two serious events were considered to be linked to the treatment with benfluorex (vertigo, urticaria). These events were known to occur with benfluorex and figured amongst the adverse events mentioned in the summary of product characteristics. The numbers of drop outs were equivalent in both groups, 20% with benfluorex compared to 25% with placebo. No modifications to blood pressure and heart rate were observed. No patients died in the course of the study.

The most frequent adverse events were known digestive disorders (primarily diarrhoea). The numbers of drop outs as a result of adverse events were low (< 5%) and comparable: 14 out of 294 in the benfluorex group and 6 out of 142 in the placebo group.

To the MAH's opinion, a certain number of adverse events are known, mainly in the digestive area (diarrhoea and abdominal pain), and are generally moderate in intensity and rarely lead to treatment discontinuation.

In conclusion, the CHMP is of the opin ion that acceptability was comparable in the benfluorex and placebo groups, with the exception of digestive disorders.

2.2.2 MOULIN study and the MOULIN open-label extension

Presentation of the MOULIN study and its extension

The Moulin study was an international, multi-centre, double-blind study controlled against a placebo assessing the efficacy and safety of 18-week treatment with 450 mg/day of benfluorex compare to a placebo of 325 type-2 diabetic patients poorly controlled by treatment with sulphonylureas (SU) and with intolerance or contra-indication to metformin.

The study continued with a 16-week open-label period intended to obtain long-term efficacy and safety data for benfluorex when combined with a SU and, if required, acarbose.

The principal objective of this study was to demonstrate the superiority of treatment with Benfluorexcompared to the placebo, when combined with a sulphonylurea, in order to control glycaemia.

The primary efficacy criterion was HbA1c (%), assessed after 0, 4, 10 and 18 weeks of treatment. The secondary criteria were measurements of fasting blood glucose and fasting insulinaemia, as well as the lipid profile assessed at each visit.

The safety criteria were the physical examination data (weight, heart rate, blood pressure), electrocardiogram, standard biological monitoring and the recording of spontaneously-reported adverse events.

The extension of the MOULIN study

The objective of this 16-week open-label extension period was to obtain additional information on the efficacy and safety of Benfluorex®, when combined with a sulphonylurea. A third hypoglycaemic drug with a different action (acarbose) was introduced, if necessary, from the 9th week after the start of the extension period.

Nearly all the patients who finished the initial blind period of the study participated in the extension, i.e. 296 patients out of 297. More than 95% (n = 282) of them completed this extension.

Discussion and conclusion on safety in the MOULIN study

The proportion of patients who presented at least one adverse event was similar in the benfluorex group and the placebo group.

The most frequent adverse events were of a gastro-intestinal nature without however leading to more frequent drop outs.

Possible cases of hypoglycaemia were observed in 8.4% of patients treated with benfluorex and in 3.8% of patients treated with the placebo without any of these incidents having been deemed to be serious. The possible cases of hypoglycaemia were not confirmed by capillary blood glucose. The cases of hypoglycaemia were linked to the insulin-secreting treatment used in combination with benfluorex in this study. They were more frequent in the benfluorex group as a result of the stricter glycaemic control.

The incidence rates of psychiatric disorders were respectively 3.6% with benfluorex and 3.1% with the placebo. The number of reported cases of depression was balanced in both groups. No possible cases of withdrawal syndrome were reported.

The incidence rates of neurological disorders were respectively 9.0% with benfluorex and 6.3% with the placebo, principally headaches. A higher number of serious adverse events were observed in the benfluorex group, mostly linked to an underlying pathology: no causal links were reported, with the

exception of one case of digestive pain. No anomalies were detected during treatment with benfluorex regarding the electrocardiogram, biological safety parameters, changes to blood pressure or heart rate.

During the **study's open-label extension period** and compared to the blind period, the adverse effects observed were of the same kind (digestive), included few cases of hypoglycaemia (5.3%) and were not serious. The number of drop outs as a result of adverse events was 9/296, i.e. 3.1% - the exact same incidence rate as observed for the placebo group during the blind period (3.8%).

In conclusion, based on the aforementioned data, the CHMP concluded:

- that the safety results of the Moulin study and its extension confirmed the known effects regarding digestive tolerance of benfluorex;
- the incidence of digestive disorders did not increase in patients who had shown intolerance to metformin.

The MAH acknowledges, in their written response, that a certain number of adverse events (mainly in the digestive area) are known.

2.2.3 PHT and cardiac valve disease pharmacovigilance survey follow-up data

The CHMP reviewed the response package provided by the MAH along with the data provided by the Member State which examined the updated results of a national PV survey (particularly the data regarding the risk of PHT and cardiac valve diseases with Benfluorex) as well as the data from a recent publication on this subject (K. Boutet *Fenfluramine-like cardiovascular side-effects of benfluorex*, Eur Respir. J. 2009; 33: 684-688).

2.2.3.1 Pulmonary Hypertension (PHT) data

Between March 2007 and September 2009, 8 new cases of PHT were reported, i.e. a total of 28 cases, including 4 apparently idiopathic cases of PHT during treatment with benfluorex. Given the incidence of apparently idiopathic PHT in the general population, the Member State considered that the number of cases of apparently idiopathic PHT linked to use of benfluorex did not appear to represent a significant signal of the pulmonary toxicity of benfluorex. However it was recommended at the time that the spontaneous reporting of cases of PHT in the general population continue to be closely monitored. This issue has been followed up since several years at the Member State level in collaboration with the MAH.

The MAH did not comment on the PHT events within their response to the list of questions addressed by the CHMP.

The CHMP noted the above mentioned conclusions reached at the time with regards to PHT events.

2.2.3.2 Valve disease data

1 - Updating of the pharmacovigilance data and the retrospective case-control study performed in Brest hospital ("Brest case-control study")

- **Pharmacovigilance data**

On 7 July 2009, the Member State reviewed thirty cases of cardiac valve disease which occurred between 1998-2009 at national level:

- 19 spontaneously reported cases (SR), including 3 cases also involving post-capillary PHT;

- 11 cases identified by the Brest RPVC following interrogation of the PMSI (Information System Medicalisation Programme).

► *Patient characteristics:*

	SR: 19	PMSI: 11
Sex	Women: 24, men: 6	
Average age of appearance (years) *Women*: 54.6 *Men*: 62.2	 53.7 54.6	 56.4 69.7
BMI (kg/m^2) *18.5 to 24.9*: 5 cases *25 to 29.9*: 7 cases *≥ 30*: 8 cases	3 5 4	2 2 4
Average length of treatment (years) 5.3	5.6	4.6
Medical history / Diathesis (number) *Smoking*: 13 *Hypothyroidism*: 9 *Diabetes*: 9 *Dyslipidemia*: 12 *Rheumatoid polyarthritis*: 2	 10 7 5 10 1	 3 2 4 2 1
Cardiac medical history/Diathesis (number)	15	
Combined drugs (number) *Levothyroxine* *SSRI antidepressant*	 9 7	

► *Type and location of the valve diseases:*

The 30 reported cases of valve disease were monovalvular in 6 cases, bivalvular in 16 cases and trivalvular in 8 cases. As regards the location of these valve diseases, 28 cases were mitral insufficiencies (serious in 17 cases), 24 cases were aortic insufficiencies and 11 cases were tricuspid insufficiencies (serious in 4 cases).

► *Anatomopathological aspect of the valves requiring surgery*

Anatomopathological diagnoses were performed on 5 patients requiring surgery.

On 29 September 2009, 11 new cases of valvulopathy related to benfluorex were reported between July 2009 and September 2009 by a national pharmacovigilance centre, including 3 that were spontaneously reported and 8 reported upon request by another national PV center. The analysis of these 11 new cases showed

- a predominance of women,

- an average of 3 years treatment

- an age of appearance most frequently identified as 55 years old

- in 9/11 cases, combination with pulmonary hypertension was reported

- as well as mitral and aortic insufficiency damage in 1 case and mitral and aortic and tricuspid damage in 1 case.

The results of the echocardiograms were documented.

It was concluded on the existence of a cardiotoxicity signal detected via spontaneous reporting and the PMSI (Computerised Medical File Database) data and on the need to confirm this signal using an epidemiological study ("Brest case control study").

- **The retrospective case-control study**

The aim of the methodology used in the Brest hospital was to identify cases of valve disease linked to benfluorex. The methodology queried the PMSI using the "valve disease and diabetes" codes and the "valve diseases and Benfluorex" codes. Compared with the report in July 2009, 4 new cases were identified by using the PMSI. Therefore, on 29 September 2009, 45 cases of valve disease had been identified:

- 19 + 3 = 22 Spontaneous reports;
- 11+ 4 = 15 (Brest) following interrogation of the PMSI;
- and 8 reports requested from the national pharmacovigilance centre based on the echocardiogram records.

The 15 "compatible" cases identified at the Brest University Hospital Centre involved 12 women and 3 men, with a mean age at diagnosis of 58 years (49-78), mean BMI of 33 kg/m^2 (24-52), with diabetes in 6 of the 12 reported cases, a mean exposure duration of 53 months (12-144), a delay between the first dose of benfluorex and diagnosis of the valve disease of 97 months (13-384), an earlier normal echocardiogram in 5 of the 7 documented cases, an exposure to a serotonin reuptake inhibitor in 8 out of 10 of the documented cases.

The damaged valves were mitral and aortic in all cases, tricuspid in 7 out of 15 cases and pulmonary in 1 out of 15 cases. In 8 of these 15 cases, valve replacement surgery was performed.

The surgery provided diagnostic and both macroscopic and microscopic comparative elements:

- At a macroscopic level, the valve lesions primarily affected the elastic fibres in the form of non-specific fibromyxoid thickening, fibrous thickening of the large and small valves including fusion of the commissures and significant retraction of the subvalvular apparatus;

- At a microscopic level, the most "specific" description was a thickening and retraction of the valves including heavy fibrosis, formed from myofibroblasts in a pauci-cellular matrix of mucopolysaccharides without inflammatory infiltration; the valves showed fibrous plaques formed from myofibroblasts with a matrix of mucopolysaccharides and collagen, causing the retraction of the valves.

The aim of this retrospective study was, as mentioned earlier, to confirm or invalidate the "valve disease" signal. This case-control study analysed all the mitral insufficiencies (MI), both isolated and combined, examined at a specific hospital since 2003. Its objective was to look for a link between exposure to benfluorex and the occurence of cases of unexplained mitral insufficiency. The source population consisted of all the patients hospitalised between 2003 and 2009 in the cardiology department or cardiac surgery service, diagnosed with MI, i.e. 622 patients. The patients with an unexplained MI formed the cases (n=27) and the patients with an explained MI formed the controls (n=54). Two controls were matched to each case based on age and sex criteria. This matching involved neither the diabetes diagnosis nor Body Mass Index. The patient, his/her family and doctors were contacted by telephone to investigate possible exposure to benfluorex using a semi-structured questionnaire, without revealing his/her case/control status.

Of the 27 identified cases, 19 had been exposed to benfluorex compared to 3 controls out of 54 having been exposed to benfluorex ($p<0.001$ i.e. odds-ratio = 40.4 (9.7 – 168.3, 95% CI)).

The adjustment based on different variables such as weight, diabetes or exposure to dexfenfluramine did not modify the signal.

In this study, several potential biases were discussed.

- **Discussions and conclusions**

The MAH reviewed the above mentioned 45 cases of valve disease and based their response on the view of an independent expert to whom the narratives of these 45 cases were entrusted for analysis. The expert analysis concerned:

- The existence or not of anatomical documentation obtained during cardiac valve surgery in patients who had been operated,

- The existence or not of echocardiography documentation for the patients who had not been operated.

The imputability analysis was performed according to published criteria for the relationship of a cardiac valve disease to a drug treatment.

Among the 17 cases of operated cardiac valve diseases, the MAH considers that:

- 6 cases characterised by histological observations corresponding to the descriptions of drug-related cardiac valve diseases and for which there is no other attributable medicinal product administration are strongly suggestive of a drug-induced cardiac valve disease related to benfluorex;

- 6 cases are possibly related to benfluorex due to compatible echocardiography or macroscopic observations, but without histological confirmation and without being able to formally discard the alternative rheumatism aetiology. Patients' age could be an indication of a rheumatism cause, as too their geographical origin, though this last criterion was not available in the case narratives;

- 3 cases have low benfluorex imputability, where the lack of any echocardiography or macroscopic documentation does not allow the exclusion of another cardiac valve disease aetiology;

- 2 cases have a description of lesions suggesting another aetiology, therefore with a very low imputability.

Among the 15 patients who had not been operated but for whom the echocardiography describes the valvular lesions, the MAH considers that:

- 10 cases have possible benfluorex imputability, as the valvular lesions are compatible, although the alternative rheumatism aetiology could not be discarded, with the same comment as before concerning the age and geographical origin;

- 5 cases have very low benfluorex imputability as the medical history or the echocardiography descriptions suggest another cardiac valve diseasescause.

In 13 cases, no echocardiography documentation of the valvular lesions was available and therefore the MAH considers that no conclusion can be reached on the degree of imputability of benfluorex.
In conclusion, according to the MAH:

- the benfluorex imputability seems probable in 6 cases and possible in 16 cases, while the main alternative is a rheumatism-related cardiac valve disease;

- the imputability is low in16 cases where the presence of valvular regurgitations is difficult to interpret in the absence of any details concerning the valvular anatomy;

- finally, the imputability is very low in 7 cases for which another aetiology seems more likely.

The Member State acknowledged the methodological shortcomings of this retrospective case-control study, as addressed by the MAH; although these methodological shortcomings might produce a difference in risk to some extent, it was concluded that the significant difference observed is not fully explained by the shortcomings and hence that the signal of a link between exposure to benfluorex and the occurrence of valvulopathy was confirmed.

After reviewing the above mentioned data provided by the MAH and the Member State, the CHMP is of the opinion that the aforementioned association between exposure to benfluorex and the occurrence of valvular abnormality is most likely established.

3 - The REGULATE study

Following the results from the pharmacovigilance survey, the market leader proposed to conduct two studies: an anatomopathological study on an exposed/unexposed basis (refused on methodological grounds) and a case control study. Finally only the REGULATE study, which had already been conducted and whose preliminary results were available, provided additional safety and efficacy data.

As mentioned by the MAH in their written response, the REGULATE study, sponsored by the brand leader, started before the emergence of the safety signal.

The Member State was provided on 29 September 2009 with the preliminary results of this study.

Presentation of the study

This was a multi-centre, randomised, double-blind study controlled against pioglitazone, lasting 52 weeks, comparing for 847 type-2 diabetic patients, insufficiently controlled by sulphonylureas (SU), the efficacy and safety of treatment with Benfluorex at the maximum recommended dose (450mg/day, 1 tablet at mealtimes, 3 tab/day), with treatment with pioglitazone at the maximum recommended dose (45 mg/day, 1 tablet with breakfast)

The aim of this new study was to compare the efficacy and safety of treatment with Benfluorex compared to treatment with pioglitazone, in combination with a SU, on glycaemic control and lipid profile.

- The principal objective was to demonstrate the non-inferiority of the combination of SU and benfluorex compared to the combination of SU and pioglitazone on the changes to HbA1c.

- The secondary objective was to demonstrate the superiority of benfluorex combined with SU compared to pioglitazone combined with SU on the level of cholesterol.

- The other secondary objectives were to assess and compare these combinations after 1 year of treatment on fasting blood glucose, fasting insulinaemia and cardiovascular risk as well as the safety and cost of these two treatments. It should be noted that an echocardiogram was recorded at t_0 before treatment initiation and at the end of the treatment, t_{52wk}.

The primary efficacy criterion was HbA1c measured at each visit (inclusion, 4, 8, 16, 28, 40 and 52 weeks). The secondary criteria were lipid parameters (LDL-cholesterol, total cholesterol, HDL-cholesterol, triglycerides at each visit), fasting blood glucose (FBG), fasting insulinaemia (HOMA-IR), C-reactive protein, waist measurement, weight.

The safety parameters were adverse events, hypoglycaemia, biological parameters, cardiac examination (ECG, echocardiogram upon inclusion and after 12 months)

Discussion and conclusion on safety in the REGULATE study

The frequency of undesirable effects was comparable between the two groups (63.7% in the benfluorex group compared to 62.9% in the pioglitazone group).

- The most frequent undesirable effects were infections and infestations, gastro-intestinal disorders, and musculoskeletal disorders.
- The emergent adverse events in the benfluorex group were hypoglycaemia and diarrhoea.
- Two patients in the benfluorex group compared to 3 in the pioglitazone group suffered a myocardial infarction, 0 compared to 1 for angina pectoris, 1 compared to 0 for congestive heart failure, 0 compared to 1 for ischemia, 0 compared to 1 for acute coronary syndrome and 1 compared to 0 for congestive cardiomyopathy.
- Finally, there were two deaths in the benfluorex group compared to 4 in the pioglitazone group: these deaths were not linked to the treatments.

More specifically, regarding the cardio-vascular safety profile, 614 patients, 309 in the benfluorex group and 305 in the pioglitazone group, had an echocardiogram at t_0 and $t_{52\ weeks}$, after exposure to the treatments for an average of 328 days.

This study revealed in the group treated with benfluorex compared to the pioglitazone group, the emergence of statistically-significant functional valve anomalies, 26.5% compared to 10.9%, ($p<0.0001$), as well as non-statistically-significant morphological valve anomalies (2.6% compared to 1.3% respectively, $p=0.264$). The functional anomalies that appeared with benfluorex had no clinical impact.

These emergent anomalies are presented in table 1, below.

Table 1

Emergent valvular functional abnormality according to grade (ECHO2)

Emergent valvular abnormality	Grade Baseline to last		Benfluorex	Pioglitazone
Aortic regurgitation		n	309	302
(N = 611)	Grade 0 to 1	n (%)	40 (12.9)	3 (1.0)
	Grade 0 to 2	n (%)	1 (0.3)	-
	Grade 1 to 2	n (%)	1 (0.3)	-
Mitral regurgitation		n	309	300
(N = 609)	Grade 0 to 1	n (%)	21 (6.8)	13 (4.3)
	Grade 1 to 2	n (%)	1 (0.3)	1 (0.3)
Tricuspid regurgitation		n	304	299
(N = 603)	Grade 0 to 1	n (%)	33 (10.9)	15 (5.0)
	Grade 1 to 2	n (%)	-	2 (0.7)
Emergent clinically relevant valvular abnomalities (grade > 1)				
(N = 612)		n	309	303
		n (%)	2 (0.7)	3 (1.0)
Statistical analysis		OR (1)	0.65	
		95% CI (2)	[0.11 ; 3.94]	
		p-value (3)	0.642	

n: number of patients in the valvular Set ; Grade 0: absent; grade 1: trivial; grade 2: mild; % calculated as number of patients affected x 100/total number of patients in the group; (1) Odds Ratio; (2) 95% Confidence interval of the odds ratio; (3) Wald test

Regarding the type of anomalies observed, the MAH considers that most valve anomalies seen during the study (and only those for which any significant difference exists between the benfluorex group and the pioglitazone group) are of "trivial" grade, i.e. lower than grade 1 in the official classification quantifying aortic and mitral valve regurgitation, which comprises 3 grades: "mild" (grade 1),

"moderate" (grade 2) and "severe" (grade 3). Moreover, to the MAH's opinion, the « trace » abnormalities are in general stable and can regress.

In their response the MAH concluded as follows:

- on the above-mentioned anomalies:

"Trivial regurgitation is extremely common in the mitral and tricuspid valves, and a little less frequent in the aortic valve, but is generally considered practically physiological. It is asymptomatic, producing no discernible murmur on auscultation, and is thus only discovered on echocardiography. The likelihood of progression is not known with any accuracy, but comparison of the frequency of progression in these instances with that of more severe cardiac valve disease suggests little or no evolution in the majority of cases. The official recommendations concerning trivial regurgitation do not call for any special monitoring protocol."

- on the risk of worsening of these functional anomalies:

"The rapidity of change in valve disease has been assessed only from the "mild" state (grade 1) onwardsand depends upon aetiology. Rheumatic cardiac valve disease progresses slowly. Degenerative cardiac valve diseases progress more rapidly but with wide variation between individuals. There is currently no treatment available to slow down the progression of constituted (mild) degenerative or rheumatic valve disease. However, regression and stabilisation have been described with anorexigenic products after discontinuation of therapy"

The CHMP took into consideration the above response from the brand leader. However the CHMP is of the opinion that despite the methodological shortcomings of this study, the results issued from the prospective REGULATE study suggest a significant increase in valve disease in the treatment arm with benfluorex (26.5% vs 10.9 %, p <0.0001), which in some cases were accompanied by morphological changes (2.6% vs 1.3%, p <0.264). The CHMP therefore considers that although the difference may not be statistically significant it is nonetheless, clinically significant.

4 – Results of a Cohort Study conducted by the French National Insurance Fund (CNAM).

Presentation of the study

This was an exposed/unexposed cohort study, whose principle objective was to look for a possible link between exposure to benfluorex and the occurrence of valve diseases.

The results concerned 1,092,858 diabetic patients of between 40 and 69 years old, including 43,208 who were exposed to benfluorex in 2006.

The risk of hospitalisation in 2007 as a result of valve insufficiency was 81/100,000 in the exposed group compared to 29/100,000 in the unexposed group, i.e. a risk multiplied by 2.77 (CI 95 [1.95: 3.93]). The risk of hospitalisation as a result of mitral insufficiency was multiplied by 2.66 (CI 95 [1.7: 4.1]). Furthermore, the risk of valve replacement surgery requiring cardiopulmonary bypass, all causes included, was multiplied by 3.4 (CI 95 [1.9: 6.1]). The absolute and relative risks in 2008 were very similar to those observed in 2007.

Discussion and conclusion on safety in the CNAM Cohort study

Results of this additional study have been provided and commented in the MAH's response document to the list of questions adopted by the CHMP. Imprecision regarding information about the diagnosis of cardiac valve disease was pointed out by the MAH in addition to the limited number of patients identified as presenting cardiac valve disease and treated with benfluorex (35 patients).

Despite these comments, these data further confirmed the safety signal of cardiac valve disorders disease risk with benfluorex.

5- Conclusions

Based on the pharmacovigilance data and the retrospective case-control study presented earlier, the CHMP considers that the signal of a link between exposure to benfluorex and the occurrence of cardiac valve diseases is confirmed. The Committee is of the opinion that the signal was supported by the results shown in the REGULATE study which revealed the occurrence of morphological and functional valve anomalies after an average of only 328 days' exposure.

Regarding spontaneous reporting data, the CHMP explains the absence of a significant number of individual case safety reports in relation to the total exposure of Benfluorex over the years by considering the type of effect, i.e. long term, cumulative: spontaneous reporting data alone is not the best method to assess risk and frequency of event. Hence, absence of data does not provide evidence on the inexistence of risk.

The time to event, which is prolonged with the use of benfluorex, could derive from a dose-response that produces cumulative, long term effects.

Therefore, the CHMP is of the opinion that aggravation of the functional anomalies in case of prolonged exposure could not be ruled out, particularly given the prolonged use of the product based on utilisation data, which showed an average exposure time of 3 years.

2.3 Benefit Risk Assessment

Updated results of the pharmacovigilance survey regarding the risk of cardiac valve diseases with benfluorex and data from a recent publication on this subject (K. Boutet *Fenfluramine-like cardiovascular side-effects of benfluorex*, Eur Respir. J. 2009; 33: 684-688) lead to the conclusion of an existence of cardiac valvulopathy and PHT in the general population of patients using benfluorex.

In addition, the retrospective case-control study conducted in accordance with the French Competent Authority in order to look for a link between exposure to benfluorex and the occurrence of unexplained mitral insufficiency (retrospective case-control study performed in a Brest hospital), establishes an association between the exposure to benfluorex and the occurrence of valvulopathy.

Based on the aforementioned data, the CHMP considers that the signal of a link between exposure to benfluorex and the occurrence of cardiac valve diseases is confirmed. The Committee is of the opinion that the signal is supported by the results shown in the REGULATE study which confirms the risk of valvulopathy with benfluorex and reveals the occurrence of morphological and functional valve anomalies after an average of only 328 days of exposure.

Finally, the results of an additional study (cohort study conducted by the French National Insurance Fund) were commented by the MAH in their response document to the List of Questions adopted by the Committee. The imprecision regarding information about the diagnosis of cardiac valve disease and the limited number of patients identified as presenting cardiac valve disease and treated with benfluorex (35 patients) were pointed out by the MAH. However, the CHMP is of the opinion that these data further confirm the safety signal of a risk of cardiac valve disorders with the use of benfluorex.

Regarding spontaneous reporting data, the CHMP explains the absence of a significant number of individual case safety reports in relation to the total exposure of Benfluorex over the years by considering the type of effect, i.e. long term, cumulative: spontaneous reporting data alone is not the best method to assess risk and frequency of event. Hence, absence of data does not provide evidence on the inexistence of risk.

The time to event, which is prolonged with the use of benfluorex, could derive from a dose-response that produces cumulative, long term effects.

Therefore, the CHMP is of the opinion that aggravation of the functional anomalies in case of prolonged exposure could not be ruled out, particularly given the prolonged use of the product based on utilisation data, which showed an average exposure time of 3 years.

As stated in the brand's leader written response, at the time of the national evaluation of the cardiac valvular abnormality, the MAH proposed to maintain benfluorex on the market with a restriction to the indication in patients with no ultrasound evidence of valve anomalies and the implementation of echocardiographic monitoring. The MAH projected to discontinue the treatment in the event of echocardiographic anomalies.

This proposal was rejected by the Member State at the time; the MAH's suggestion is now discarded by the CHMP. The CHMP is of the opinion that additional echocardiographic monitoring as proposed by the MAH could not solve this issue due to the fact that echocardiographic monitoring prevent the use in patients with previous valvulopathy but do not prevent the development in patients who have no previous abnormalities.

Based on the confirmed increased risk of cardiac valvulopathy and the very limited efficacy on glycaemic parameters, the CHMP considers that the MAH's proposal was not acceptable.

3 OVERALL CONCLUSION

The updated results of the second national Pharmacovigilance survey, the preliminary data from 3 clinical studies (the retrospective case-control study performed in a Brest hospital, the REGULATE trial and the data from the French National Insurance Fund) and the recent publication from K. Boutet show the serious risk of cardiac morphological and functional valvulopathies and pulmonary hypertension associated with the use of benfluorex.

Benfluorex is used as an *"Adjuvant therapy of overweight diabetics, in combination with an appropriate diet"*. The MAH, in their written response, considers that there is a consistent significant clinical effect on blood glucose control in all the studies performed with benfluorex in overweight type 2 diabetic patients. However the CHMP, after review of the data provided by the MAH and the Member State, considers that the benefit of benfluorex is only limited in the treatment of type 2 diabetes as an adjunct in the management of type 2 diabetes mellitus in overweight patients.

Taking all these elements into account, the CHMP concluded that the medicinal products containing benfluorex are harmful under the normal conditions of use, and that the benefit/risk balance for benfluorex is not considered favourable. Therefore the Committee recommended the revocation of the Marketing Authorisations for the medicinal products referred to in Annex I.

4 ANNEXES

The list of the names of the medicinal products, Marketing Authorisation Holders, pharmaceutical forms, strengths and route of administration in the Member States are set out in Annex I to the Opinion.

5 ATTACHMENTS

1. Notification of referral for review under Article 107 of Directive 2001/83/EC, as amended received from France on 25 November 2009.
2. Assessment report of France dated 26 November 2009.

3. List of Questions (EMEA/CHMP/776192/2009) as adopted by the CHMP on 2 December 2009.
4. Rapporteur's assessment report on the MAH responses to the List of Questions dated 11 December 2009.
5. Co-rapporteur's assessment report on the MAH responses to the List of Questions dated 11 December 2009.

COMMISSION EUROPÉENNE

Bruxelles, le 14.6.2010
C(2010)4127

DÉCISION DE LA COMMISSION

du 14.6.2010

concernant, dans le cadre de l'article 107 de la directive 2001/83/CE du Parlement européen et du Conseil, les autorisations de mise sur le marché des médicaments à usage humain contenant la substance active «benfluorex»

DÉCISION DE LA COMMISSION

du 14.6.2010

concernant, dans le cadre de l'article 107 de la directive 2001/83/CE du Parlement européen et du Conseil, les autorisations de mise sur le marché des médicaments à usage humain contenant la substance active «benfluorex»

(Texte présentant de l'intérêt pour l'EEE)

LA COMMISSION EUROPÉENNE,

vu le traité sur le fonctionnement de l'Union européenne,

vu la directive 2001/83/CE du Parlement européen et du Conseil du 6 novembre 2001 instituant un code communautaire relatif aux médicaments à usage humain[1], et notamment son article 107,

vu l'avis de l'Agence européenne des médicaments, formulé le 18 mars 2010 par le comité des médicaments à usage humain, saisi le 2 décembre 2009,

considérant ce qui suit:

(1) Les médicaments à usage humain autorisés par les États membres doivent répondre aux exigences de la directive 2001/83/CE.

(2) À la suite de l'évaluation des données de pharmacovigilance concernant les médicaments à usage humain qui contiennent la substance active «benfluorex», la République française a informé l'agence, conformément à l'article 107, paragraphe 1, de la directive 2001/83/CE, que l'autorisation ou les autorisations de mise sur le marché devaient être suspendues.

(3) Le comité a préparé un avis, dont les conclusions figurent à l'annexe II de la présente décision, recommandant qu'une décision soit prise pour retirer les autorisations de mise sur le marché des médicaments concernés.

(4) Les mesures prévues par la présente décision sont conformes à l'avis du comité permanent des médicaments à usage humain,

[1] JO L 311 du 28.11.2001, p. 67.

A ADOPTÉ LA PRÉSENTE DÉCISION:

Article premier

Les États membres concernés retirent les autorisations nationales de mise sur le marché des médicaments visés à l'annexe I, sur la base des conclusions scientifiques et des motifs de retrait des autorisations de mise sur le marché figurant à l'annexe II.

Article 2

Les États membres sont destinataires de la présente décision.

Fait à Bruxelles, le 14.6.2010

Par la Commission
Paola TESTORI COGGI
Directeur général

ANNEXE I

LISTE REPRENANT LES NOMS DE FANTAISIE, LES FORMES PHARMACEUTIQUES, LE DOSAGE DES MÉDICAMENTS, LA VOIE D'ADMINISTRATION ET LES TITULAIRES DES AUTORISATIONS DE MISE SUR LE MARCHÉ DANS LES ÉTATS MEMBRES (EEE)

Etat membre	Titulaire de l'autorisation de mise sur le marché	Nom de fantaisie	Dosage	Forme Pharmaceutique	Voie d'administration
Chypre	Les Laboratoires Servier 22, rue Garnier F- 92200 Neuilly-sur-Seine France	Lipophoral Tablets 150mg	150mg	Comprimé	Voie orale
France	Les laboratoires Servier 22 rue Garnier F-92200 Neuilly-sur-Seine France	Mediator	150 mg	Comprimé	Voie orale
France	Mylan SAS 117 allée des Parcs 69800 Saint-Priest France	Benfluorex Mylan	150 mg	Comprimé	Voie orale
France	Qualimed 117 allée des Parcs 69800 Saint-Priest France	Benfluorex Qualimed	150 mg	Comprimé	Voie orale
Luxembourg	Les Laboratoires Servier 22, rue Garnier F- 92200 Neuilly-sur-Seine France	Mediator	150mg	Comprimé	Voie orale
Portugal	Servier Portugal - Especialidades Farmacêuticas, Lda. Av. António Augusto de Aguiar 128, 1069-133 Lisboa Portugal	Mediator	150 mg	Comprimé enrobé	Voie orale

ANNEXE II

CONCLUSIONS SCIENTIFIQUES ET MOTIFS DU RETRAIT DES AUTORISATIONS DE MISE SUR LE MARCHÉ PRÉSENTÉS PAR L'AGENCE EUROPÉENNE DES MÉDICAMENTS

CONCLUSIONS SCIENTIFIQUES

RÉSUMÉ GÉNÉRAL DE L'ÉVALUATION SCIENTIFIQUE DES MÉDICAMENTS CONTENANT DU BENFLUOREX (voir annexe I)

Le benfluorex est utilisé comme adjuvant dans la prise en charge du diabète de type 2 chez les patients en surcharge pondérale. L'indication thérapeutique actuellement autorisée en France est l'utilisation comme «*Traitement adjuvant du régime adapté chez les diabétiques avec surcharge pondérale*». Le benfluorex agit sur le métabolisme des hydrates de carbone. Chez l'animal, on a pu observer les effets suivants:
- facilitation de la précipitation et de l'utilisation du glucose dans les cellules (rat);
- réduction de l'hyperglycémie chez le rat diabétique (privé ou non d'insuline), diminution de l'hyperglycémie (mesurée par l'aire de test de tolérance au glucose) chez le lapin.
Le benfluorex n'a aucune action sur la sécrétion d'insuline.

Les médicaments à base de benfluorex sont autorisés dans quatre États membres de l'UE sous une formulation en comprimés, le produit n'ayant été commercialisé que dans deux pays (la France et le Portugal) jusqu'au retrait des autorisations de mise sur le marché en novembre 2009 (voir annexe I pour la liste des médicaments à base de benfluorex autorisés dans l'UE). À Chypre et au Luxembourg, les médicaments contenant du benfluorex n'étaient plus commercialisés.

Le 25 novembre 2009, l'autorité compétente française (Afssaps) a émis une alerte rapide informant les États membres, l'Agence européenne des médicaments et la Commission européenne, conformément à l'article 107 de la directive 2001/83/CE, telle que modifiée, de sa décision de suspendre les autorisations de mise sur le marché pour tous les médicaments contenant du benfluorex en France, en raison d'une augmentation du risque de signal de cardiotoxicité (maladies valvulaires cardiaques) avec le benfluorex.

La décision de l'autorité compétente française était fondée sur les résultats actualisés d'une étude de pharmacovigilance, les données préliminaires de 3 études cliniques (l'étude rétrospective cas-témoin réalisée dans un hôpital de Brest, l'essai REGULATE et les données du fonds national d'assurance maladie française) et d'une publication récente (K. Boutet *Fenfluramine-like cardiovascular side-effects of Benfluorex,* Eur. Respir. J. 2009; 33: 684-688), qui ont décelé un risque de maladies des valves cardiaques et d'hypertension pulmonaire (HTP) chez les patients traités par le benfluorex.

Après réception de l'avis d'alerte rapide, l'autorité compétente portugaise a également décidé de suspendre l'autorisation de mise sur le marché de tous les médicaments à base de benfluorex au Portugal, le 30 novembre 2009.

Le CHMP a examiné la question conformément à l'article 107, paragraphe 2, de la directive 2001/83/CE, telle que modifiée, dans le cadre d'une procédure écrite lors des réunions plénières du CHMP de décembre 2009 et de mars 2010.

Sécurité

Les résultats actualisés de l'étude de pharmacovigilance concernant le risque de maladies des valves cardiaques avec le benfluorex et les données d'une publication récente sur ce sujet (K. Boutet *Fenfluramine-like cardiovascular side-effects of Benfluorex,* Eur. Respir. J. 2009; 33: 684-688) ont amené à conclure à l'existence d'une valvulopathie cardiaque et d'HTP dans la population générale des patients utilisant le benfluorex.

De plus, l'étude rétrospective cas-témoin réalisée à Brest afin de chercher un lien entre l'exposition au benfluorex et la survenue d'unc insuffisance mitrale inexpliquée établit une association entre l'exposition au benfluorex et l'apparition d'une valvulopathie.

Sur la base des données susmentionnées, le CHMP considère que le lien entre l'exposition au benfluorex et la survenue de maladies des valves cardiaques est confirmé. Le comité est d'avis que le lien est étayé par les résultats obtenus dans l'étude REGULATE, qui confirme le risque de valvulopathie avec le benfluorex et révèle l'apparition d'anomalies morphologiques et fonctionnelles des valves après seulement 328 jours d'exposition en moyenne.

En outre, les résultats d'une autre étude (étude de cohorte menée par le Fonds national de l'assurance maladie française) ont fait l'objet de commentaires de la part du TAMM dans son document de réponse à la liste de questions adoptée par le comité. Le manque de précision des informations relatives au diagnostic de maladie des valves cardiaques et le nombre limité de patients identifiés comme présentant une maladie des valves cardiaques et traités par le benfluorex (35 patients) ont été soulignés par le TAMM. Le CHMP maintient cependant son avis que ces données confirment elles aussi le signal de sécurité indiquant un risque de maladie des valves cardiaques lors de l'utilisation du benfluorex.

Enfin, se fondant sur les sources de données disponibles, le CHMP estime que le nombre de rapports spontanés de valvulopathies cardiaques associées au benfluorex est considérablement sous-estimé en raison du volume limité de données recueillies à partir des rapports spontanés dans cette situation, comme par exemple:
- le type d'effet du benfluorex (valvulopathie qui reste cliniquement asymptomatique pendant une longue période);
- le temps écoulé avant la survenue de l'événement (une très longue période d'exposition au benfluorex est nécessaire pour induire des modifications valvulaires).

Par conséquent, le CHMP considère que l'aggravation des anomalies fonctionnelles en cas d'exposition prolongée ne pouvait pas être exclue, en particulier au vu de l'utilisation prolongée du produit sur la base de données d'utilisation qui ont fait apparaître un temps d'exposition moyen de 3 ans.

Comme le déclare le TAMM dans sa réponse par écrit, au moment de l'évaluation nationale de l'anomalie valvulaire cardiaque, il a proposé de maintenir le benfluorex sur le marché avec une restriction pour l'indication chez les patients ne présentant pas de signes d'anomalies valvulaires à l'échographie et la mise en œuvre d'une surveillance échocardiographique. Le TAMM a prévu d'interrompre le traitement en cas d'anomalies échocardiographiques.

Le CHMP n'a pas accepté cette proposition. Il estime que la surveillance échocardiographique additionnelle proposée par le TAMM ne pourrait pas apporter de solution à ce problème, du fait que la surveillance échocardiographique évite l'utilisation chez des patients présentant une valvulopathie antérieure, mais n'en évite pas le développement chez des patients qui ne présentent pas d'anomalies antérieures.

Rapport bénéfice/risque

Le benfluorex est utilisé comme «*Traitement adjuvant du régime adapté chez les diabétiques avec surcharge pondérale*». Dans sa réponse par écrit, le TAMM considère qu'il y a un effet clinique significatif consistant sur le contrôle de la glycémie dans toutes les études réalisées avec le benfluorex chez des patients en surcharge pondérale présentant un diabète de type 2. Toutefois, le CHMP constate que le benfluorex est approuvé uniquement en tant que traitement adjuvant dans le traitement du diabète de type 2 chez les patients en surcharge pondérale: sur la base d'une importance très limitée de l'efficacité chez les patients diabétiques, il n'a jamais été accordé une indication en tant que monothérapie pour le traitement du diabète pour le benfluorex. En conséquence, le CHMP, après examen des données fournies par le TAMM et l'État membre, considère que le bénéfice du benfluorex n'est que limité dans la prise en charge du diabète de type 2.

Les résultats actualisés de la seconde étude nationale de pharmacovigilance, les données préliminaires de 3 études cliniques (l'étude rétrospective cas-témoin réalisée dans un hôpital de Brest, l'essai

REGULATE et les données de l'étude du Fonds national de l'assurance maladie française), ainsi que la publication récente de K. Boutet, démontrent le risque grave de valvulopathies cardiaques morphologiques et fonctionnelles et d'hypertension pulmonaire, associé à l'utilisation du benfluorex.

Le comité a noté que des anomalies valvulaires cardiaques morphologiques et fonctionnelles peuvent s'observer après seulement 328 jours d'exposition en moyenne. En outre, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée n'est pas exclue; cela suscite une inquiétude particulière étant donnée l'utilisation prolongée du produit, avec une durée d'exposition moyenne de 3 ans (sur la base des données d'utilisation).

Compte tenu de tous ces éléments, le CHMP a conclu que les médicaments à base de benfluorex sont nocifs dans les conditions normales d'utilisation et que le rapport bénéfice/risque pour benfluorex n'est pas considéré comme étant favorable. En conséquence, le comité a recommandé le retrait des autorisations de mise sur le marché pour les médicaments mentionnés dans l'annexe I.

MOTIFS DU RETRAIT DES AUTORISATIONS DE MISE SUR LE MARCHÉ

Considérant que

- le comité a pris en considération la procédure au titre de l'article 107 de la directive 2001/83/CE, telle que modifiée, pour les médicaments à base de benfluorex;

- le comité a conclu, après avoir examiné les données disponibles, que l'utilisation du benfluorex est nocive dans les conditions normales d'utilisation et conduit à une hypertension pulmonaire et à des valvulopathies cardiaques. Ces valvulopathies peuvent induire un affaiblissement progressif de la fonction cardiaque et des symptômes cliniques associés nécessitant, dans les cas graves, une chirurgie cardiaque;

- le comité a noté que des anomalies valvulaires cardiaques morphologiques et fonctionnelles peuvent s'observer après seulement 328 jours d'exposition en moyenne. En outre, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée n'est pas exclue, ce qui suscite une inquiétude particulière étant donné l'utilisation prolongée du produit, avec une durée d'exposition moyenne de trois ans (sur la base de données d'utilisation);

- le comité a examiné le rapport bénéfice-risque du benfluorex dans les conditions normales d'utilisation et a estimé que le risque prouvé susmentionné de maladie des valves cardiaques n'est pas acceptable, compte tenu du fait que le bénéfice du benfluorex n'est que limité dans le traitement du diabète de type 2;

- le comité, à la lumière des résultats ci-dessus, a conclu que le rapport bénéfice/risque des médicaments à base de benfluorex n'est pas favorable dans les conditions normales d'utilisation.

En application des dispositions de l'article 107, paragraphe 2, de la directive 2001/83/CE, telle que modifiée, le comité des médicaments à usage humain (CHMP) de l'Agence recommande le retrait des autorisations de mise sur le marché pour tous les médicaments à base de benfluorex énumérés dans l'annexe I.

Annexe 4-47

afssaps

Agence française de sécurité sanitaire
des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

Saint-Denis, le 20 JUIL. 2010

Madame le Pharmacien responsable
LES LABORATOIRES SERVIER
22 rue Garnier
92200 NEUILLY-SUR-SEINE CEDEX

Lettre recommandée avec avis de réception
1A 039 356 56 04 5

Dossier suivi par : BP/DBM/DR

Réf. : VNL 10008 (CIS 6 242 648 7)
COM AMM 484

Madame,

Je vous prie de bien vouloir trouver ci-joint la décision de retrait de l'autorisation de mise sur le marché de la spécialité pharmaceutique :

MEDIATOR 150 mg, comprimé enrobé.

La présente décision peut faire l'objet d'un recours contentieux devant la juridiction administrative compétente dans un délai de deux mois à compter de la date de réception.

Je vous prie d'agréer, Madame, l'expression de ma considération distinguée.

Le Directeur Général

Jean MARIMBERT

afssaps
Agence française de sécurité sanitaire des produits de santé
Direction de l'Evaluation des Médicaments et des Produits Biologiques

Saint-Denis, le 20 JUIL. 2010

Réf. : VNL 10008 (CIS 6 242 648 7)
COM AMM 484

DECISION

du 20 JUIL. 2010

portant retrait de l'autorisation de mise sur le marché du médicament :

MEDIATOR 150 mg, comprimé enrobé

LE DIRECTEUR GENERAL DE L'AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Vu la directive 2001/83/CE du Parlement européen et du Conseil du 6 novembre 2001 instituant un code communautaire relatif aux médicaments à usage humain, notamment l'article 107 ;

Vu le code de la santé publique, cinquième partie, notamment les articles L. 5121-9, L. 5121-20, R. 5121-21 et suivants, ainsi que l'article R.5121-158 ;

Vu la décision du Directeur général de l'Agence française de sécurité sanitaire des produits de santé (Afssaps) en date du 24 novembre 2009, portant suspension à compter du 30 novembre 2009 de l'autorisation de mise sur le marché (AMM) de la spécialité pharmaceutique MEDIATOR 150 mg, comprimé enrobé et ce, dans l'attente de la décision de la Commission européenne prise en application de l'article 107 de la directive susmentionnée ;

Vu l'avis de l'Agence Européenne des Médicaments (EMA) formulé le 18 mars 2010 par le Comité des Médicaments à Usage Humain (CHMP) ;

Vu la décision de la Commission européenne en date du 14 juin 2010, jointe en annexe à la présente décision ;

Vu l'avis de la Commission d'AMM prévu à l'article R. 5121-50 du code de la santé publique, en date du 1er juillet 2010, par lequel elle se prononce contre le maintien sur le marché de la spécialité pharmaceutique MEDIATOR 150 mg, comprimé enrobé ;

Vu la lettre du 6 juillet 2010 informant Les Laboratoires Servier de l'intention de l'Afssaps de retirer l'AMM de la spécialité pharmaceutique MEDIATOR 150 mg, comprimé enrobé et les invitant à présenter leurs observations ;

Vu la réponse des Laboratoires Servier en date du 15 juillet 2010 ;

Considérant le principe général de prééminence de la protection de la santé publique énoncé par le second considérant de la directive 2001/83/CE précitée ;

Considérant qu'aux termes des articles L.5121-9 et R.5121-47 du code de la santé publique, l'AMM peut être retirée notamment lorsque l'évaluation des effets thérapeutiques positifs du médicament au regard des risques pour la santé du patient ou la santé publique liés à sa qualité, sa sécurité ou son efficacité n'est pas considérée comme favorable ou lorsque l'effet thérapeutique annoncé fait défaut ;

Considérant que les notions de nocivité et d'effet thérapeutique ne peuvent être examinées qu'en relation réciproque et n'ont de signification relative qu'appréciées en fonction de l'état d'avancement de la science et compte tenu de la destination du médicament ;

Considérant que l'exigence d'une évaluation du rapport bénéfice/risque présenté par un médicament ne vise pas exclusivement l'octroi de l'AMM, mais implique une évaluation continue ;

Considérant l'alerte rapide émise par l'Afssaps le 25 novembre 2009, informant l'ensemble des Etats membres, l'EMA et la Commission européenne conformément à l'article 107 de la directive 2001/83/CE précitée, de sa décision de suspendre les AMM de tous les médicaments contenant du benfluorex en France, en raison de l'augmentation du risque de cardiotoxicité (maladies valvulaires cardiaques) ;

Considérant qu'au terme de l'évaluation qu'il a menée et ayant concerné l'ensemble des médicaments contenant du benfluorex autorisés dans l'Union européenne, le CHMP de l'EMA a conclu que l'utilisation du benfluorex est nocive dans les conditions normales d'utilisation et conduit à des valvulopathies cardiaques. Ces valvulopathies peuvent induire une altération progressive de la fonction cardiaque et des symptômes cliniques associés nécessitant, dans les cas graves, une chirurgie cardiaque de remplacement des valves. Il a également noté que des anomalies valvulaires cardiaques morphologiques et fonctionnelles peuvent s'observer après seulement 328 jours d'exposition en moyenne. En outre, une aggravation des anomalies fonctionnelles en cas d'exposition prolongée n'est pas exclue, ce qui suscite une inquiétude particulière étant donné l'utilisation prolongée du produit, avec une durée moyenne d'exposition de trois ans (sur la base de données d'utilisation) ;

Considérant qu'après avoir examiné le rapport bénéfice/risque du benfluorex dans les conditions normales d'utilisation, il a estimé que le risque prouvé susmentionné de maladie des valves cardiaques n'est pas acceptable, compte tenu du fait que le bénéfice du benfluorex n'est que limité dans le traitement du diabète de type 2 ;

Considérant que, au vu de ces éléments, le CHMP a adopté le 18 mars 2010 un avis recommandant à la Commission européenne d'enjoindre aux Etats membres de retirer les AMM de tous les médicaments à base de benfluorex ;

Considérant que suite à cet avis, la Commission européenne a, par décision du 14 juin 2010, demandé aux Etats membres concernés de retirer les AMM délivrées au niveau national des médicaments contenant du benfluorex, dont votre spécialité MEDIATOR 150 mg, comprimé enrobé et ce, en application des dispositions de l'article 107, paragraphe 2 de la directive 2001/83/CE précitée, au motif que l'évaluation des effets thérapeutiques positifs de ces produits au regard des risques pour la santé du patient liés à leur sécurité n'est pas favorable dans les conditions normales d'emploi ;

Considérant l'obligation incombant aux Etats membres de l'Union européenne de prendre toute mesure nécessaire à la mise en œuvre d'une décision de la Commission européenne prise dans le cadre de l'article 107 de la directive 2001/83/CE précitée ;

DECIDE:

ARTICLE 1er
L'autorisation de mise sur le marché octroyée validée le 22 avril 1987 à la spécialité pharmaceutique dénommée :

MEDIATOR 150 mg, comprimé enrobé,

dont le titulaire est :
LES LABORATOIRES SERVIER

est retirée sous toutes ses présentations.

ARTICLE 2
Le titulaire doit prendre toutes dispositions, notamment auprès des détenteurs de stocks, en vue de faire cesser la délivrance au public de la spécialité.

ARTICLE 3
Conformément au 3ème alinéa de l'article L. 5124-11 du code de la santé publique, l'exportation de la spécialité est interdite.

ARTICLE 4
Le Directeur de l'Evaluation des Médicaments et des Produits Biologiques et le Directeur de l'Inspection et des Etablissements sont chargés, chacun en ce qui le concerne, de l'exécution de la présente décision qui sera publiée par extrait au journal officiel de la République Française.

Fait à Saint-Denis, le 20 JUIL. 2010

Le Directeur Général

Jean MARIMBERT

Annexe 4-48

Rapport de déclarations

Agents Afssaps ayant déclaré un lien avec le laboratoire SERVIER

Date d'extraction de FIDES : 05/01/2011 - Période de mandats actifs : du 01/01/1993 au 05/01/2011

BERTHIER Gerard PERSONNEL
Déclaration du 06/04/2009 :
PAR - INSTITUT DE RECHERCHE SERVIER. [cadre de recherche en cancérologie] - [conjointe] - [du 01/10/1985 au]
Déclaration du 29/03/2006 :
PAR - INSTITUT DE RECHERCHE SERVIER. [cadre de recherche en cancérologie] - [conjointe] - [du 01/10/1985 au]

BINE SCHECK Florence PERSONNEL
Déclaration du 11/01/2010 :
{Autre} - . [inchangé par rapport à la dernière déclaration] - [ ]
Déclaration du 18/02/2009 :
{Autre} - JANSSEN. [CDI medecin assistant/médecin produit] - [ ] - [du 01/01/1986 au 01/02/1988]
{Autre} - UPSA-BMS. [CDI medecin de gamme puis Directeur Médical Gammes thérapeutiques] - [ ] - [du 01/02/1988 au 31/05/1998]
{Autre} - IRIS SERVIER. [Chef de projet international senior] - [ ] - [du 01/06/1999 au 28/02/2001]
{Autre} - COPPELIA. [Directeur Médical] - [ ] - [du 01/04/2001 au 30/06/2002]
Déclaration du 21/03/2006 :
LD-ODE - LABORATOIRES JANSSEN. [medecin assistant/médecin produit] - [CDI] - [du 01/01/1986 au 01/02/1988]
LD-ODE - LABORATOIRESUPSA PUIS IDEMGROUPE BMS. [medecin de recherche clinique
Médecin de gammes
Directeur médical Gammes thérapeutiques] - [CDI] - [du 01/02/1988 au 31/05/1998]
LD-ODE - IRIS/SERVIER. [Chef de Projet International senior] - [CDI] - [du 01/06/1999 au 28/02/2001]
LD-ODE - AGENCE MéDICALE COPPéLIA. [Directeur Médical] - [CDI] - [du 01/04/2001 au 30/06/2002]

DAUBIN Claire PERSONNEL
Déclaration du 03/12/2008 :
PAR - LABORATOIRE SERVIER. [Responsable Projet Internet] - [Conjoint] - [du

01/01/2007 au]

DE VERDELHAN Arnaud PERSONNEL
GT REFERE
Déclaration du 01/12/2009 :
Absence de lien
Déclaration du 03/12/2008 :
Absence de lien
Déclaration du 07/11/2007 :
Absence de lien
Déclaration du 03/03/2006 :
LD-ODE - AVENTIS PASTEUR MSD. [responsable technico-réglementaire] - [CDD] - [du 03/11/2004 au 11/03/2005]
LD-ODE - LES LABORATOIRES SERVIER. [Stagiaire (6 mois)
Intérim cadre enregistrement international (6 mois)] - [Stage puis intérim] - [du 22/09/2003 au 30/09/2004]

DEMOLIS Pierre PERSONNEL
AMM
COPratiqu
Exp.AMM
+GTPTC
+Exp.CEPP
+GTPTC2
+GTCARDIO
Déclaration du 08/06/2010 :
Absence de lien
Déclaration du 28/02/2006 :
Absence de lien
Déclaration du 11/04/2003 :
VB - ASTRA ZENECA - BOEHRINGER INGELHEIM - THERVAL MEDICAL - PFIZER - NOVARTIS - MENARINI - ORION. [AEMSSI (Association loi 1901) Service Hématologie - Hôpital de Bicêtre]
Déclaration du 05/03/2003 :
IP-EC - SERONO.
IP-EC - NOVARTIS.
IP-EC - AMGEN.
IP-EC - UCB.
IP-EC - LILLY.
IP-EC - BMS.
IP-EC - PFIZER.
IP-AC - ORION PHARMA. [Organisation d'études cliniques]
IP-AC - SERONO. [Organisation d'études cliniques]
IP-AC - NOVARTIS. [Organisation d'études cliniques]
IP-CF - SERVIER.
IP-CF - ASTRA ZENECA.
IP-CF - MENARINI.

VB - Divers laboratoires mentionnés ci-dessus. [Hôpital de Bicêtre AEMSSI (Association 1901)]
Déclaration du 29/06/2000 :
IP-AC - SCORPION - Agence de communication domaine pharmacologie cardiovasculaire. [Conseil technique sur aspects pharmacologiques antihypertenseurs]
IP-CF - ASTRA ZENECA, GLAXO WELLCOME, SANOFI SYNTHELABO. [Diverses interventions Symposia : pharmacologie de anti-HTA, physipathologie de l'HTA]
VB - BIOCODEX France. [1 Essai actuellement terminé - Analyse en cours : Association Claude Bernard]

FEDRIGO-DOUSSET Caroline PERSONNEL
Déclaration du 08/04/2009 :
PAR - SERVIER. [Directeur régional] - [conjoint]
PAR - SERVIER. [Directeur régional] - [conjoint]
Déclaration du 27/03/2006 :
PAR - SERVIER. [Directeur régional] - [conjoint]
PAR - SERVIER. [Directeur régional] - [conjoint]

HUEBER Stephanie PERSONNEL
Déclaration du 18/03/2009 :
PAR - LABORATOIRE SERVIER. [Chef de projet préclinique] - [Belle-Soeur] - [du 02/12/2008 au]
Déclaration du 20/02/2008 :
CF-AUD - SFPT. [Société française de pharmacologie et de thérapeutique. Congrès annuel Toulouse 2007] - [ ] - [du 12/04/2007 au 12/04/2007]
PAR - LABORATOIRE SMITH AND NEPHEW. [Visiteuse Médicale] - [Soeur] - [du 14/01/2008 au]
Déclaration du 03/03/2006 :
PAR - LABORATOIRE MENARINI. [Visiteuse Médicale] - [Soeur] - [du 01/07/2004 au]

JACQUET Alexis PERSONNEL
Déclaration du 23/11/2010 :
PAR - LABORATOIRE SERVIER. [Chef de Département pré-clinique cancérologie] - [Conjoint] - [du 01/01/2001 au]
Déclaration du 08/03/2010 :
PAR - LABORATOIRE SERVIER. [Chef de Département pré-clinique cancérologie] - [Conjoint] - [du 01/01/2001 au]
Déclaration du 21/10/2008 :
Absence de lien

Déclaration du 24/05/2004 :
PAR - SERVIER. [Conjoint]

LEREBOURSPIGEONNIERE
Sylvie PERSONNEL
Déclaration du 06/05/2010 :
IF - ROCHE HOLDING. [Actions] - [>=5000 €
ou >=5% du capital] - [du 01/01/1983 au]
PAR - SERVIER. [Directeur de la division
cardiorespiratoire] - [Conjoint] - [du 01/12/1989 au]
Déclaration du 03/06/2008 :
PAR - SERVIER. [Directeur de la division
cardiorespiratoire] - [Conjoint] - [du 01/12/1989 au]
Déclaration du 14/04/2006 :
PAR - SERVIER. [Directeur de la division
cardiorespiratoire] - [Conjoint] - [du 01/12/1989 au]

LESOURD Monique PERSONNEL
Déclaration du 11/03/2010 :
Absence de lien
Déclaration du 11/03/2009 :
{Autre} - IRIS. [salariée] - [ ] - [du 15/10/1988 au
27/07/2005]
Déclaration du 16/04/2008 :
{Autre} - INSTITUT DE RECHERCHE
INTERNATIONALE SERVIER. [industrie
pharmaceutique] - [ ] - [du 15/10/1988 au
27/07/2005]
Déclaration du 17/08/2007 :
{Autre} - SERVIER. [salariée] - [ ] - [du 15/10/1988
au 27/07/2005]

MARLIAC Nathalie PERSONNEL
Déclaration du 01/12/2010 :
PAR - SERVIER. [Secrétaire
] - [Belle-soeur]
Déclaration du 23/02/2010 :
Absence de lien
Déclaration du 25/02/2009 :
Absence de lien
Déclaration du 01/04/2008 :
Absence de lien
Déclaration du 08/08/2007 :
Absence de lien
Déclaration du 23/03/2006 :
Absence de lien

MOUKHEIBER Carole PERSONNEL
Déclaration du 26/02/2010 :
PAR - SERVIER. [Conseiller pour les
opérations internationales] - [père] - [du 01/10/2009
au]
Déclaration du 25/02/2009 :
PAR - SERVIER. [Directeur général des
opérations internationales (Afrique, Asie,

Dom/Tom)] - [père] - [du 01/11/1978 au 30/09/2009]
Déclaration du 17/04/2008 :
PAR - SERVIER. [Directeur général des opérations internationales (Afrique, Asie, Dom/Tom)] - [père] - [du 01/11/1978 au]
Déclaration du 28/02/2006 :
PAR - SERVIER. [Directeur général des opérations internationales (Afrique, Asie, Dom/Tom)] - [père] - [du 01/11/1978 au]

Extraction RAPPORT DPI 2009
Membres instances ayant déclaré un lien avec le laboratoire SERVIER

ALLAUZEN Nadine GTCNP PCC Titulaire **Déclaration du 30/01/2009 :**
LD - SCIENCE UNION (SERVIER) [Chef de Département Affaires Réglementaires] [CDI] du 01/05/1997 au

AMBROSI Pierre COPratiqu Titulaire **Déclaration du 30/09/2009 :**
RE-AUT - BOEHRINGER-INGELHEIM [Micardis, dossier de transparence] [Rémunération personnelle] du 10/06/2009 au
Déclaration du 02/01/2009 :
EC-INV - MSD [Ezetimibe Etude MK653 A-808] [coordinateur national (étude internationale) honoraires versés à une association] du 01/01/2004 au 31/12/2007
EC-CO - SERVIER [Psychotrope (interprétation d'ECG) (étude en cours)] [honoraires versés à une association]
IP-AC - PIERRE FABRE [Avis avant achat éventuel de la molécule - ranolazine] [rémunération personnelle] du 01/01/2007 au 31/12/2007
IP-AC - NOVARTIS [Aliskiren] [rémunération personnelle] du 01/01/2008 au 31/12/2008
CF-AUD - SERVIER [Congrès européen de cardiologie] du 01/09/2008 au 30/09/2008
VB - [Budgets de recherches des 188 PU et PH membres de l'association] [ADEREM] du 01/01/2003 au

BAILLET-GUFFROY
Arlette
CNP
GTCOSIngr
GTCNP PCC
GTCOSdoss
Titulaire
Titulaire
Titulaire
Titulaire
Déclaration du 28/11/2009 :
LD-AR - EXPANSCIENCE [Consultant enregistrement France] [rémunération personnelle (rémunération régulière)]
LD-AR - SERVIER [Consultant enregistrement international] [rémunération personnelle (contrat 1 an renouvelable)]
RE-AUT - DOW CORNING [CEP] [rémunération personnelle] du 01/01/2009 au 31/12/2009
Déclaration du 26/03/2009 :
LD-AR - ADIR [Conseil en CMC (en cours)] [rémunération personnelle]
LD-AR - EXPANSCIENCE [Conseil en analyse et module 3 (en cours)] [rémunération personnelle]
LD-AR - SERVIER [Consultant CMC (contrat 1 an renouvelable)]

BAILLIART Olivier OAM Titulaire **Déclaration du 04/09/2009 :**
PAR - SERVIER [Directeur ingénieur informatique] [fils] du 01/01/2004 au
PAR - SERVIER [Directeur ingénieur informatique] [fils] du 01/01/2004 au

BAKCHINE Serge AMM
GTNPA
Titulaire

Titulaire
Déclaration du 16/12/2009 :
IP-AC - SERVIER [conseil scientifique étude CL2-38093-005. phase IIb (Alzheimer)] [Rémunération personnelle] du 01/01/2009 au 31/12/2009
IP-AC - BIOGEN [participation à 1 advisory board (activité troubles cognitifs et SEP)] [Aucune rémunération] du 01/01/2009 au 31/12/2009
IP-AC - FONDATION LUNDBECK [participation à 1 advisory board (activités démence)] [Rémunération personnelle] du 01/01/2000 au 31/12/2009
IP-AC - WYETH [Conseil methodologique (tests neuropsychologie) études alzheimer] [Rémunération personnelle] du 01/01/2009 au 31/12/2009
EC-CO - PIERRE FABRE [PARKINSON (fatigue) /Etude DC0158 AM 401 1B prolongation de l'inclusion] [co-investigateur] du 30/12/2009 au 30/06/2010
EC-CO - WYETH [ALZHEIMER/etude 31333K1-bapizumab (reprise étude suspendue)] [co-investigateur] du 01/09/2009 au 01/09/2012
EC-CO - IRIS-SERVIER [ALZHEIMER/CL2-38093-005. phase IIb] [coinvestigateur et conseiller scientifique pour l'étude] du 02/11/2009 au 30/06/2010

BLIN Olivier GEBIOméd Titulaire **Déclaration du 17/04/2009 :**
CF-AUD - SERVIER [Congrès européen de Neurologie à Barcelone]
RE-DE - UCB PHARMA [Rémunération personnelle]
EC-CO - TROPHOS [Aide logistique]
EC-CO - TAHIO [Aide logistique]
EC-CO - SERVIER [Aide logistique]
EC-CO - SCHERING [Aide logistique]
EC-CO - SCHERING PLOUGH [Aide logistique]
EC-CO - QUINTILES [Aide logistique]
EC-CO - KENDLE [Aide logistique]
EC-CO - PFIZER [Aide logistique]
EC-CO - NEUROSEARCH ACADIA [Aide logistique]
EC-CO - MUNDI PHARMA [Aide logistique]
EC-CO - MERCK [Aide logistique]
EC-CO - LILLY [Aide logistique]
EC-CO - KENDLE [Aide logistique]
EC-CO - IPSEN [Aide logistique]
EC-CO - EISAI [Aide logistique]
EC-CO - EXILIS [Aide logistique]
EC-CO - BMS [Aide logistique]
EC-CO - BIOPROJET [Aide logistique]
EC-CO - ROCHE [Aide logistique]
EC-CO - BAYER [Aide logistique]
EC-CO - AVANTAGE NUTRITION [Aide logistique]
EC-CO - ASTRA ZENECA [Aide logistique]
EC-CO - ARIAD [Aide logistique]
EC-CO - AMGEN [Aide logistique]
EC-CO - ALLERGAN [Aide logistique]
EC-CO - ABSCIENCE [Aide logistique]
Déclaration du 03/03/2009 :
CF-AUD - SERVIER [Congrès des Pharmacologues du Sud-Est à Montpellier]
CF-AUD - PFIZER [Journées Interdisciplinaires à Monaco]
CF-AUD - EUTHERAPIE [APA à Washington]
CF-INT - SANOFI-AVENTIS [Sarudant à Paris] [Rémunération personnelle]
CF-INT - SERVIER [Congrès européen de Barcelone (Valdoxan) P2T à clermont-Ferrand] [Rémunération personnelle]
CF-INT - BMS [Valence (France) Ponta Delgada (Açores) Nimes (France) Uzès

(France)] [Rémunération personnelle]
IP-AC - UCB [Seglor] [Rémunération personnelle]
IP-AC - MAYOLI-SPINDLER [Météoplasmine Mégamag] [Rémunération personnelle]
IP-AC - PIERRE FABRE [V0191 Debrumyl] [Rémunération personnelle]
RE-AUT - CRCI PACA [Dossiers : 06-013-C0109 07-013-C-0079 08-013-C-0034] [Rémunération personnelle]
RE-DE - CEPHALON [Armolafinil] [Rémunération personnelle]
RE-DE - AP-HP [Résilience] [Rémunération personnelle]
RE-DE - GW PHARMA [Sativex] [Rémunération personnelle]
RE-DE - WYETH [Bapineuzumab] [Rémunération personnelle]

BONNEVIE Lionel
BIOVIG Suppléant
Déclaration du 20/03/2007 :
CF-AUD - SERVIER [Journées européennes SFC - Paris] du 18/01/2006 au 18/01/2006
CF-AUD - ASTRAZENECA [MSDA - Marrakech] du 24/05/2006 au 24/05/2006
CF-AUD - MERCK-LIPHA [Heart Failure - Helsinki] du 17/06/2006 au 17/06/2006
CF-AUD - ASTRAZENECA [European society of cardiology : congrès annuel (Barcelone)] du 02/09/2006 au 06/09/2006

BORDET Régis STUP Titulaire **Déclaration du 02/06/2009 :**
LD-AR - GENFIT [Conseiller scientifique] [rémunération institution] du 01/01/2003 au
EC-INV - SERVIER [Evaluation d'agents neuroprotecteurs] [expérimentateur principal] du 01/01/2001 au 31/12/2005
EC-INV - ASTRA ZENECA [Evaluation d'agents neuroprotecteurs] [expérimentateur principal] du 01/01/2005 au 31/12/2007
EC-CO - GENFIT / PFIZER [Etudes des effets neuroprotecteurs de l'atorvastatine] [expérimentateur non principal] du 01/01/2006 au 31/12/2007
RE-AUT - LUNDBECK [Rapport pour la Commission de la transparence sur la rasagiline] [rémunération institution] du 01/01/2008 au
CF-INT - JANSSEN CILAG, LUNDBECK, PFIZER, EISAI, SANOFI AVENTIS, BOEHRINGER INGELHEIM [rémunération personnelle]
CF-AUD - SERVIER [ECNP 2007 - Vienne] du 01/09/2007 au 30/09/2007

BOUCCARA Didier GT POO Titulaire **Déclaration du 16/01/2009 :**
LD-AR - GROUPE AMPLIFON [Participation à un groupe assurant régulièrement (2 à 3 fois par an) une formation consacrée aux vertiges et à leurs explorations] [rémunération personnelle] du 01/01/2006 au
EC-CO - PHRC [Evaluation des implants de l'oreille moyenne dans la stratégie thérapeutique de la réhabilitation auditive - étude randomisée multicentrique APHP] [Co-investigateur : réalisation des évaluations cliniques] du 01/01/2007 au 31/12/2009
EC-CO - [Acetyl leucine - étude multicentrique randomisée Acetyl leucine à différentes posologies versus placebo, au cours de la névrite vestibulaire] [Coinvestigateur : réalisation des évaluations cliniques] du 30/01/2008 au 31/01/2009
IP-AC - SERVIER [Rédaction d'un article concernant les résultats de l'étude France Cochlée] [aucune rémunération] du 15/01/2007 au 15/10/2007
IP-AC - UCB PHARMA [Rédaction d'un rapport ponctuel] [aucune rémunération] du 01/01/2005 au 31/03/2005

CF-AUD - SERVIER [10 th International Conference on cochlear implants and other implantable auditory technologies - San Diego] du 10/04/2008 au 12/04/2008
CF-AUD - ENTENDRE [Enseignement Post-Universitaire du Collège National d'Audioprothèse - Paris] du 05/12/2008 au 05/12/2008

BOULENGER Jean-Philippe
GTNPA Titulaire **Déclaration du 08/08/2009 :**
CF-INT - JANSSEN [Rencontre scientifique sur les antipsychotiques à action prolongée (Montpellier)] [rémunération personnelle] du 10/06/2009 au 10/06/2009
CF-INT - BIOCODEX [Symposium sur anxiété aux différents stades de la vie (aspects biologiques)] [rémunération personnelle] du 03/06/2009 au 03/06/2009
CF-INT - SERVIER [Congrès de la WPA , Florence : symposium agomélatine (Valdoxan)] [Rémunération personnelle] du 02/04/2009 au 03/04/2009
IP-AC - LUNDBECK DANEMARK [Board scientifique escitalopram] [rémunération personnelle] du 06/05/2009 au 06/05/2009
CF-INT - SANOFI-AVENTIS TUNISIE [Symposium : Innovations thérapeutiques dans la dépression (Athènes)] [rémunération personnelle] du 01/11/2008 au 02/11/2008
CF-INT - LILLY [Congrès CIPPEG : état dépressif du sujet âgé (Montpellier)] [rémunération personnelle] du 04/12/2008 au 04/12/2008
CF-INT - SANOFI-AVENTIS TUNISIE [Symposium sur troubles anxieux et leur traitement (Tozeur)] [rémunération personnelle] du 14/03/2009 au 15/03/2009
CF-INT - LILLY [Congrès CIPPEG (Montpellier)] [rémunération personnelle] du 12/12/2008 au 12/12/2008
CF-INT - SANOFI-AVENTIS [Symposium innovation thérapeutique , Athènes] [Rémunération personnelle] du 01/11/2008 au 02/11/2008
EC-CO - BIOCODEX [Caractérisation psychophysiologique des troubles de l'adaptation . Pas de produit impliqué dans cette étude] [membre du comité scientifique] du 01/01/2009 au
EC-CO - SIGMA-TAU [Etude Lysanxia vs Xanax dans le sevrage des traitements benzodiazépiniques] [membre du comité scientifique] du 01/01/2009 au
EC-INV - LUNDBECK [LUAA21004 : étude de prévention de rechute dans trouble anxieux généralisé] [coordonnateur national] du 01/06/2008 au
EC-CO - SANOFI-AVENTIS [Programme-pilote d'accès au médicament en santé mentale dans les pays en développement] [membre du comité scientifique] du 01/01/2008 au

BRION Jean-Daniel CS Titulaire **Déclaration du 08/02/2009 :**
EC-INV - LABORATOIRES SERVIER [Recherche pharmacochimique de molécules à potentialité thérapeutique] [Contrat de recherche : Université Paris-Sud - CNRS - SERVIER Responsable de la synthèse chimique des molécules] du 01/10/2000 au 30/09/2009

CHABRIAT Hugues GTNPA Titulaire **Déclaration du 27/01/2009 :**
LD-AR - LUNDBECK [Membre du steering committee (étude DIAS 4 : desmoteplase et infarctus cérébral)] [rémunération personnelle] du 01/06/2008 au 31/12/2010
LD-AR - SERVIER [Memebre du steering committee pour la sous étude IRM (étude PERFORM, terutroban et infarctus cérébral)] [rémunération personnelle] du 01/01/2008 au 31/12/2011
LD-AR - JOHNSON & JOHNSON [Membre de l'Adjudication Committee]

[rémunération personnelle] du 01/01/2008 au 31/12/2011
EC-INV - LUNDBECK [Desmoteplase] [investigateur principal et coordonnateur en France] du 01/11/2008 au 31/12/2010
EC-INV - DELEGATION RECHERCHE CLINIQUE PHRC CADASIL [Suivi d'une cohorte de patients] [investigateur principal] du 01/01/2006 au 31/12/2011
EC-CO - DELEGATION RECHERCHE CLINIQUE PHRC [Identification des gènes impliqués dans les leucoencéphalopathies vasculaires - cohorte et analyse clinique] [co-investigateur] du 01/01/2007 au 31/12/2011
CF-AUD - LUNDBECK [Réunion VASCOG - Singapour] du 01/01/2009 au 31/01/2009

CHAMINADE Pierre CNP
GTBIOTECH
GTAllergb
GTCNP ALG
Titulaire
Titulaire
Titulaire
Titulaire
Déclaration du 13/02/2009 :
VB - TECHNOLOGIES SERVIER [Contrat de Recherche / Thèse CIFRE] [Faculté de Pharmacie Paris Sud Laboratoire de Chimie Analytique] du 01/01/2009 au 01/01/2012

CHASSANY Olivier COQualif
GTPMF
Titulaire
Titulaire
Déclaration du 20/03/2009 :
IP-AC - SERVIER [Conseil sur les critères de qualité de vie pour une étude clinique dans la coronaropathie (SIGNIFY)] [Rémunération institution] du 14/01/2009 au

CHAVATTE Philippe GTCNP PCC Titulaire **Déclaration du 12/09/2006 :**
VB - SERVIER [Bourses de thèse] [ICPAL] du 01/01/2003 au
VB - SERVIER [Taxes d'apprentissage] [ICPAL] du 01/01/2003 au
VB - SERVIER [subventions] [EA 1043] du 01/01/2003 au

CLAUDE Jean-Roger AMM
GTPRECLIN
GTONCO
GTcardio/
GT INC
Titulaire
Titulaire
Titulaire
Titulaire
Titulaire
Déclaration du 02/03/2009 :
LD-AR - BMS [Consultant tous produits] [rémunération personnelle] du 01/02/1990 au
LD-AR - BAYER PHARMA [Consultant tous produits] [rémunération personnelle] du 01/01/1987 au
LD-AR - GSK [Consultant tous produits] [rémunération personnelle] du 01/01/2001 au

LD-AR - SERVIER [Consultant tous produits] [rémunération personnelle] du 01/01/1972 au
LD-AR - MERCK THERAMEX [Consultant tous produits] [rémunération personnelle] du 01/01/1989 au 30/06/2008
LD-AR - NEGMA [Consultant tous produits] [rémunération personnelle] du 01/01/1999 au 31/12/2007
LD-AR - PIERRE FABRE [Consultant tous produits] [rémunération personnelle] du 01/10/2007 au
RE-DE - GUERBET [Produits de contraste IRM] [rémunération personnelle] du 01/01/1987 au
RE-DE - SERVIER [PROTELOS - COVERSYL et dérivés] [rémunération personnelle] du 01/01/1987 au
RE-DE - PIERRE FABRE [NAVELBINE] [rémunération personnelle] du 01/01/1989 au 31/12/2007
CF-INT - MULTIPLES [Multiples : tous les ans depuis 40 ans] [zucune rémunération] du 01/01/1967 au
PAR - SERVIER [Directeur de la toxicologie] [conjoint] du 01/01/1993 au

CORBE Christian GTAutomob Titulaire **Déclaration du 27/06/2006 :**
EC-INV - INSTITUT SERVIER [Trimétazidine 35] [coordinnateur] du 01/01/1998 au 31/12/2007
EC-INV - INSTITUT SERVIER [Ivabradine] [membre du Safety committee en ophtalmologie] du 01/01/2000 au 31/12/2007
CF-INT - IPSEN [Royaumont] [rémunération personnelle] du 01/01/2004 au 31/12/2006
CF-INT - OPTIC 2000 [Djerba] [rémunération personnelle] du 01/01/2005 au 31/12/2005

CORRUBLE
Emmanuelle
GTNPA Titulaire **Déclaration du 03/03/2009 :**
LD-AR - EUTHERAPIE [Conseil] [rémunération personnelle] du 01/01/2006 au
EC-INV - SERVIER INTERNATIONAL [Coordination d'essai] [coordonateur] du 01/01/2007 au 31/12/2010
EC-INV - LILLY France [Coordianation d'essai] du 01/01/2003 au 31/12/2007
CF-INT - SERVIER [ECNP-Environnement dépression] [Rémunération personnelle] du 01/09/2008 au 30/09/2008
CF-INT - BMS [Symposium lancement Aripiprazole] [Rémunération personnelle] du 01/05/2008 au 31/05/2008
CF-INT - EUTHERAPIE [Encéphale-Agomélatine + environnement dépression] [Rémunération personnelle] du 01/05/2009 au 31/05/2009
CF-AUD - UCB-Pharma [American Psychiatric Association] du 01/05/2008 au 31/05/2008

CORTET Bernard GT RA Titulaire **Déclaration du 26/05/2008 :**
IP-AC - MSD [FOSAVANCE] [Rémunération personnelle] du 30/11/2007 au
IP-AC - ROCHE GSK [Bonviva] [rémunération personnelle - activités de conseil 2/3 réunions annuelles et par laboratoire] du 01/01/2005 au
IP-AC - NYCOMED [Preotact] [rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire] du 01/01/2006 au 31/12/2008
IP-AC - SERVIER [Protelos] [rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire] du 01/01/2005 au 31/12/2009
IP-AC - NOVARTIS [Aclasta] [rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire] du 01/01/2005 au

CROCHET Pierre-Dominique
CNDM Suppléant **Déclaration du 02/12/2009 :**
EC-INV - MEDTRONIC [Etude Endeavor (stent actif)] [Investigateur principal] du 01/01/2003 au 31/12/2005
EC-CO - CORDIS [Stent Cypher] [Investigateur] du 01/01/2003 au 31/12/2005
CF-INT - MENARINI [Imagerie cardiologique] [Rémunération personnelle] du 17/11/2005 au 17/11/2005
CF-AUD - SORIN [Congrés Hitech Cardio] du 25/01/2007 au 25/01/2007
CF-AUD - SERVIER [ESC] du 01/09/2008 au 01/09/2008
CF-AUD - MEDITRONIC [Hitech Cardio] du 24/11/2009 au 24/11/2009
Déclaration du 09/01/2009 :
CF-AUD - SERVIER [ESC - Munich] du 01/09/2008 au 30/09/2008
CF-AUD - MEDTRONIC [HITECH cardio - Marseille] du 01/01/2009 au 31/01/2009
CF-AUD - TERUMO [HITECH cardio - Marseille] du 01/01/2008 au 31/01/2008

DAMIEN Gérard GTCNP PCA Titulaire **Déclaration du 02/04/2009 :**
LD-AR - GROUPE DE RECHERCHE SERVIER [CONSULTANT CMC] [Rémunération personnelle] du 02/04/2008 au
LD-AR - GROUPE DE RECHERCHE SERVIER [CONSULTANT CMC] [Aucune rémunération] du 02/04/2008 au 03/04/2008

DANCHIN Nicolas GTcardio/ Titulaire **Déclaration du 11/08/2008 :**
PAR - SERVIER [Médecin direction scientifique France] [épouse]
CF-INT - ASTRA-ZENECA, BAYER, BMS, BOEHRINGER INGELHEIM, GSK, LILLY, MSD, NEGMA, NOVARTIS, PFIZER, SANOFI AVENTIS, SERVIER [Rémunération personnelle]
EC-INV - PFIZER, SERVIER [Pas de produit] [Pfizer et Servier ont fourni des grants pour le registre d'infarctus de la SFC FAST-MI, dont je suis investigateur principal]
EC-INV - SERVIER [Trimetazidine Ivabradine] [trimetazidine : (investigateur - coordonateur étude VASCO) ivabradine : (coordonateur national étude BEAUTIFUL)] du 01/01/2005 au

DE JONG Hendrik-Jan GTCNP PCA Titulaire **Déclaration du 15/02/2009 :**
LD-ODE - SERVIER [Conseiller scientifique] [CDI]

DESSI Fréderic COPratiqu Titulaire **Déclaration du 10/05/2006 :**
LD-AR - SERVIER [veille bibliographique sur les troubles cognitifs] [rémunération personnelle] du 01/01/2000 au 31/03/2006

DETILLEUX Michel AMM
GTPMF
GTGaléniq
Titulaire
Titulaire
Titulaire
Déclaration du 19/06/2009 :
LD-AR - ADIR (GROUPE SERVIER) [Acivité de consultant pour la conception et le déroulement des études cliniques. Veille scientifique.] [Rémunération personnelle] du 01/05/2009 au 30/04/2010
EC-INV - AP-HP [baclofène] [Investigateur principal] du 01/04/2009 au 31/12/2012

DEVILLIER Philippe AMM
GTPTCalle
GT POO
Suppléant
Titulaire
Titulaire
Déclaration du 01/10/2009 :
CF-AUD - STALLERGèNES [AAAAI EAACI]
CF-INT - STALLERGèNES [EAACI Varsovie 2009 AAACI - Washington 2009] [Aucune rémunération]
PAR - BOEHRINGER INGELHEIM [déléguée médicale (en cours)] [conjoint]
VB - SERVIER [Pharmacologie pré-clinique de sécurité] [UPRES EA 220] du 01/01/2007 au 31/12/2009
VB - SANOFI AVENTIS [Recherche pré-clinique] [UPRES EA 220] du 01/01/2003 au
CF-AUD - BOEHRINGER INGELHEIM [P2T Pharmacologie France (tous les ans depuis 5 ans)]
CF-AUD - CHIESI , SCHERING PLOUGH [JPA & CNAA - Paris (tous les ans depuis 5 ans)]
CF-AUD - SCHERING PLOUGH [JPD - Paris (tous les ans depuis 5 ans)]
CF-AUD - SCHERING PLOUGH [EAACI 2008 (tous les ans depuis 5 ans)]
CF-AUD - GLAXOSMITHKLINE, BOEHRINGER INGELHEIM [ERS Europe (tous les ans depuis 5 ans)]
CF-AUD - GLAXOSMITHKLINE, MSD [ATS - USA (Tous es ans depuis 5 ans)]
CF-INT - BOEHRINGER INGELHEIM [P2T Pharmacologie France]
CF-INT - SCHERING PLOUGH [JPD - Paris]
CF-INT - CHIESI, SCHERING PLOUGH [JPA & CNAA - Paris]
CF-INT - SCHERING PLOUGH [AAACI 2005 - USA]
CF-INT - BOEHRINGER INGELHEIM, GLAXOSMITHKLINE, CHIESI, ASTRA ZENECA [CPLF France]
IP-AC - SANOFI AVENTIS [Comité d'expert "safety" développement clinique (en cours)]
IP-AC - STALLERGENES [Groupe experts statistiques - méthodologie développement (en cours)]
IP-AC - CHIESI SA [Groupe d'experts (en cours)]
IP-AC - BIOPROJET PHARMA [Expertise scientifique et médicale - préclinique et clinique (en cours)]
IP-AC - BOEHRINGER-INGELHEIM [Groupe d'experts BPCO (en cours)]
IP-AC - ASTRAZENECA [Groupe d'experts ASTHME - BPCO (en cours)]
IP-AC - GLAXOSMITHKLINE [Expertise scientifique et médicale - pré-clinique et clinique (en cours)]
EC-CO - GLAXOSMITHKLINE [Observatoire (en cours)] [collaborateur (expertise scientifique et statistique)]
EC-CO - SERVIER [Etude pré-clinique / pharmacologie pré-clinique de sécurité : ligands récepteurs histamine (en cours)] [expérimentateur]
EC-CO - SCHERING PLOUGH [Observatoire Scoring rhinite] [investigateur]

DOUCET Jean AMM
GT DEUG
Titulaire
Titulaire
Déclaration du 26/05/2009 :
VB - NOVO-NORDISK [Subvention pour une étude épidémiologique prospective sur les patients diabétiques âgés (sans intervention thérapeutique)]

[Association GERODIAB (loi 1901)] du 15/12/2008 au
VB - MERCK-SERONO [Subvention pour une étude épidémiologique prospective sur les patients diabétiques âgés (sans intervention thérapeutique)] [Association GERODIAB (loi 1901)] du 15/12/2008 au
CF-AUD - NOVO-NORDISK [Réunion Perspectives 2020, Paris] du 06/04/2009 au 07/04/2009
CF-AUD - SERVIER [Congrès de l'ALFEDIAM, Strasbourg] du 17/03/2009 au 20/03/2009

DRICI Milou-Daniel VIG
GTPRECLIN
GTcardio/
Suppléant
Titulaire
Titulaire
Déclaration du 18/03/2009 :
IP-AC - LUNDBECK SA [Conseils en développement du sertindole] [Rémunération personnelle/institution] du 01/11/2008 au 31/05/2009
GEBIOméd Titulaire CF-INT - SERVIER [Formation médicale continue: présentation de l'étude
Advance] [Rémunération personnelle/institution] du 01/12/2008 au 31/12/2008
CF-INT - SERVIER [Formation médicale continue: présentation de l'étude Advance] [Rémunération personnelle/institution] du 01/12/2007 au 31/12/2007
LD-AR - LUNDBECK SA [Sertindole] [Rémunération personnelle/institution] du 01/01/2008 au 01/01/2009
LD-AR - MEDA PHARMA [Activité de Conseil] [Rémunération personnelle/institution] du 01/01/2008 au
LD-AR - DAICHI-SANKYO [Membre Comité de Conseil SEVIKAR] [Rémunération personnelle/institution] du 01/10/2008 au
CF-INT - BOEHRINGER INGELHEIM [Formation médicale continue de délégués médicaux] [rémunération personnelle] du 17/03/2009 au 17/03/2009

DULY-BOUHANICK
Béatrice
GT DEUG
GEBIOméd
Titulaire
Titulaire
Déclaration du 09/10/2009 :
IP-AUT - SERVIER [DIU d'HTA (Tours)] [Remboursement de frais de déplacement] du 15/05/2009 au 15/05/2009
CF-AUD - SERVIER [ALFEDIAM strasbourg] du 17/03/2009 au 20/03/2009
CF-AUD - NOVARTIS [reunion coeur et diabète Paris] du 06/02/2009 au 07/02/2009
IP-AC - LILLY [exenatide: plan de développement] [Rémunération personnelle] du 01/06/2009 au 30/06/2009
EC-CO - BMS [essai multicentrique MB 102 029 dapagliflozine] [investigateur local toulouse] du 07/11/2008 au

FERON Jean-Marc CNDM Titulaire **Déclaration du 30/11/2009 :**
EC-CO - AMGEN [Etude phase 2 AMG 785] [Investigateur] du 01/12/2009 au
EC-CO - SERVIER [Etude Protelos >Pseudarthrose] [Investigateur] du 01/12/2009 au
VB - STRYKER [Educational Grant 2009] [Osteosynthesis and Trauma Care foundation France]
VB - LEO PHARMA [educational grant 2009] [Osteosynthesis and Trauma Care

foundation France]
CF-INT - HERAUS [Palacademie Berlin Ciment chirurgical] [Rémunération personnelle]
CF-INT - SERVIER [Actualité en biologie osseuse Conférencier Paris] [Rémunération personnelle]
IP-AC - NOVARTIS [conseil] [Rémunération personnelle] du 01/07/2009 au
IP-AC - AMGEN [advisory board] [Rémunération personnelle] du 18/06/2009 au
CF-INT - BIOMET [AAOS Las Vegas USA 2009] [Rémunération personnelle]
LD-AR - STRYKER [Brevet, contrat d'exploitation commerciale] [Rémunération personnelle]
CF-INT - STRYKER [JODFDF Martinique 03/08 Workshop traumatologie] [Rémunération personnelle]
CF-INT - LEO PHARMA [Journée Franco européenne d'orthopédie Cork IRL Organisation scientifique] [Rémunération personnelle]
CF-INT - LEO PHARMA [JODFDF Martinique 03/08 Symposium traumatologie] [Rémunération personnelle]
LD-AR - ZIMMER [Brevet, contrat d'exploitation commerciale] [Rémunération personnelle]
CF-AUD - LEO PHARMA [EFORT congress Nice 06/08] [hébergement transport]
CF-AUD - STRYKER [AAOS San Francisco USA 02/08] [hébergement transport]
CF-AUD - STRYKER [JOFDF Martinique 03/08] [hébergement transport]
CF-AUD - STRYKER [réunion OTC fondation Nice 06/08] [hébergement transport]
CF-AUD - STRYKER [International Trauma Congress Barcelona Spain 04/08] [hébergement transport]
VB - SANOFI AVENTIS [Subvention 06/08] [Assoc Chirurgie orthop et communication : Co&Co]

GAYOT Anne AMM
CNP
COPédia
GTPH
GTMG
GTCNPGalé
GTCNP FN
GT PIP
GTGaléniq
Titulaire
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Titulaire
Droit
Déclaration du 17/06/2009 :
CF-INT - INTERNATIONAL DRUG DEVELOPMENT [Développement pharmaceutique validation du procédé] [aucune rémunération] du 01/05/2007 au 31/05/2007
CF-INT - ANDRE REY [Développement pharmaceutique Process Analytical Technology] [rémunération personnelle] du 01/07/2008 au 31/07/2008
CF-AUD - THERAMEX [Académie Theramex] du 01/05/2009 au 31/05/2009

VB - ASTRA-MACO PHARMA-MERCK-TRADIPHAR-SERVIER-BOIRON [Taxe d'apprentissage] [Laboratoire de pharmacotechnie industrielle]
VB - GSK - BMS [Taxe d'apprentissage] [Laboratoire de pharmacotechnie industrielle]
VB - GENFIT [Etudes de caractérisation des matières premières] [Laboratoire de pharmacotechnie industrielle] du 01/01/2008 au 31/12/2008

GINOT Yves-Michel GTCNP PCB Titulaire **Déclaration du 24/03/2009 :**
LD-ODE - TECHNOLOGIE SERVIER [salarié] [CDI] du 01/01/1985 au

GODEFROY Olivier GEBIOméd Titulaire **Déclaration du 08/03/2009 :**
EC-INV - SERVIER [PERFORM/ accident vasculaire cérébral] [investigateur principal] du 01/01/2006 au
EC-INV - BIOGEN [BG12/sclérose en plaques] [investigateur principal] du 01/03/2009 au
EC-INV - ESAI [Hippocampe/ trouble cognitif léger-M Alzheimer] [Investigateur principal] du 01/01/2008 au
CF-INT - EISAI, NOVARTIS, JANSSEN, LUNDBECK, GSK, SERVIER/EUTHERAPIE, BIOGEN [EPU dans les domaines de la neurologie] [rémunération institution] du 01/01/2001 au
CF-AUD - EISAI, NOVARTIS, JANSSEN, LUNDBECK, GSK, SERVIER/EUTHERAPIE, BIOGEN, SCHERING [EPU participation congrès] du 01/01/2001 au
VB - EISAI, NOVARTIS, JANSSEN, LUNDBECK, GSK, SERVIER/EUTHERAPIE, BIOGEN [versement <15% du budget de fonctionnement de l'association "ADER"] du 01/01/2001 au 31/12/2006

GROUIN Jean-Marie GTNPA
GT POO
Titulaire
Titulaire
Déclaration du 26/03/2009 :
LD-AR - LFB [Membre groupe experts] [Rémunération personnelle] du
GT RA Titulaire 01/01/2004 au
IP-AC - GENZYME-LFB-STALLERGES-MAIOLI-SPINDLER-IR FABRE - NOVARTIS-PFIZER-CHIESI-EXPANSCIENCES-BOEHRINGER-WYETHTHEA-GUERBET-GLAXO-SERVIER-ALLERGAN-JANSEN [Conseil ponctuel en en méthodologie et en statistiques sur les essais cliniques] [Rémunération personnelle]

GUILLOUZO André GT INC Titulaire **Déclaration du 15/01/2008 :**
LD-AR - SERVIER [Consultance, tous produits] [Rémunération personnelle] du 01/01/2006 au 31/12/2008

HUET DE BAROCHEZ Bruno
GTCNPGalé Titulaire **Déclaration du 23/11/2009 :**
LD-ODE - SERVIER INDUSTRIE [Employé] [CDI] du 01/01/2009 au
LD-ODE - SERVIER INDUSTRIE [Employé] [CDI] du 01/01/2009 au
Déclaration du 25/03/2009 :
LD-ODE - SERVIER INDUSTRIE [Employé] [CDI] du 01/01/2004 au 31/12/2008

Bruno
GTCNPGalé Titulaire **Déclaration du 23/11/2009 :**
LD-ODE - SERVIER INDUSTRIE [Employé] [CDI] du 01/01/2009 au

LD-ODE - SERVIER INDUSTRIE [Employé] [CDI] du 01/01/2009 au
Déclaration du 25/03/2009 :
LD-ODE - SERVIER INDUSTRIE [Employé] [CDI] du 01/01/2004 au 31/12/2008

IMBS Jean-Louis VIG
GEPGR
Suppléant
Titulaire
Déclaration du 03/11/2008 :
CF-INT - LABORATOIRE SERVIER [Invitation Congrès 5 et 6 novembre 2008 - Paris] [Aucune rémunération] du 05/11/2008 au 06/11/2008
Déclaration du 27/05/2008 :
CF-INT - LABORATOIRES ROCHE - PARIS [4èmes journées d'échanges sur la recherche clinique] [Aucune rémunération] du 17/12/2007 au 17/12/2007

JACQUOT Christian CS
AMM
COPédia
GTPRECLIN
GTMG
GTNPA
GT RA
GT DEUG
Titulaire
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Titulaire
Déclaration du 24/03/2009 :
RE-DE - STRAGEN PHARMA [Bioéquivalence EE/Desogestrel] [Rémunération personnelle] du 22/01/2009 au 25/01/2009
RE-AUT - INNOTHERA [Diosmine cp 500mg - En cours de validation] [rémunération personnelle] du 03/02/2009 au
RE-AUT - LAFON [Phloroglucinol 160 mg] [Rémunération personnelle] du 25/02/2009 au 26/02/2009
IP-AC - SANOFI [Conseils protocole générique - 1/2 journée] [Rémunération personnelle] du 10/03/2009 au 10/03/2009
IP-AC - BIOGARAN [Conseils protocole générique - 1/2 journée] [Rémunération personnelle] du 20/03/2009 au 20/03/2009
IP-AC - RECORDATI [Conseils en pharmacoculpés] [1/2 journée Rémunération personnelle] du 23/03/2009 au 23/03/2009
PAR - JANSSEN CILAG [Responsable marketing (en cours)] [Enfant] du 04/02/2008 au
PAR - AFSSAPS [Rédacteur Pharma (en cours)] [Belle-fille]
Déclaration du 15/01/2009 :
RE-DE - STRAGEN PHARMA [Bioéquivalence EE/ gestodene (2 jours)] [rémunération personnelle] du 01/07/2008 au 31/07/2008
RE-DE - STRAGEN PHARMA [Bioéquivalence adapalene gel/ crème (2 jours)] [rémunération personnelle] du 01/08/2008 au 31/08/2008
RE-DE - ARMEES [Bioéquivalence doxycycline (1 jour)] [rémunération partagée personnelle/institution] du 01/05/2008 au 31/05/2008
RE-DE - GALENIX [Bioéquivalence gluconnage (1 jour)] [rémunération

personnelle] du 01/04/2008 au 30/04/2008
RE-AUT - SERVIER [Biodisponibilité diosmine pour Belgique et Espagne (1 jour)] [rémunération personnelle] du 01/12/2008 au 31/12/2008
IP-AC - SANOFI [Conseils sur protocole générique (2 x 1/2 journée)] [rémunération personnelle] du 01/10/2008 au 31/10/2008
IP-AC - SANOFI [Conseils sur protocole générique (2 x 1/2 journée)] [rémunération personnelle] du 01/12/2008 au 31/12/2008
IP-AC - BIOGARAN [Conseils sur protocole générique (4 x 1/2 journée)] [rémunération personnelle] du 01/01/2008 au 31/03/2008
IP-AC - RECORDATI [Conseils en cinétique humaine (2 x 2 heures)] [rémunération personnelle] du 01/04/2008 au 30/04/2008
IP-AC - RECORDATI [Conseils en cinétique humaine (2 x 2 heures)] [rémunération personnelle] du 01/05/2008 au 31/05/2008
IP-AC - RECORDATI [Conseils en cinétique humaine (2 x 2 heures)] [rémunération personnelle] du 01/11/2008 au 30/11/2008
PAR - JANSSEN CILAG [Responsable marketing Europe] [fils] du 04/02/2008 au
PAR - AFSSAPS [rédacteur pharmaceutique] [Belle-fille] du 01/04/1998 au
{Autre} - ERREKATA (Italie) [Rapport bioéquivalence sur manidipine générique (2 jours 1/2)] du 01/09/2008 au 30/09/2008

KAHAN André GT RA Titulaire **Déclaration du 08/06/2006 :**
LD-AR - ACTELION [comité scientifique sclérodermie] [rémunération personnelle] du 01/01/2003 au
EC-INV - GENEVRIER [étude clinique / Chondrosulf] [investigateur coordonateur] du 01/01/1999 au
EC-INV - EXPANSCIENCE [étude clinique / Piasclédine] [investigateur coordonateur] du 01/01/2003 au
EC-INV - ROCHE [étude clinique / MABTHERA] [investigateur coordonateur] du 01/01/2006 au
EC-INV - AB SCIENCE [étude clinique / AB 1010] [investigateur coordonateur] du 01/01/2005 au
EC-CO - ROCHE [étude clinique / MRA] [co-investigateur] du 01/01/2005 au
EC-CO - ABBOTT [étude clinique / HUMIRA] [co-investigateur] du 01/01/2005 au
EC-CO - SERVIER [étude clinique / Ranélate Strontium] [co-investigateur] du 01/01/2002 au 31/12/2005
EC-CO - LILLY [étude clinique / PTH] [co-investigateur] du 01/01/2005 au
RE-DE - NEGMA [évaluation dossier / DIACERHEINE (réponse à des questions)] [rémunération personnelle] du 01/01/2002 au
CF-INT - GENEVRIER- IBSA [congrès EULAR - congrès Suisse – étude Chondrosulf] [rémunération personnelle] du 01/01/2006 au 31/01/2006
VB - ABBOTT, WYETH, ACTELION, ROCHE, MERCK [subvention : prix de recherche à l'INSERM] [Association CERMOSA] du 01/01/2005 au 31/12/2005
VB - LUNAR [subvention : remboursement frais d'enseignement d'ostéodensitométrie] [Association CERMOSA] du 01/01/2005 au

KHAYAT David GTONCO Titulaire **Déclaration du 12/12/2007 :**
LD-AR - ROCHE [conseil] [Rémunération personnelle]
LD-AR - PANACEA [conseil] [Rémunération personnelle]
LD-AR - ANTIGENICS [conseil] [Rémunération personnelle]
EC-CO - PFIZER [axitinib phase 2] [co investigateur]
EC-INV - SANOFI AVENTIS [aflibercept phase 2] [principal investigateur]
LD-AR - LILLY [conseil] [Rémunération personnelle]
LD-AR - SERVIER [conseil] [Rémunération personnelle]

LD-AR - ASTRAZENECA [conseil] [Rémunération personnelle]
EC-INV - PIERRE FABRE [Vinflunine phase 3] [principal investigateur]

LAINÉ-CESSAC
Pascale
VIG
STUP
Titulaire
Droit
Déclaration du 09/02/2009 :
CF-AUD - SERVIER [Pharmacologues de l'Ouest Tours] du 12/06/2008 au 13/06/2008

LAMBROZO Jacques OAM Titulaire **Déclaration du 01/11/2009 :**
LD-AR - LABORATOIRE SERVIER [Consultant] [Rémunération personnelle] du 01/01/1990 au
LD-AR - BOUYGUES TELECOM [Conseil scientifique] [Rémunération personnelle] du 01/01/2002 au

LAPEYRE-MESTRE
Maryse
VIG
STUP
GEPGR
Suppléant
Titulaire
Titulaire
Déclaration du 09/02/2009 :
{Autre} - LABORATOIRE SERVIER [Prix Paul Mirouze] [Prix décerné par l'Académie Nationale de Médecine (sur présentation de projet de recherche sur médicaments antidiabétiques et cancer colo-rectal) financé par le laboratoire Servier] du 18/12/2007 au 18/12/2007

LARDOUX Hervé VIG Suppléant **Déclaration du 05/02/2007 :**
CF-INT - SCHERING-PLOUGH [3 réunions (Corbeil-Essonnes) : "nouveaux Hypolipemic " Ezétimibe] [rémunération personnelle] du 01/01/2005 au 31/12/2006
CF-INT - TOSHIBA [ESC 2006 (Barcelone - Espagne) : Symposium Imagerie Cardio vasculaire] [rémunération personnelle] du 01/01/2007 au 31/12/2007
CF-AUD - SERVIER [ACC 2006 - rapporteur des séances d'échocardiographie
- "ACC LIVE"]

LASSMANN-VAGUE Véronique
GT DEUG Titulaire **Déclaration du 25/06/2009 :**
Néant (Absence de lien)
CF-AUD - ROCHE DIAGNOSTICS [Paris congres DELF (Diabete Education Langue Française)] du 04/02/2009 au 05/02/2009
CF-AUD - SERVIER [Rome congrès EASD (European association for the study of diabetes)] du 16/09/2008 au 20/09/2008
CF-AUD - SERVIER [STRASBOURG-congrèsALFEDIAM] du 17/03/2009 au 20/03/2009
CF-AUD - VITALAIRE [EASD - Amsterdam - étude épidémiologique sur pompes] du 01/09/2007 au 10/09/2007
CF-INT - VITALAIRE [Capetown - IDF - résultats étude épidémiologique sur pompe à insuline] [aucune rémunération] du 01/12/2006 au 10/12/2006

EC-INV - VITALAIRE [Etude épidémiologique sur les pompes à insuline en France] [co-investigateur] du 01/01/2004 au 31/12/2007
IP-AC - NOVO NORDISK [Consultant pour l'étude LEVEMIR chez le sujet âgé] [rémunération personnelle] du 01/01/2006 au 31/01/2008

LAVILLE Maurice COQualif Suppléant **Déclaration du 16/11/2007 :**
CF-INT - SHIRE [Conférence hyperphosphorémie et IRC (La Pitié)] [Rémunération personnelle] du 01/01/2007 au 31/01/2007
CF-INT - SERVIER [Conférence hypertension et rein] [Rémunération personnelle] du 01/01/2007 au 31/12/2007
CF-INT - CHIESI [Conférence hypertension et rein] [Rémunération personnelle] du 01/01/2007 au 31/12/2007
CF-INT - ROCHE [Ateliers de néphrologie] [Rémunération personnelle] du 01/01/2006 au 31/12/2007
IP-AC - BOEHRINGER [Board Micardis] [Rémunération personnelle] du 01/01/2007 au 31/12/2007
EC-INV - ROCHE [Essai NH20052] [coordonateur France] du 01/06/2007 au 31/12/2009
EC-INV - ASPREVA [Etude ALMS] [coordonateur France] du 01/01/2005 au 31/12/2009
EC-CO - KERYX [Essai Sulodexide] [co-investigateur] du 01/01/2006 au 31/12/2008
EC-INV - AMGEN [Essai EVOLVE] [investigateur] du 01/01/2007 au 31/12/2010
CF-AUD - JANSSEN-CILAG [American Society of Nephrology - San Diego nov. 2006] du 01/11/2006 au 30/11/2006
LD-AR - SHIRE [Advisory Board - Fosrénol] [rémunération personnelle / institution] du 01/01/2005 au 31/12/2009

LE HEUZEY Jean-Yves AMM
GTcardio/
Titulaire
Titulaire
Déclaration du 31/10/2008 :
EC-INV - BOEHRINGER INGELHEIM [Dabigatran] [coordinateur RELY] du 01/10/2008 au
EC-INV - SERVIER [Ivabradine] [Membre DSMD étude SHIFT] du 01/04/2008 Au

LE PAPE Alain GT INC Titulaire **Déclaration du 12/11/2009 :**
IF - BIOPHARMA CONSULTING [1 action < 5,000 Euros] du 01/01/2002 au
LD-AR - MDS PHARMA SERVICES [Consulting en imagerie in vivo pour le développement pharmaceutique] [Rémunération personnelle/institution] du 01/01/1997 au 31/12/2005
LD-AR - GUERBET [Consulting en imagerie in vivo pour le développement pharmaceutique] [Rémunération personnelle/institution] du 01/01/2009 au 31/12/2010
EC-CO - SERVIER [Technologie Orléans - Toxicologie Gidy : imagerie pour le développement pharmaceutique et la toxicologie] [Direction scientifique, contats CNRS - En cours] du 01/01/2007 au
EC-CO - CERB Baugy [Développement de nouvelles stratégies d'imagerie en cancérologie, inflammation, infection] [Direction scientifique, contrat CNRS - En cours] du 01/01/2000 au
RE-AUT - PIERRE FABRE Médicament Toulouse [Etude par imagerie de l'activité pharmacologique du TOPAAL comprimé] [Rémunération

personnelle/institution] du 01/01/2007 au 31/12/2007
IP-AC - SANOFI AVENTIS [Oncologie expérimentale - Vitry sur Seine] [Conseil en imagerie in vivo pour le développement de nouveaux anti-cancéreux - tous produits - Rémunération institution - En cours] du 01/01/2005 au
IP-AC - PIERRE FABRE [Oncologie expérimentale - Toulouse] [Conseil en imagerie in vivo pour le développement de nouveaux anti-cancéreux - tous produits - Rémunération institution - En cours] du 01/01/2004 au
CF-INT - MDS [Pharmacologie de sécurité - Conférence imagerie en recherche précliniques aux colloques de Lyon - En 2005 et 2008] [Aucune rémunération]
CF-INT - Groupe Métabolisme et Pharmacocinétique GMP [2007 - Conférence sur l'imagerie des biomarqueurs de l'inflammation et du cancer - Gien] [Aucune rémunération]
CF-INT - Société Française de Toxicologie [2008 - L'imagerie pour la biodistribution et la toxicologie des nanoparticules - Paris] [Aucune rémunération]
CF-INT - Société Française de Pathologie Toxicologique [2009 - Imagerie des biomarqueurs pour l'évaluation de l'efficacité et la sécurité des médicaments - Paris] [Aucune rémunération]
CF-INT - ORION CONCEPT [2009 - Application de l'imagerie à la R&D en dermocosmétologie - Orléans] [Aucune rémunération]
VB - PIERRE FAFBRE MEDICAMENT [Toulouse - Contrat de collaboration ou de prestation] [Bénéficiaire : CNRS] du 01/01/2004 au 31/12/2011
VB - SERVIER [Orléans - Contrat de collaboration ou de prestation] [Bénéficiaire : CNRS] du 01/01/2007 au 31/12/2011
VB - MDS PHARMA SERVICES [L'Arbresle - Contrat équipe conseil] [Bénéficiaire : CNRS] du 01/01/1995 au 31/12/1997
VB - CERB [Contrat de collaboration ou de prestation] [Bénéficiaire : CNRS] du 01/01/2009 au 31/12/2010
PAR - BIOPHARM CONSULTING [Tours - Actionnaire - Epouse - En cours] du 01/01/2002 au
{Autre} - [Conseils Régionaux et Organismes Scientifiques] [Expertise de projet - En cours] du 01/01/2002 au

LEPINE Jean-Pierre AMM
GTNPA
GTAutomob
GTGaléniq
Suppléant
Titulaire
Titulaire
Droit
Déclaration du 15/12/2009 :
IP-AUT - SERVIER [VALORISER VOTRE RECHERCHE] du 30/01/2009 au 30/01/2009

LERONDEL Stéphanie GT INC Titulaire **Déclaration du 12/11/2009 :**
IF - BIOPHARM CONSULTING TOURS [1 action] [<5000e ou 5% du capital] du 01/01/2002 au
LD-AR - LABORATOIRES GUERBET [Consulting en imagerie in viVo pour le développement pharmaceutique] [rémunération personnelle et institution] du 01/01/2009 au 31/12/2010
EC-CO - SERVIER [Imagerie pour le développement pharmaceutique et la toxicologie - techologie Orléans, toxicologie Gidy (en cours)] [co-direction scientifique, contrat CNRS] du 01/01/2007 au
EC-CO - CERB BAUGY [Développement de nouvelles stratégies d'imagerie en

cancérologie, inflammation, infection (en cours)] [co-direction scientifique, contrat CNRS] du 01/01/2009 au
RE-AUT - PIERRE FABRE [Evaluation par imagerie chez l'animal de l'activité du TOPAAL comprimé (Médicaments -Toulouse)] [rémunération institution] du 01/01/2007 au 31/12/2007
IP-AC - SANOFI AVENTIS [Conseil en imagerie in vivo et développement pharmaceutique oncologique - tous produits - Oncologie expérimentale Vitrysur-Seine (en cours)] [rémunération institution] du 01/01/2005 au
IP-AC - PIERRE FABRE [Conseil en imagerie et développement pharmaceutique oncologique - tous produits - Oncologie Toulouse (en cours)] [rémunération institution] du 01/01/2004 au
CF-INT - SOCIETE FRANCAISE DE PATHOLOGIE TOXICOLOGIQUE [Imagerie des biomarqueurs pour l'évaluation de l'efficacité et de la sécurité des médicaments Paris] [aucune rémunération] du 01/01/2009 au 31/12/2009
VB - PIERRE FABRE [Contrat de collaboration ou de prestation (Médicaments Toulouse)] [CNRS] du 01/01/2004 au 31/12/2011
VB - SERVIER ORLEANS [Contrat de collaboration ou de prestation] [CNRS] du 01/01/2007 au 31/12/2011
PAR - BIOPHARM CONSULTING TOURS [Actionnaire (en cours)] [Père] du 01/01/2002 au

LOKIEC François GTONCO Titulaire **Déclaration du 24/06/2008 :**
CF-AUD - ABBOTT [Chicago Congès de l'ASCO] du 29/05/2008 au 03/06/2008
CF-AUD - ASTRA ZENECA [San Diego/Congrès de l'AACR] du 12/04/2008 au 16/04/2008 CF-INT - ASTRA ZENECA [Paris Post AACR/Molécules de tout à l'heure] [Aucune rémunération] du 22/05/2008 au 22/05/2008
IP-AC - BIONEST [Evaluation de portefeuille] [Rémunération personnelle] du 07/04/2008 au 07/04/2008
LD-ODE - SERVIER [Expert] [rémunération personnelle] du 01/01/1992 au
LD-ODE - GSK [Board experts nationaux] [rémunération personnelle] du 01/01/2003 au
LD-ODE - SANOFI AVENTIS [Board international] [rémunération personnelle] du 01/01/2003 au
CF-INT - AMGEN [Sorrente /Echanges Européens Soins de Support en Oncologie/Cardiotoxicité des fluoropyrimidines] [Rémunération personnelle] du 15/05/2008 au 18/05/2008
EC-CO - ALLOS [Etude préclinique/Pralatrexate] [collaborateur] du 07/12/2007 au
EC-CO - ACCESS PHARMACEUTICAL [Etude préclinique/Prolindac] [collaborateur] du 12/12/2007 au
Déclaration du 17/03/2008 :
LD-AR - SERVIER [Consultant] [Rémunération personnelle] du 01/01/1999 au
LD-AR - SERVIER [consultant] [rémunération personnelle] du 01/01/1999 au
EC-INV - BIOALLIANCE [IRN - Transdurg] [Expérimentateur principal] du 01/01/2008 au
EC-INV - BIOALLIANCE [Loramyc] [Expérimentateur principal] du 01/01/2009 au
EC-INV - ALLOS [Pralatrexate] [Expérimentateur principal] du 01/01/2006 au
EC-INV - BIOALLIANCE [IRN-TRANSDURG] [Expérimentateur principal] du 01/01/2008 au
EC-INV - BIOALLIANCE [LORAMYC] [Expérimentateur principal] du 01/01/2009 au
EC-INV - ALLOS [PRALATREXATE] [collaborateur] du 01/01/2006 au
EC-CO - ACCESS [Etude PK] [Collaborateur] du 01/01/2006 au
EC-CO - ACCESS [Etude PK] [collaborateur] du 01/01/2008 au 31/12/2008

EC-CO - ENJON [Expertise dossier EZN-260] du 01/01/2009 au 31/12/2009
IP-RE - WYETT [Expertise dossier] [rémunération personnelle] du 01/01/2008 au 31/12/2008
RE-DE - WYETH [Exertise dossier] [Rémunération personnelle] du 01/01/2008 au 31/12/2008
RE-DE - ENJON [Expertise dossier EZN-260] du 01/01/2009 au 31/12/2009
CF-INT - ASTRA ZENECA [Congrès de l'AACR - Pas de produit] [Aucune rémunération] du 01/01/2008 au 31/12/2008 CF-INT - ABBOTT [Congrès de l'ASCO - Pas de produit] [Aucune
rémunération]
CF-INT - ASTRA ZENECA [congrès de l'AACR. Pas de produit] [aucune rémunération] du 01/01/2008 au
CF-INT - ABBOTT [congrès de l'ASCO . Pas de produit] [aucune rémunération]

MARZIN Daniel AMM
GTPRECLIN
GTCOSIngr
GTCOSdoss
Titulaire
Titulaire
Titulaire
Titulaire
Déclaration du 30/03/2009 :
LD-AR - INNATE PHARMA [Expertise et conseil en Toxicologie (en cours)] [rémunération personnelle] du 01/01/2004 au
LD-AR - INSTITUT DE RECHERCHE PIERRE FABRE [Expertise et conseil en Toxicologie (en cours)] [rémunération personnelle] du 01/01/2004 au
IP-RE - BIOLOGIE SERVIER, LFB, FAUST PHARMACEUTICALS, NEGMA du 01/01/2004 au 31/12/2004
IP-RE - FOURNIER,OTL PHARMA, JOLY JATEL, SUBSTIPHARM, ADIR du 01/01/2005 au 31/12/2005
IP-RE - NEGMA LERADS, TROPHOS, FAUST PHARMACEUTICALS, LFB, ORPHAN, ANACONDA PHARMA, MAPREG du 01/01/2006 au 31/12/2006
IP-RE - BAXTER, NOVAGALI, NOVEXEL, NEGMA LERADS, FAUST PHARMACEUTICALS, GALDERMA, PROSTRAKAN PHARMA, ADIR du 01/01/2007 au 31/12/2007
IP-RE - ANACONDA PHARMA, NICOX, R ET D PHARMA, CARL ZEISS MEDITEC, IPRAD, MACO PHARMA, NOVAGALI PHARMA, ADIR, ORPHAN EUROPE, BIO ALLIANCE PHARMA, ETHYPHARM, MAPREG du 01/01/2008 au 31/12/2008
IP-RE - ORPHAN EUROPE, IDA INDUSTRIAL PARK du 01/01/2009 au 31/12/2009
{Autre} - BIOLOGIE SERVIER [Bourse CIFRE d'une doctorante] du 01/01/2006 au 31/12/2009

MASSARD Sandrine CNHV Suppléant **Déclaration du 13/08/2009 :**
PAR - SERVIER MONDE [RESPONSABLE DU DROIT DES SOCIETES] [MARI] du 01/09/1997 au

MICALLEF-ROLL Joëlle GEPGR Titulaire **Déclaration du 14/10/2008 :**
EC-CO - SANOFI-AVENTIS [Etude de Phase 1 - SSR103800] [COINVESTIGATEUR] du 01/09/2008 au 31/12/2008
EC-INV - AP-HM [Essai clinique - Pravastatine/zolandronate] [Co-Investigateur] du 06/10/2008 au 31/12/2012
Déclaration du 01/02/2008 :

EC-CO - PIERRE FABRE [Etude Déanol PK] [Co-investigateur] du 01/01/2007 au 31/12/2007
EC-CO - PIERRE FABRE [Etude de phase 1 L0014 IN 102 tanganil] [Coinvestigateur] du 01/01/2007 au 31/12/2007
EC-CO - SANOFI-AVENTIS [Etude phase 1 EXM 10497 Kétamine] [Coinvestigateur] du 01/03/2007 au 31/05/2008
CF-AUD - SERVIER [XIIème séminaire de Pharmacologie] [auditeur] du 06/12/2007 au 08/12/2007
CF-INT - HAS [GT Protocole de sevrage des benzodiazépines chez le sujet agé] [Aucune rémunération] du 06/02/2007 au 31/12/2007
EC-CO - LACTALIS [Etude physiologique] [Co-investigateur] du 01/02/2007 au 31/12/2007
EC-CO - SANOFI-AVENTIS [Etudes marqueurs physiologiques] [Coinvestigateur] du 31/01/2007 au 31/12/2007
EC-CO - SANOFI AVENTIS [Etude phase 1 INT 6078] [Co-investigateur] du 01/01/2007 au 31/01/2008
EC-CO - SANOFI AVENTIS [Etude phase 1 INT6078] [co-investigateur] du 01/01/2007 au 31/01/2008
EC-INV - AP-HM [Etude épidémiologique cas témoins ecstasy] [Investigateur Coordonnateur] du 28/02/2003 au 31/12/2008
EC-INV - AP-HM [Essai clinique Acide ascorbique] [Investigateur coordonnateur] du 01/09/2005 au 31/10/2008
EC-INV - AP-HM [Essai clinique THC] [investigateur coordonnateur] du 01/03/2003 au 31/10/2008

PAGES Jean-Christophe
GEBIOgén Titulaire **Déclaration du 08/05/2008 :**
IP-AUT - SERVIER [Conseil classement de vecteurs] du 27/11/2007 au 27/11/2007
IP-AUT - VECTALYS [Conseil classement de vecteurs (en cours)] du 01/06/2006 au

PIETTE François CS Titulaire **Déclaration du 16/04/2008 :**
LD-AR - SERVIER [Conseil médical] [rémunération personnelle] du 01/01/1995 au 31/12/2009
IP-AC - IPSEN [Etude GuidAge TANAKAN] [aucune rémunération] du 01/01/2000 au 31/12/2010
CF-INT - ETABLISSEMENTS THERMAUX [Paris : Plan des établissements thermaux dans la prévention chez les sujets âgés] [rémunération personnelle] du 01/01/2007 au 31/12/2007
CF-INT - MEDEC [Paris : La consultation de prévention à 70 ans] [rémunération personnelle] du 01/01/2007 au 31/12/2007
VB - MEDIALIS - AGEIS [Convention pour un partenariat hôpital - entreprise : technologie pour personne âgée] [APHP] du 01/01/2007 au

PONCELET Pascal GTcardio/ Titulaire **Déclaration du 27/01/2009 :**
IP-AUT - BAYER [symposium Leipzig tt hta et diabète] [rémunération personnelle] du 26/09/2008 au 28/09/2008
IP-AUT - IPSEN [fmc Boulogne s/ Mer tt hta diabète] [rémunération personnelle]
IP-AUT - RECORDATI [fmc place des diurétiques] [rémunération personnelle] du 12/06/2008 au 12/06/2008
IP-AUT - NOVARTIS [board régional alikirene] [rémunération personnelle] du 03/07/2008 au 03/07/2008

IP-AUT - EUTHERAPIE [fmc hyvet indapamide] [rémunération personnelle] du 06/11/2008 au 06/11/2008
IP-AUT - BOEHRINGER INGELHEIM [fmc ontarget telmisartan] [rémunération personnelle] du 08/04/2008 au 08/04/2008
IP-AUT - BOEHRINGER INGELHEIM [board ontarget 3 réunions] [rémunération personnelle] du 17/12/2007 au 17/03/2008
IP-AUT - IPSEN [board expert Valsartan] [rémunération personnelle] du 26/06/2008 au 26/06/2008
EC-CO - MENARINI [observatoire tt de l'insuffisance cardiaque en cardiologie libérale étude devenir] [rémunération personnelle] du 12/12/2007 au 30/12/2009
IP-AUT - IPSEN [présentation congrès ACC] [rémuneration personnelle] du 17/03/2008 au 12/04/2008
IP-AUT - NOVARTIS [board régional rasilez] [rémunération personnelle] du 12/04/2008 au 12/04/2008
IP-AUT - IPSEN [fmc Strasbourg] [rémunération personnelle] du 19/06/2008 au 19/06/2008
CF-INT - MENARINI [congrès club cardiologie du sport Nancy symposium pas de tt] [Rémunération personnelle] du 19/09/2008 au 20/09/2008
CF-INT - NOVARTIS [congrès CCS Nancy symposium sur le risque] [Rémunération personnelle] du 19/09/2008 au 19/09/2008
IP-AUT - NOVARTIS [aliskirene et âge Lille] [rémunération personnelle] du 27/12/2007 au 27/12/2007
IP-AUT - SERVIER [vidéo transmission AHA] [rémunération personnelle] du 20/11/2007 au 20/11/2007
IP-AUT - NOVARTIS [hta résistante Lille] [rémunération personnelle] du 17/12/2007 au 17/12/2007
EC-CO - NOVARTIS [exforge] [mesure de la rigidite artérielle, rôle purement technique] du 12/05/2008 au 28/02/2009
CF-INT - DAIICHY SANKYO [sfhta Paris olmetec étude des doses prescrites par rapport aux doses recommandées] [Aucune rémunération] du 19/12/2008 au 19/12/2008
CF-INT - IPSEN [AHA Nouvelle-Orléans rapport du congres pas de tt] [Rémunération personnelle] du 10/11/2008 au 12/11/2008
CF-AUD - DAIICHY SANKYO [ESC Munich] du 31/08/2008 au 02/09/2008
CF-AUD - SERVIER [ESH Berlin] du 14/06/2008 au 17/06/2008
CF-AUD - BOEHRINGER INGELHEIM [ACC Chicago ontarget telmisartan] du 22/03/2008 au 26/03/2008

PRADEAU Dominique GTCNP FN Titulaire **Déclaration du 06/11/2009 :**
CF-INT - SERVIER [Conférences H. MOISSAN : préparation au concours de Praticien Hospitalier Pharmacien] [Aucune rémunération]
Déclaration du 04/09/2009 :
Néant (Absence de lien)

QUENEAU Patrice STUP Titulaire **Déclaration du 01/10/2008 :**
IF - THUASNE PARTICIPATION SAS [Actions - capitaux propres - détention en cours à ce jour] [2 sur 2 777 481 titres] du 25/04/2006 au
IF - THUASNE SAS [Actions - capitaux propres - détention en cours à ce jour - Avant 1994] [2 sur 65 000 titres]
LD - THUASNE PARTICIPATIONS SAS [Administrateur - Mandat en cours - Fin AG 2009] [Nomination AG] du 04/08/2006 au 31/12/2009
LD - THUASNE SAS [Administrateur - Mandat en cours - Fin AG 2010] [Nomination AG] du 15/12/2004 au 31/12/2010
LD-AR - THUASNE SAS [Conseil, évaluation thérapeutique sur les effets de la

contention lombaire - produits THUASNE] [rémunération personnelle] du 14/01/2003 au 13/01/2008
IP-AC - THUASNE SAS [Participation au Congrès P2T 2008 - Clermont Ferrand : présentation d'un poster sur les effets de la contention lombaire dans le traitement des lombalgies subaiguës (par la ceinture Lomba - Cross Activity de THUASNE)] [rémunération personnelle] du 09/04/2008 au 11/04/2008
PAR - THUASNE PARTICIPATION SAS [Président (mandataire non salariée / contrat de travail suspendu)] [soeur] du 08/12/2005 au 31/12/2009
PAR - THUASNE SAS [Président (mandataire non salariée / contrat de travail suspendu)] [soeur] du 15/12/2004 au 31/12/2010
PAR - SERVIER [Cadre] [fils] du 01/05/1995 au

RENACCO Elisabeth GTPH Titulaire **Déclaration du 24/09/2009 :**
PAR - SERVIER [Cadre supérieur à l'international] [enfant] du 01/08/2005 au

ROBERT-GNANSIA Elisabeth
GTGROSS/A Titulaire **Déclaration du 14/06/2006 :**
RE-AUT - GALDERMA [Evaluation des données 'grossesse " sur " Différine"] [rémunération versée à une institution]
RE-AUT - WYETH [évaluation des données grossesse sur "Enbrel"] [rémunération versée à une institution]
IP-AC - SERVIER [Dossier de passage en OTC pour "Pneumorel"] [rémunération institution]
CF-AUD - SERVIER [Teratology Society - Tucson (Az) Invitation en échange de l'écriture d'un rapport détaillé sur le congrès] du 23/06/2006 au 28/06/2006

TCHORELOFF Pierre-Cyril
GTCNPGalé Titulaire **Déclaration du 27/11/2009 :**
IP-AC - ETHYPHARM [Travaux sur les films d'enrobage et leur stabilité] [Rémunération institution]
Déclaration du 07/02/2009 :
{Autre} - BIOALLIANCE [Suivi de travaux Master] [Travaux ne faisant pas l'objet de rémunération personnelle mais pouvant être contractuellement accompagnés de supports financiers au niveau du laboratoire de recherche auquel je suis rattaché] du 01/01/2009 au 31/07/2009
IP-AC - NOVARTIS [Formation continue. Intervention sur site.] [Rémunération personnelle/institution] du 10/01/2009 au 17/02/2009
IP-AC - SERVIER [Formation continue. Intervention sur site.] [Rémunération personnelle/institution] du 19/01/2009 au 20/01/2009
RE-AUT - SANOFI-AVENTIS [expertise sur les procédés de compression] [Rémunération institution] du 01/01/2009 au

THOMAS Thierry GT RA Titulaire **Déclaration du 03/12/2009 :**
CF-AUD - ALLIANCE
CF-INT - LILLY [Rémunération personnelle]
CF-INT - MSD [Aucune rémunération]
CF-INT - SERVIER [Rémunération personnelle]
CF-INT - IPSEN [Aucune rémunération]
CF-INT - AMGEN [Rémunération personnelle]
CF-INT - ROCHE [Rémunération personnelle]
CF-INT - NOVARTIS [Rémunération personnelle]
CF-INT - ALLIANCE [Rémunération personnelle]

TILLEMENT Jean-Paul AMM Suppléant **Déclaration du 20/12/2009 :**
IP-AC - AUCUNE ACTUELLEMENT [fixation plasmatique des médicaments maladies mitochondriales] [Aucune rémunération]
LD-AR - ADIR (GROUPE SERVIER) [trimétazidine, ajouté aux liquides de conservation d'organes] [Rémunération personnelle] du 01/10/2007 au
TISSIER Renaud GEBIOgén Titulaire **Déclaration du 30/06/2008 :**
LD-AR - SOGEVAL (LABORATOIRE PHARMACEUTIQUE VETERINAIRE) [Consultance pour le développement d'un produit destiné à usage vétérinaire] [rémunération personnelle] du 01/01/2007 au 31/12/2008
EC-CO - SERVIER [Participation à deux études pré-cliniques] [expérimentateur non principal] du 01/01/2005 au 31/12/2008
EC-CO - PIERRE FABRE [Participation à une étude pré-clinique] [expérimentateur non principal] du 01/01/2005 au 31/12/2006
IP-AC - SOGEVAL (LABORATOIRE PHARMACEUTIQUE VETERINAIRE) [Consultance pour le développement d'un produit destiné à usage vétérinaire] [rémunération personnelle] du 01/01/2007 au 31/12/2008
CF-AUD - SERVIER [Invitation comme participant au congrès de l'international Society for Heart Research - Bologne] du 01/06/2007 au 30/06/2007
CF-AUD - SERVIER [Invitation comme participant à l'European Society of Cardiology - Vienne] du 01/09/2007 au 30/09/2007
CF-AUD - SERVIER [Invitation comme participant à l'European Society of Cardiology - Munich] du 01/09/2008 au 30/09/2008
PAR - CEPHALON [Responsable BPC Europe] [conjointe] du 01/01/2006 au

VASSAL Gilles COPédia Titulaire **Déclaration du 28/03/2009 :**
EC-INV - RHONE POULENC RORER [Phase II pédiatrie - Irinotecan] [investigateur principal] du 01/01/1999 au 31/12/2002
EC-INV - SANOFI [Phase I pédiatrie - Oxaliplatine] [Investigateur principal] du 01/01/2001 au 31/12/2003
EC-INV - PIERRE FABRE [Etude pharmacologique : bulsilvex] [investigateur principal] du 01/01/2001 au 31/12/2006
EC-INV - PIERRE FABRE [Etude toxicologique : Busilvex] [expérimentateur] du 01/01/2006 au
EC-INV - ROCHE [Etude phase II R1507] [investigateur principal] du 01/01/2007 au 31/12/2009
EC-CO - SANOFI AVENTIS [Etude préclinique : anticorps anti IFG1R] [Co investigateur] du 01/01/2005 au 31/12/2007
EC-CO - ASTRA ZENECA [Etude préclinique : GEFITINIB] [Co investigateur] du 01/01/2003 au 31/12/2005
EC-CO - NOVARTIS [Etude préclinique GLIVEC] [Co investigateur] du 01/01/2003 au 31/12/2005
IP-AC - ROCHE [Conseil - Bevacizumab, anti IGF1R, Erlotinib, Trastuzumab] [Rémunération Institution] du 01/01/2006 au
IP-AC - SANOFI AVENTIS [Conseil - anti igf1r] [rémunération institution] du 01/01/2006 au 31/12/2006
IP-AC - PHARMAMAR [Conseil - Aplidine - ET 743] [Rémunération personnelle] du 01/01/2007 au
IP-AC - NOVARTIS [Conseil - Zometa] [rémunération institution] du 01/01/2007 au 31/12/2008
IP-AC - LILLY [Conseil - Gemcitabine - alimta] [aucune rémunération] du 01/01/2005 au
IP-AC - PFIZER [Conseil - Irinotecan] [Aucune rémunération] du 01/01/2006 au 31/12/2006
IP-AC - PIERRE FABRE [Conseil - Busulfan] [Aucune rémunération] du 01/01/2007 au 31/12/2007

IP-AC - SANOFI AVENTIS [Conseil - AVE 1582] [Aucune rémunération] du 01/01/2008 au 31/12/2008
CF-INT - PIERRE FABRE [Dusseldorf - réunion Greffeutrs - Pharmacologie du Busulfan] [Rémunération institution] du 01/01/2007 au 01/01/2007
CF-INT - PIERRE FABRE [Hambourg EBMT - Pharmacologie Busilvex] [Rémunération personnelle] du 01/01/2006 au 01/01/2006
CF-INT - PIERRE FABRE [Londres - réunions greffeurs - pharmacologie du Busulfan] [rémunération personnelle] du 01/01/2005 au 01/01/2005
CF-INT - PIERRE FABRE [Geneve EBMT - pharmacologie Bulilvex] [rémunération personnelle] du 01/01/2004 au 01/01/2004
CF-INT - SANOFI AVENTIS [Vancouver - SIOPE : chimiothérapie des cancers pédiatriques] [rémunération personnelle] du 01/01/2005 au 01/01/2005
CF-AUD - PFIZER [Chicago - asco] du 01/01/2008 au 01/01/2008
CF-AUD - ROCHE [SAN DIEGO - AACR] du 01/01/2008 au 01/01/2008
CF-AUD - PFIZER [CHICAGO - ASCO] du 01/01/2007 au 01/01/2007
CF-AUD - ROCHE [LOS ANGELES AACR] du 01/01/2007 au 01/01/2007
CF-AUD - LILLY [ATLANTA - ASCO] du 01/01/2006 au 01/01/2006
CF-AUD - ROCHE [WASHINGTON - AACR] du 01/01/2006 au 01/01/2006
CF-AUD - PIERRE FABRE [ORLANDO AACR] du 01/01/2005 au 01/01/2005
VB - ASTRA ZENECA, SANOFI AVENTIS, BMS, GLAXOSMITHKLINE, NOVARTIS, ROCHE, PHARMAMAR, AMGEN, MERCK, PFIZER, J&J, SCHERING PLOUGH, BAYER, MGI PHARMA, WYETH, LILLY, SERVIER

VEXIAU Patrick GTantiHPV
GT REFERE
GT IMPLIC
GT RISQUE
Titulaire
Titulaire
Titulaire
Titulaire
Déclaration du 02/11/2009 :
LD-AR - MSD [Groupe d'experts pour la SITAGLIPTINE (JANUVIA, JANUMET) En cours] [Rémunération personnelle] du 01/01/2007 au
LD-AR - ALMIRALL [Groupe d'experts pour Vaniqa (en cours)] [Rémunération personnelle] du 01/01/2007 au
EC-CO - NOVO NORDISK [Etude prédictive insuline LEVEMIR.] [Investigateur] du 01/11/2005 au 30/11/2006
EC-CO - NOVO NORDISK [Etude sur la liraglutide] [Investigateur] du 01/05/2009 au 31/05/2010
EC-CO - AVENTIS [Etude épidémiologique MONODIA] [Investigateur] du 01/09/2003 au 31/03/2005
EC-CO - LILLY [Etude multicentrique / insuline inhalée] [Investigateur] du 01/12/2006 au 30/06/2007
EC-CO - MSD [Etude multicentrique/ Januvia] [Investigateur] du 01/06/2007 au 31/12/2009
EC-CO - MERCK SERONO [Etude multicentrique glucophage poudre] [Coordonnateur] du 01/01/2009 au 31/12/2010
IP-RE - ALMIRALL [Rapport sur Vaniqa. Demande de remboursement] [Rémunération personnelle] du 01/09/2009 au 30/09/2009
RE-DE - PIERRE FABRE MEDICAMENT [Patch à la testostérrone] [Rémunération personnelle] du 01/01/2005 au 01/01/2005
RE-DE - ALMIRALL [VANIQA] [Rémunération personnelle] du 01/09/2009 au 01/09/2009

IP-AC - SCHWARTZ PHARMA [Réunions d' experts : dysfonction érectile] [Rémunération personnelle] du 01/03/2006 au 30/01/2008
IP-AC - NOVO NORDISK [Expertise sur les transferts d'insulines humaines aux analogues] [Rémunération personnelle] du 01/01/2006 au 31/12/2006
IP-AC - SANOFI-AVENTIS [Expertise ponctuelle ACOMPLIA] [Rémunération personnelle] du 01/03/2007 au 31/03/2007
IP-AC - LILLY [Réalisation de documents sur les PREMIX. HUMALOGMIX 25 et 50] [Rémunération personnelle] du 01/01/2007 au 30/09/2007
IP-AC - LILLY [Conférence de presse "10 ans d'humalog"] [Rémunération personnelle] du 01/01/2007 au
CF-INT - MERCK [Conférence de presse à paris pour le produit DIABION] [Rémunération personnelle] du 01/05/2006 au
CF-INT - LILLY [Conférence de presse à Paris pour le produit HUMALOG] [Rémunération personnelle] du 01/02/2007 au CF-INT - ABBOTT [Conférence de presse à Paris pour le produit FREE STYLE]
[Rémumération personnelle] du 01/05/2008 au
CF-INT - LILLY [Conférence de presse à Paris pour le produit BYETTA] [rémunération personnelle] du 01/07/2008 au
CF-INT - NOVO [Conférence de presse à Paris] [Rémunération personnelle] du 01/12/2008 au
CF-INT - MERCK LIPHA [Conférence de presse à Paris pour le produit GLUCOPHAGE poudre] [Rémunération personnelle] du 01/05/2009 au
CF-AUD - SERVIER [Congrès EASD ROME] du 01/09/2008 au
CF-AUD - VITALAIR [Congrès ALFEDIAM BRUXELLES] du 01/03/2008 au
CF-AUD - AMGEN [Réunion d'experts Cannes (intervenant)] du 01/06/2008 au
CF-AUD - IPSEN [Congrès d' Endocrinologie,LILLE] du 01/10/2008 au
CF-AUD - NOVO [Congrès ALFEDIAM] du 01/03/2007 au
CF-AUD - SANOFI AVANTIS [Congrès EASD AMSTERDAM] du 01/09/2007 au
CF-AUD - PIERRE FABRE [Réunion d'experts AVENE] du 01/03/2007 au
CF-AUD - SANOFI AVANTIS [Réunion d'experts Cannes] du 01/01/2006 au
CF-AUD - ROCHE [Congrès ALFEDIAM] du 01/03/2009 au
CF-AUD - LILLY [Congrès international diabètes fédération monTréal] du 01/10/2009 au
VB - LABORATOIRES PHARMACEUTIQUES [Lien: secrétaire général de l'association]
VB - Laboratoires pharmaceutiques, DIRECTION GENERALE DE LA SANTE, CNAMTS [Lien: Secrétaire général de l'association. Il s'agit de financement pour les programmes (information, prévention, accompagnement therapeutiques...aucun financement personnel, financement sur projet, l'ensemble des financements sont disponibles sur intenet : www.afd.asso.fr] [Association française des diabétiques. Date de début > 5ans]
{Autre} - AFD [Défense de l'interêt de l'association française des diabétiques, en particulier dans ce cadre par rapport à l'industrie pharmaceutique, volonté d'une neutralité vis-à vis des industries concurrentes : secrétaire général de l'association, travail d'interêt publique, association reconnue d'utilité publique.] [En cours Travail d'intérêt public. Association reconnue d'utilité publique.] du 01/03/2003 au

VICAUT Eric COQualif Titulaire **Déclaration du 04/12/2006 :**
LD-AR - PFIZER - SERVIER [Expertise statistique - Groupe européen d'expert en microcirculation]
LD-AR - ABBOTT [Expertise statistique]
IP-EC - ASTRA [Membre du Comité scientifique français Hypo essai Centaurus Rosuvastatin] [Expertise méthodologique] du 01/01/2005 au 31/12/2007
IP-AC - ABBOTT [Expertise méthodologique pour étude SYNAGIS]

IP-AC - IPSEN - BIOTECH [Conseil pour analyse Essai GFEA06 - Essai Botox - Hormonothérapie dans le cancer du sein]
IP-AC - AVENTIS [Conseil méthodologique pour registre Plavix chez le patient coronarien Analyse registre RIVIERA]
IP-AC - FERRING [Expertise pour observation pharmacovigilance]
CF-INT - SERVIER [Conférence microcirculation et perfusion tissulaire - PRETERAX]
CF-INT - PFIZER [Conférence microcirculation]
VB - THERVAL - MEDICAL [Subvention recherche] du 06/01/2006 au 06/01/2006

VOIRIOT Pascal GTA
GTcardio/
Titulaire
Titulaire
Déclaration du 31/03/2009 :
EC-INV - DIVERSES BIOTECH ET MID SIZE LAB [Lecture Centralisée ECG pour Novexel, Basilea, Bioline, Trophos, Galderma, Medtronic, Paion, Negma, Chiesi encore en cours ou terminée depuis moins de 2ans] [>50 études] du 01/01/2006 au
EC-INV - TEVA [Lecture Centralisée ECG] [1 étude phase 2] du 01/04/2007 au 01/04/2008
EC-INV - UCB [Lecture Centralisée ECG] [2 études phase1 1 études phase2] du 01/01/2006 au 31/05/2009
EC-INV - MERCK SERONO [Lecture Centralisée ECG] [3 études phase 1 Oncologie] du 01/02/2007 au
EC-INV - ROCHE [Lecture Centralisée ECG] [3 études phase1] du 01/08/2007 au 31/03/2009
EC-INV - SERVIER [Lecture Centralisée ECG] [2 études phase1 6 études phase 2/3] du 01/02/2006 au 31/03/2009
EC-INV - GSK [Lecture Centralisée ECG] [2 études phase1 1 étude phase 3] du 01/05/2005 au 01/09/2008
EC-INV - WYETH [Lecture Centralisée ECG] [4 études phase1] du 01/01/2005 au 31/03/2009
EC-INV - SANOFI AVENTIS [Lecture centralisée ECG Service de gestion de dossier pour activité d'adjudication Lecture centralisée ABPM Lecture centralisée printout ICD] [>10 études phase 2 3 études phase 2/3] du 01/04/2002 au 31/03/2009
LD-ODE - CARDIABASE [Fondateur et actuel PDG de cette entreprise spécialisée dans la lecture centralisée de documents cardiologiques (core lab)] [PDG] du 01/02/1999 au
EC-INV - DAICHII [Lecture Centralisée ABPM] [1 étude de phase 3] du 07/07/2008 au EC-INV - CARDIOME [Lecture Centralisée ECG] [1 étude de phase 3] du 08/10/2007 au 15/12/2009
EC-INV - PIERRE FABRE MEDICAMENT [Lecture Centralisée ECG] [6 études phase 1-phase 2 incluant une étude QT] du 05/11/2007 au 31/03/2009

ZUBER Mathieu GTCNPGalé Titulaire **Déclaration du 10/04/2008 :**
LD-AR - SANOFI - AVENTIS [Conseil scientifique états généraux de l'athérothrombose / Plavix ®] [rémunération personnelle] du 01/10/2007 au 31/10/2008
LD-AR - SANOFI - AVENTIS [Membre comité des évènements / étude OBSERVE / Plavix ®] [rémunération personnelle] du 01/06/2007 au 31/12/2009
EC-CO - SANOFI AVENTIS - BMS [Plavix ®] [co-investigateur] du 01/01/2006 au 31/12/2007

EC-CO - BOEHRINGER INGELHEIM [Asasantine®] [co-investigateur] du 01/01/2006 au 31/12/2007
EC-CO - SERVIER [Terutroban] [co-investigateur] du 01/01/2007 au 31/12/2009
EC-CO - JOHNSON & JOHNSON [RIVAROXABAN] [co-investigateur] du 01/01/2007 au 31/12/2010
RE-AUT - DIRECTION POUR LA RECHERCHE CLINIQUE [Dossiers PHRC] [aucune rémunération]
CF-INT - SANOFI AVENTIS - BMS [antiplaquettaires et AVC / Plavix ®] [rémunération personnelle - institution]
CF-INT - EUTHERAPIE [HTA et AVC / FLUDEX ®] [rémunération personnelle - institution]
CF-INT - PFIZER [Cholestérol et AVC / TAHOR®] [rémunération personnelle - institution]
CF-AUD - SANOFI AVENTIS [AAN - COPAXONE® / Boston] du 01/04/2007 au 30/04/2007
CF-AUD - SANOFI AVENTIS [Colloque unités neurovasculaires - Plavix® / Bordeaux] du 01/04/2007 au 30/04/2007
CF-AUD - BOEHRINGER INGELHEIM [European Stroke Conference / ASASANTINE®] du 01/05/2008 au 31/05/2008

Fabienne BARTOLI - Demande de l'IGAS concernant les DPI

De : Fabienne BARTOLI
À : aquilino morelle
Date : Lundi 10 Janvier 2011 20:20
Objet : Demande de l'IGAS concernant les DPI
CC : Anne-Carole.BENSADON@igas.gouv.fr; Etienne Marie; Jean MARIMBERT; eti...
Pièces jointes : DPI experts externes - SERVIER.xls

Bonsoir,

Comme convenu à l'instant avec aquilino, je vous envoie l'état récapitulatif (sous forme de tableau) des déclarations publiques d'intérêts des experts externes ayant déclaré un lien avec le laboratoire SERVIER depuis 1999.

A noter : les déclarations d'intérêts de Pierre DEMOLIS, Philippe LECHAT et Carmen KRET-JAIS sont mentionnées dans cette requête en tant qu'anciens experts externes.
Toutefois, les liens déclarés sont relativement anciens (il date de 1999 pour Mme KERFT-JAIS...)

Nous restons à votre disposition pour toute question complémentaire sur ce sujet

Cordialement,

FB

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61289 AGID		Yves	17/03/2004	IP-EC	GLAXO SMITHKLINE				
61289 AGID		Yves	17/03/2004	IP-RE	SERVIER				
61289 AGID		Yves	17/03/2004	IP-AC	SERVIER				
61289 AGID		Yves	17/03/2004	IP-AC	GLAXO				
61289 AGID		Yves	17/03/2004	IP-AC	LILLY				
61289 AGID		Yves	17/03/2004	IP-AC	NOVARTIS				
61289 AGID		Yves	17/03/2004	IP-AC	MEDTRONIC				
61289 AGID		Yves	17/03/2004	IP-CF	GLAXO				
61289 AGID		Yves	17/03/2004	IP-CF	NOVARTIS				
61289 AGID		Yves	17/03/2004	IP-CF	LILLY				
61289 AGID		Yves	17/03/2004	VB	GLAXO				
61289 AGID		Yves	17/03/2004	VB	NOVARTIS				
61289 AGID		Yves	17/03/2004	VB	LILLY				
60219 AIACH		Martine	04/07/2000	VB	SERVIER	INSERM			
60219 AIACH		Martine	04/07/2000	VB	BIOMERIEUX	INSERM			
60219 AIACH		Martine	04/07/2000	VB	Divers	Expertises, colloques, etc. : INSERM ou ADEBIOPHARMA			
10003 ALBENGRES		Edith	15/10/1999	IP-EC	SERVIER	Une étude in vitro pour une molécule en développement			
10003 ALBENGRES		Edith	20/05/1999	IP-CF	UCB	Cétirizine			
10003 ALBENGRES		Edith	01/01/1999	IP-EC	SERVIER	Trimétazidine			
10003 ALBENGRES		Edith	01/01/1999	IP-RE	SERVIER	Trimétazidine			
10003 ALBENGRES		Edith	01/01/1999	IP-CF	UCB	Cétirizine			
10003 ALBENGRES		Edith	01/01/1998	IP-AUT	UCB				
10005 ALLAIN		Hervé	28/08/2004	IP-EC	BRISTOL MYERS SQUIBB	Aripiprazole, essai phase IV			
10005 ALLAIN		Hervé	28/08/2004	IP-EC	ONO	Essai international - SLA, essai phase II SLA			
10005 ALLAIN		Hervé	28/08/2004	IP-RE	JANSEN CILAG	Risperdal BPSD, Démence			
10005 ALLAIN		Hervé	28/08/2004	IP-AC	SERVIER	Phase I, Alzheimer, conseil de développement (mémoire, alzheimer)			
10005 ALLAIN		Hervé	28/08/2004	IP-CF	LUNDBECK	EPU Alzheimer			
10005 ALLAIN		Hervé	04/02/2004	IP-EC	BRISTOL MYERS SQUIBB	Aripiprazole et psychose			
10005 ALLAIN		Hervé	04/02/2004	IP-EC	ONO (Japon/Uk)	Essai SLA			
10005 ALLAIN		Hervé	04/02/2004	IP-RE	SCHWARZ - PHARMA	Interaction DHE - Triptans			
10005 ALLAIN		Hervé	04/02/2004	IP-RE	JANSSEN CILAG	Dossier AMM - Risperidone			
10005 ALLAIN		Hervé	04/02/2004	IP-AC	JANSSEN CILAG	Workshop et rapport sur le futur de la pharmacologie des démences (THEMA 3)			
10005 ALLAIN		Hervé	04/02/2004	IP-CF	LUNDBECK	Lancement Memantine - Démence			
10005 ALLAIN		Hervé	04/02/2004	IP-CF	LUNDBECK	Antidépresseurs / chiralité			
10005 ALLAIN		Hervé	04/02/2004	IP-CF	JANSSEN CILAG	Traitement des démences			
10005 ALLAIN		Hervé	31/01/2001	IP-EC	SCHERING	Lisuride			
10005 ALLAIN		Hervé	31/01/2001	IP-EC	SANOFI SYNTHELABO	Tiapride			
10005 ALLAIN		Hervé	31/01/2001	IP-EC	SANOFI SYNTHELABO	Zolpidem			
10005 ALLAIN		Hervé	31/01/2001	IP-EC	TEVA	Dola			
10005 ALLAIN		Hervé	31/01/2001	IP-RE	SANOFI SYNTHELABO	Zolpidem			
10005 ALLAIN		Hervé	31/01/2001	IP-AC	SERVIER	Piribedil			
10005 ALLAIN		Hervé	31/01/2001	IP-AC	FABRE	Démence			
10005 ALLAIN		Hervé	31/01/2001	IP-AC	SANOFI SYNTHELABO	Psychoses			
10005 ALLAIN		Hervé	31/01/2001	IP-AC	SANOFI SYNTHELABO ; SERVIER ; UCB	NeuroPsychopharmaco			
10005 ALLAIN		Hervé	21/02/2000	IP-EC	SCHERING	Essais Lisuride			
10005 ALLAIN		Hervé	21/02/2000	IP-EC	SANOFI SYNTHELABO	Essais TIAGE/Tiapride			
10005 ALLAIN		Hervé	21/02/2000	IP-EC	SANOFI SYNTHELABO	Zolpidem Hypnolique			
10005 ALLAIN		Hervé	21/02/2000	IP-AC	AVENTIS	Consulting Hypnotique Zopiclone			
10005 ALLAIN		Hervé	21/02/2000	IP-CF	SERVIER	Conférences à l'étranger			
10005 ALLAIN		Hervé	21/02/2000	IP-CF	IPSEN BEAUFOUR	Conférences à l'étranger			
10005 ALLAIN		Hervé	31/01/2000	IP-EC		Les derniers : Tiapride ; Psychopharmacologie (in press) ; Lisuride ; Eur neurologie (in press) ; BTD ; IPA (in press)			
10005 ALLAIN		Hervé	31/01/2000	IP-CF		La plupart des conférences sont sur internet : www.med.univ-rennes1.fr/etud/pharmaco			
10005 ALLAIN		Hervé	30/11/1999	IP-EC	LILLY France	Un essai peyolide (Parkinson)			
10005 ALLAIN		Hervé	30/11/1999	IP-EC	SYNTHELABO	Un essai mullicentrique (TIAGE)			
10005 ALLAIN		Hervé	30/11/1999	IP-EC	SCHERING	Un essai Lisuride (Parkinson)			
10005 ALLAIN		Hervé	30/11/1999	IP-EC	ZENECA	Migraine pharmaco-épidémiologie			
10005 ALLAIN		Hervé	30/11/1999	IP-AC	GLAXO WELLCOME	Observatoire KOEMIE (Rennes) migraine à CITROEN			
10005 ALLAIN		Hervé	30/11/1999	IP-CF	SERVIER	Conférence sur l'ischémie cérébrale et le Parkinson			
10005 ALLAIN		Hervé	30/11/1999	IP-CF	NOVARTIS	Conférence sur les ICOMT			
10005 ALLAIN		Hervé	01/01/1999	IP-EC	LILLY	Toutes les molécules en développement dans la maladie d'Alzheimer			
10005 ALLAIN		Hervé	01/01/1999	IP-RE	UCB PHARMA	Nootropyl			
10005 ALLAIN		Hervé	01/01/1999	IP-EC	ROCHE	Essai Tolcapone			
10005 ALLAIN		Hervé	01/01/1999	IP-EC	EISAI	Essai Arial - Aricept			
10005 ALLAIN		Hervé	01/01/1999	IP-RE	UCB	Piracetam (1997)			
10005 ALLAIN		Hervé	01/01/1999	IP-CF	BIOGEN	Conférences sur les interférone bêta dans la SEP			
10005 ALLAIN		Hervé	01/01/1999	IP-AUT	MASSON et SKB	Rédaction d'un livre sur les comorbidités dans la dépression			
10005 ALLAIN		Hervé	01/01/1999	VB	UCB PHARMA	Rapports 1997 : versement à l'Association de recherche en gériatrie et gérontologie (AREGG)	Association de Recherche en Gériatrie et Gérontologie (AREGG)		
10006 ALLAIN		Pierre	01/01/1999	VB	LILLY	Contrat de recherche : Association			
10006 ALLAIN		Pierre	01/01/1999	VB	DEBIOPHARM	association			
10006 ALLAIN		Pierre	01/01/1999	VB	SANOFI	Université d'Agers			
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Madhaus Allemagne				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Marion Merrell Dow				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Lilly				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	SKB				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Parke Davis				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Servier				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Pfizer				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Synthélabo				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Ipsen				
10005 ALLAIN		Hervé	01/01/1998	IP-AUT	Eurofonum				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10005	ALLAIN	Hervé	01/01/1998	IP-RE	UCB pharma	Nootropyl			
10005	ALLAIN	Hervé	01/01/1998	IP-AUT	BIOGEN				
10005	ALLAIN	Hervé	01/01/1998	VB		Conférences, séminaires, versement à l'AREGG			
10006	ALLAIN	Pierre	01/01/1998	VB	Servier	Association Arpta			
10006	ALLAIN	Pierre	01/01/1998	VB	Déblopharm	Association Arpta			
10006	ALLAIN	Pierre	01/01/1998	PAR	MSD	Acquisition d'exemplaires d'un ouvrage rédigé par P. Allain			
10006	ALLAIN	Pierre	01/01/1998	PAR	Glaxo Wellcome	Acquisition d'exemplaires d'un ouvrage rédigé par P. Allain			
64568	ALLAUZEN	Nadine	30/01/2009	LD	SCIENCE UNION (SERVIER)	Chef de Département Affaires Réglementaires	CDI	05/1997	
64568	ALLAUZEN	Nadine	10/01/2008	LD	SCIENCE UNION (SERVIER)	Chef de Département Affaires Réglementaires	CDI	05/1997	
64568	ALLAUZEN	Nadine	12/09/2006	LD	SCIENCE UNION (SERVIER)	Chef de Département Affaires Réglementaires	CDI	05/1997	
64568	ALLAUZEN	Nadine	12/09/2006	CF-INT	IP : SITE	Séminaires sur les variations pharmaceutiques	aucune rémunération	12/2004	11/2006
55655	ALPEROVITCH	Annick	14/06/2010	LD-AR	LA-SER	Consultance (méthodologie)	Rémunération personnelle	04/2010	
55655	ALPEROVITCH	Annick	17/04/2009	RE-AUT	OSEO	Maladie d'Alzheimer	Rémunération personnelle	10/2008	12/2008
55655	ALPEROVITCH	Annick	07/12/2007	IP-AC	SANOFI SYNTHELABO	Comité scientifique d'un observatoire	Aucune rémunération		12/2007
55655	ALPEROVITCH	Annick	07/12/2007	IP-AC	UCB-PHARMA	Comité scientifique d'un observatoire	Aucune rémunération		12/2008
55655	ALPEROVITCH	Annick	07/12/2007	IP-AC	SANOFI AVENTIS	CS de l'étude post-AMM / Plavix	aucune rémunération	01/2004	
55655	ALPEROVITCH	Annick	07/12/2007	VB	LUNDBECK	Etude post AMM de la mémantine	Inserm Transfert/inserm	01/2003	12/2007
55655	ALPEROVITCH	Annick	08/04/2006	IP-AC	INSTITUT ATHEROTHROMBOSE	Athérothrombose	Rémunération personnelle	01/2003	12/2004
55655	ALPEROVITCH	Annick	08/04/2006	IP-AC	SANOFI AVENTIS	CS de l'étude post-AMM plavix	aucune rémunération	01/2004	
55655	ALPEROVITCH	Annick	08/04/2006	IP-AC	ASTRAZENECA	CS de l'étude post-AMM crestor	aucune rémunération	01/2005	12/2005
55655	ALPEROVITCH	Annick	08/04/2006	VB	SANOFI AVENTIS	Soutien à une étude de cohorte (3C)	Université Bordeaux 2	01/2000	12/2005
55655	ALPEROVITCH	Annick	08/04/2006	VB	LUNDBECK	Etude post AMM de la mémantine	Inserm Transfert/inserm	01/2003	12/2007
55655	ALPEROVITCH	Annick	14/03/2006	IP-AC	SANOFI-SYNTHELABO	Comité scientifique d'un observatoire	Aucune rémunération		
55655	ALPEROVITCH	Annick	14/03/2006	IP-AC	UCB-PHARMA	Comité scientifique d'un observatoire	Aucune rémunération		
55655	ALPEROVITCH	Annick	14/03/2006	VB	SANOFI SYNTHELABO	INSERM		01/2000	12/2005
55655	ALPEROVITCH	Annick	04/02/2004	IP-AC	SANOFI SYNTHELABO	Comité scientifique d'un observatoire			
55655	ALPEROVITCH	Annick	04/02/2004	IP-AC	UCB-PHARMA	Comité scientifique d'un observatoire			
55655	ALPEROVITCH	Annick	04/02/2004	VB	SANOFI-SYNTHELABO	INSERM			
55655	ALPEROVITCH	Annick	07/05/1999	IP-CF	SERVIER	Formation			
55655	ALPEROVITCH	Annick	07/05/1999	VB	EISAI PFIZER	INSERM			
55655	ALPEROVITCH	Annick	07/05/1999	VB	SERVIER	INSERM			
55655	ALPEROVITCH	Annick	01/01/1999	VB	MSD	Convention INSERM-MSD (soutien d'une étude épidémiologique)	INSERM		
10007	ALTMAN	Jean-Jacques	26/10/2010	LD-AR	BAYER	ACARBOSE : produit	rémunération institution	01/2010	12/2010
10007	ALTMAN	Jean-Jacques	26/10/2010	LD-AR	SERVIER	MEDIATOR : produit	rémunération institution	01/2010	12/2010
10007	ALTMAN	Jean-Jacques	26/10/2010	LD-AR	NOVONORDISK	DETEMIR	rémunération institution	01/2010	12/2010
10007	ALTMAN	Jean-Jacques	26/10/2010	CF-AUD	BMS	EASD -		09/2010	09/2010
10007	ALTMAN	Jean-Jacques	07/09/2009	EC-CO	NOVONORDISK	Insuline Détémir	co-investigateur	01/2007	12/2009
10007	ALTMAN	Jean-Jacques	07/09/2009	RE-AUT	BAYER	Analyse de registre de dossier épidémiologique	rémunération personnelle	01/2006	12/2009
10007	ALTMAN	Jean-Jacques	07/09/2009	IP-AC	NOVO NORDISK	Insuline en général	rémunération personnelle	01/2006	12/2009
10007	ALTMAN	Jean-Jacques	07/09/2008	EC-CO	NOVONORDISK	Insuline Détémir	co-investigateur	01/2007	12/2009
10007	ALTMAN	Jean-Jacques	07/09/2008	RE-AUT	BAYER	Analyse de registre de dossier épidémiologique	rémunération personnelle	01/2006	12/2009
10007	ALTMAN	Jean-Jacques	07/09/2008	RE-AUT	SERVIER	avis DPP V	rémunération institution	01/2006	12/2009
10007	ALTMAN	Jean-Jacques	07/09/2008	IP-AC	NOVONORDISK	Insuline en général	rémunération personnelle	01/2006	12/2009
10007	ALTMAN	Jean-Jacques	14/11/2007	EC-CO	NOVONORDISK	insuline Détémir	co-investigateur	10/2007	11/2008
10007	ALTMAN	Jean-Jacques	14/11/2007	RE-AUT	BAYER	analyse des registres Entred et Ecodia	Rémunération personnelle	01/2007	10/2008
10007	ALTMAN	Jean-Jacques	14/11/2007	RE-AUT	SERVIER	avis sur DPP V	Rémunération personnelle	01/2007	12/2008
10007	ALTMAN	Jean-Jacques	14/11/2007	IP-AC	NOVONORDISK	insulines en général	Rémunération personnelle	01/2007	
10007	ALTMAN	Jean-Jacques	14/11/2007	RE-AUT	SERVIER	Avis sur DPP V	rémunération institution	01/2006	12/2009
10007	ALTMAN	Jean-Jacques	07/06/2006	RE-AUT	NOVONORDISK	intérêts des analogues de l'insuline	rémunération personnelle	01/2005	12/2009
10007	ALTMAN	Jean-Jacques	07/06/2006	IP-AC	SERVIER	Degré de prise en charge du diabète, y compris non médicamenteuse	rémunération personnelle	01/2004	12/2006
10007	ALTMAN	Jean-Jacques	07/06/2006	CF-AUD	MSD	Congrès de l'ADA (American Diabete Association) Washington : généralité sur le diabète		06/2006	06/2006
10007	ALTMAN	Jean-Jacques	07/06/2006	RE-AUT	BAYER	L'acarbose a t'il un avenir ?	rémunération personnelle	06/2004	07/2004
10007	ALTMAN	Jean-Jacques	22/02/2005	LD	NOVONORDISK	Pour l'insuline - consultation régulière		01/2000	12/2005
10007	ALTMAN	Jean-Jacques	22/02/2005	LD	SERVIER	pour anti-diabétique consultation régulière		01/2000	12/2005
10007	ALTMAN	Jean-Jacques	22/02/2005	IP-AC	BMS, BAYER	pour anti-diabétique		01/2003	12/2005
10007	ALTMAN	Jean-Jacques	22/02/2005	IP-EC	MENARINI	pour le glucoday		01/2003	12/2005
10007	ALTMAN	Jean-Jacques	22/02/2005	IP-CF		Congrès scientifique sans relation avec l'industrie			
10007	ALTMAN	Jean-Jacques	22/02/2005	CF-AUD	PFIZER	TAHOR	auditeur	01/2004	12/2004
10007	ALTMAN	Jean-Jacques	11/04/2003	IP-EC	NOVONORDISK	Phase III - Insuline			
10007	ALTMAN	Jean-Jacques	11/04/2003	IP-EC	AVENTIS	Phase III - Insuline			
10007	ALTMAN	Jean-Jacques	11/04/2003	IP-AC	SERVIER	Analyse projets nouvelles molécules			
10007	ALTMAN	Jean-Jacques	11/04/2003	IP-AC	AMYLIN	Analyse rapport d'expertise			
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	ROCHE				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	SANOFI				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	PARKE DAVIS				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	TAKEDA				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	NOVO NORDISK				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	DAKOTA PHARM				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	HOECHST MARION ROUSSEL				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	LAFON				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	FRESENIUS				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	BAYER				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	BOOTS PHARMA				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	RHONE POULENC RORER				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	ABBOTT				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	UPSA				
10007	ALTMAN	Jean-Jacques	01/01/1999	IP-EC	ARKOPHARMA				
10007	ALTMAN	Jean-Jacques	01/01/1998	IP-AUT	Pfizer				
10007	ALTMAN	Jean-Jacques	01/01/1998	IP-AUT	Lilly				
10007	ALTMAN	Jean-Jacques	01/01/1998	IP-AUT	Novo Nordisk				
10007	ALTMAN	Jean-Jacques	01/01/1998	IP-AUT	Hoechst				
60220	AMARENCO	Pierre	19/11/2008	EC-INV	SANOFI	Essais cliniques	investigateur	01/2008	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60220	AMARENCO	Pierre	19/11/2008	EC-INV	PFIZER	Essais cliniques	Investigateur	01/1998	
60220	AMARENCO	Pierre	30/05/2006	EC-INV	PFIZER	Essai thérapeutique en double aveugle - Atorvastatine vs placebo	investigateur coordonnateur	01/2003	12/2006
60220	AMARENCO	Pierre	30/05/2006	EC-CO	SANOFI	Essai thérapeutique / Plavix	co-investigateur	01/2003	12/2004
60220	AMARENCO	Pierre	30/05/2006	EC-CO	ASTRA ZENECA	Essai thérapeutique / NXY-059	co-investigateur	01/2003	12/2006
60220	AMARENCO	Pierre	30/05/2006	EC-CO	LILLY	Essai thérapeutique / Reopro	co-investigateur	01/2003	12/2005
60220	AMARENCO	Pierre	30/05/2006	EC-CO	BOEHRINGER INGELHEIM	Essai thérapeutique / Actilyse	co-investigateur	01/2002	12/2006
60220	AMARENCO	Pierre	30/05/2006	CF-INT	MSD	AVL	rémunération institution	01/2003	
60220	AMARENCO	Pierre	30/05/2006	CF-INT	PFIZER	AVL	rémunération institution	01/2004	12/2006
60220	AMARENCO	Pierre	30/05/2006	CF-INT	SANOFI	AVL	rémunération institution	01/2006	
60220	AMARENCO	Pierre	09/04/2006	EC-INV	PFIZER	Essai clinique	investigateur principal	01/2002	12/2006
60220	AMARENCO	Pierre	09/04/2006	EC-CO	PFIZER	Essai clinique	co-investigateur	01/1998	12/2006
60220	AMARENCO	Pierre	09/04/2006	EC-CO	SANOFI	Essai clinique	co-investigateur	01/2003	
60220	AMARENCO	Pierre	09/04/2006	EC-CO	ASTRA ZENECA	Essai clinique	co-investigateur	01/2003	
60220	AMARENCO	Pierre	09/04/2006	EC-CO	BOEHRINGER INGELHEIM	Essai clinique	co-investigateur	01/2003	
60220	AMARENCO	Pierre	09/04/2006	EC-CO	LILLY	Essai clinique	co-investigateur	01/2004	12/2005
60220	AMARENCO	Pierre	09/04/2006	CF-INT	SANOFI, PFIZER, NOVARTIS, MERCK	pathologie neuro vasculaire	rémunération personnelle / institution	01/2003	12/2006
60220	AMARENCO	Pierre	09/04/2006	VB	EISAI	Etude épidémiologique	SOS ATTAQUE CEREBRALE	01/2005	12/2005
60220	AMARENCO	Pierre	09/04/2006	VB	BOEHRINGER INGELHEIM	Essai clinique	SOS ATTAQUE CEREBRALE	01/2006	12/2008
60220	AMARENCO	Pierre	09/04/2006	VB	SANOFI	Etude épidémiologique	SOS ATTAQUE CEREBRALE	01/2005	12/2005
60220	AMARENCO	Pierre	09/04/2006	VB	PFIZER	Essai clinique	SOS ATTAQUE CEREBRALE	01/2002	12/2005
60220	AMARENCO	Pierre	16/03/2005	IP-AC	PFIZER	Atorvastatine - Membre du Steering Committee de l'étude SPARCL (Atorvastatine vs placebo ou prévention secondaire de l'AVC (Accident Vasculaire Cérébral)			
60220	AMARENCO	Pierre	16/03/2005	IP-EC	PFIZER	Etude Atorvastatine vs placébo chez 128 patients ayant 1 infarctus lacunaire			
60220	AMARENCO	Pierre	16/03/2005	IP-AC	PFIZER, NOVARTIS, MSD, SANOFI-AVENTIS	interventions au cours des 3 dernières années			
60220	AMARENCO	Pierre	16/03/2005	IP-CF	PFIZER, SANOFI, BOEHRINGER-INGELHEIM				
60220	AMARENCO	Pierre	22/09/2003	IP-EC	PFIZER				
60220	AMARENCO	Pierre	22/09/2003	IP-EC	SANOFI, BRISTOL MYERS SQUIBB				
60220	AMARENCO	Pierre	22/09/2003	IP-EC	SERVIER				
60220	AMARENCO	Pierre	22/09/2003	IP-EC	ASTRA ZENECA				
60220	AMARENCO	Pierre	22/09/2003	IP-EC	BOEHRINGER INGELHEIM				
60220	AMARENCO	Pierre	22/09/2003	IP-EC	LILLY				
60220	AMARENCO	Pierre	22/09/2003	IP-CF	PFIZER				
60220	AMARENCO	Pierre	22/09/2003	IP-CF	ASTRA ZENECA				
60220	AMARENCO	Pierre	22/09/2003	IP-CF	SANOFI, BRISTOL MYERS SQUIBB				
60220	AMARENCO	Pierre	22/09/2003	VB	PFIZER				
60220	AMARENCO	Pierre	22/09/2003	VB	BOEHRINGER INGELHEIM				
60220	AMARENCO	Pierre	13/06/2003	IP-EC	PFIZER				
60220	AMARENCO	Pierre	13/06/2003	IP-EC	SANOFI				
60220	AMARENCO	Pierre	13/06/2003	IP-AC	PFIZER				
60220	AMARENCO	Pierre	13/06/2003	IP-AC	ASTRA ZENECA				
60220	AMARENCO	Pierre	13/06/2003	IP-AC	SANOFI				
60220	AMARENCO	Pierre	13/06/2003	IP-CF	PFIZER				
60220	AMARENCO	Pierre	13/06/2003	IP-CF	ASTRA ZENECA				
60220	AMARENCO	Pierre	13/06/2003	IP-CF	BMS				
60220	AMARENCO	Pierre	13/06/2003	IP-CF	SANOFI				
60220	AMARENCO	Pierre	13/06/2003	IP-CF	BOEHRINGER INGELHEIM				
60220	AMARENCO	Pierre	25/09/2000	IP-EC	NEGMA	Essai randomisé Statine vs placebo			
60220	AMARENCO	Pierre	25/09/2000	IP-EC	ASTRA ZENECA	Essai randomisé Mélagatron vs AVK			
60220	AMARENCO	Pierre	25/09/2000	IP-EC	BRISTOL MYERS SQUIBB	Essai randomisé POST (phase aiguë IC)			
60220	AMARENCO	Pierre	25/09/2000	IP-EC	SANOFI	Essai randomisé MATCH			
60220	AMARENCO	Pierre	25/09/2000	IP-EC	AVENTIS	Essai randomisé Enoxoparine vs placebo			
60220	AMARENCO	Pierre	25/09/2000	IP-CF	PFIZER	AVC			
60220	AMARENCO	Pierre	25/09/2000	IP-CF	BRISTOL MYERS SQUIBB	AVC			
60220	AMARENCO	Pierre	25/09/2000	IP-CF	BOEHRINGER INGELHEIM	AVC			
60220	AMARENCO	Pierre	25/09/2000	IP-CF	BAYER	AVC			
61700	AMBROSI	Pierre	03/09/2010	CF-AUD	SERVIER	Congrès européen de cardiologie (Stockholm)		08/2010	09/2010
61700	AMBROSI	Pierre	30/09/2009	RE-AUT	BOEHRINGER-INGELHEIM	Micardis, dossier de transparence	Rémunération personnelle	06/2009	
61700	AMBROSI	Pierre	02/01/2009	EC-INV	MSD	Ezetimibe Etude MK653 A-808	coordinateur national (étude internationale) honoraires versés à une association	01/2004	12/2007
61700	AMBROSI	Pierre	02/01/2009	EC-CO	SERVIER	Psychotrope (interprétation d'ECG) (étude en cours)	honoraires versés à une association		
61700	AMBROSI	Pierre	02/01/2009	IP-AC	PIERRE FABRE	Avis avant achat éventuel de la molécule - ranolazine	rémunération personnelle	01/2007	12/2007
61700	AMBROSI	Pierre	02/01/2009	IP-AC	NOVARTIS	Aliskiren	rémunération personnelle	01/2008	12/2008
61700	AMBROSI	Pierre	02/01/2009	CF-AUD	SERVIER	Congrès européen de cardiologie		09/2008	09/2008
61700	AMBROSI	Pierre	02/01/2009	VB		Budgets de recherches des 188 PU et PH membres de l'association	ADEREM	01/2003	
61700	AMBROSI	Pierre	28/11/2007	IP-CF	SERVIER	Congrès européen de cardiologie (les frais d'inscription et d'hébergement ont été pris en charge par le laboratoire SERVIER)		01/2007	12/2007
61700	AMBROSI	Pierre	28/11/2007	IP-EC	SERVIER	Rémunération d'un essai clinique inférieur à 1 000 euros par le laboratoire SERVIER, la somme a été versée en totalité à une association		01/2007	12/2007
61700	AMBROSI	Pierre	28/11/2007	IP-RE	NOVARTIS	Expertise d'un dossier (rémunération par le laboratoire NOVARTIS)		01/2007	12/2007
61700	AMBROSI	Pierre	15/04/2006	EC-INV	ASTRA	CRESTOR	investigateur		12/2004
61700	AMBROSI	Pierre	15/04/2006	EC-INV	MSD	Ezetimibe	Coordinateur national rémunération partagée personnelle/institution □ honoraire pour EPU (moins de 3000 euros en partie réservés à une assossiation	01/2004	
61700	AMBROSI	Pierre	15/04/2006	CF-INT	PFIZER	Marseille			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61700	AMBROSI	Pierre	15/04/2006	CF-INT	ASTRA	lipides - HTA	rémunération partagée personnelle/institution□ honoraire pour EPU (moins de 3000 euros en partie réservés à une assossiation		
61700	AMBROSI	Pierre	15/04/2006	CF-INT	DADE BEHRING	Paris	rémunération partagée personnelle/institution□ honoraire pour EPU (moins de 3000 euros en partie réservés à une assossiation		
61700	AMBROSI	Pierre	15/04/2006	CF-AUD	SERVIER	Stockholm - ESC		09/2005	09/2005
61700	AMBROSI	Pierre	15/04/2006	CF-AUD	SERVIER	Paris - SFC		01/2006	01/2006
61700	AMBROSI	Pierre	05/10/2004	IP-AUT	SERVIER	Remboursement de frais de déplacement au congrès européen de cardiologie			
61700	AMBROSI	Pierre	05/10/2004	VB	ASTRA ZENECA	Etude Ariane : conclusion de patients en 2003, versement de l'ADERM		01/2003	12/2003
61700	AMBROSI	Pierre	22/03/2004	VB	ADIR	ADEREM	Sommes modestes		
61700	AMBROSI	Pierre	22/03/2004	VB	ASTIA	ADEREM	Sommes modestes		
61700	AMBROSI	Pierre	04/09/2003	IP-CF	BRISTOL MYERS SQUIBB	1 conférence en 2001			
61700	AMBROSI	Pierre	04/09/2003	IP-AUT	SERVIER	Prise en charge des frais de déplacement et d'hébergement au congrès européen de cardiologie 2002-2003			
61700	AMBROSI	Pierre	04/09/2003	IP-AUT	FOURNIER	Idem congrès de l'EAS 2002			
61700	AMBROSI	Pierre	04/09/2003	VB	ASTRA ZENECA	Investigateur essai Ariane 2003 - ADEREM			
61700	AMBROSI	Pierre	04/09/2003	VB	FOURNIER	Coordonnateur essai 2002 - ADEREM			
61700	AMBROSI	Pierre	21/02/2003	VB		Coordination d'essais cliniques : ADEREM			
61700	AMBROSI	Pierre	21/02/2003	VB		Investigateur d'essais cliniques : ADEREM			
61700	AMBROSI	Pierre	21/02/2003	(Autre)		Prise en charge par l'industrie de 1 à 2 déplacements annuels en congrès			
55652	ANDREJAK	Michel	13/04/2010	Néant					
55652	ANDREJAK	Michel	06/04/2010	Néant					
55652	ANDREJAK	Michel	30/03/2009	CF-AUD	BIOPHARMA	Congrès de Société Européenne de Cardiologie Berlin Sept 2008		09/2008	09/2008
55652	ANDREJAK	Michel	24/04/2008	CF-INT	OCTOPHARMA	Symposium OCTOPHARMA actualités en immunologie clinique	Rémunération institution	10/2007	10/2007
55652	ANDREJAK	Michel	28/03/2007	EC-INV	SERVIER MEDICAL	Essai clinique/ Prétérax étude entre 01/01/1999 et 31/12/2003	coordonnateur	01/1999	12/2003
55652	ANDREJAK	Michel	11/12/2006	EC-INV	SERVIER MEDICAL	Coordinateur essai clinique - Prétérax (prindopril, indapamide)	Coordinateur	01/1999	12/2003
55652	ANDREJAK	Michel	30/01/2006	EC-INV	SERVIER MEDICAL	Coordonnateur étude Strathe/ Prétérax - 2004 (date de publication des résultats de l'étude)	Investigateur coordonnateur	01/2001	12/2004
55652	ANDREJAK	Michel	30/01/2006	CF-AUD	SERVIER MEDICAL	Journées Européennes de la SFC (Société Française de Cardiologie) (2 jours)		01/2006	01/2006
55652	ANDREJAK	Michel	23/11/2004	IP-EC	SERVIER MEDICAL	Essais thérapeutiques (association Périndopril-Indapamide, PRETERAX dans l'HTA)			
55652	ANDREJAK	Michel	23/11/2004	(Autre)	SCHERING PLOUGH	Invitation Congrès Société Européen de Cardiologie août 2004			
55652	ANDREJAK	Michel	27/01/2004	IP-EC	SERVIER MEDICAL	Essai therapeutique STRATHE (Preterax)			
55652	ANDREJAK	Michel	27/01/2004	IP-CF	SERVIER MEDICAL	Conférence dans le domaine de l'HTA			
55652	ANDREJAK	Michel	09/01/2001	IP-EC	SERVIER MEDICAL	Essais cliniques			
55652	ANDREJAK	Michel	09/01/2001	IP-EC	ROCHE	Travaux scientifiques : études de pharmacocinétique			
55652	ANDREJAK	Michel	09/01/2001	IP-CF	AVENTIS	Action de formation auprès de cardiologues			
55652	ANDREJAK	Michel	09/01/2001	IP-AUT	ASTRA ZENECA	Invitation à un congrès médical			
55652	ANDREJAK	Michel	10/02/2000	IP-EC	SERVIER MEDICAL	Essais cliniques			
55652	ANDREJAK	Michel	10/02/2000	IP-EC	GLAXO WELLCOME	Essais cliniques			
55652	ANDREJAK	Michel	16/12/1999	IP-EC	SERVIER	Essai thérapeutique dans l'HTA			
55652	ANDREJAK	Michel	16/12/1999	IP-EC	SANOFI	Essai thérapeutique dans l'HTA			
55652	ANDREJAK	Michel	16/12/1999	IP-EC	TAKEDA	Essai thérapeutique dans l'HTA			
55652	ANDREJAK	Michel	16/12/1999	IP-CF	SYNTHELABO	1999 : intervention lors d'un symposium sur les anti-histaminiques lors du congrès francais d'allergologie			
55652	ANDREJAK	Michel	16/12/1999	IP-CF	BOEHRINGER INGELHEIM	Compte rendu du congrès européen de Cardiologie à Amiens (sept 1999)			
55652	ANDREJAK	Michel	15/12/1999	IP-EC	SERVIER	Essai thérapeutique			
55652	ANDREJAK	Michel	15/12/1999	IP-EC	SANOFI	Essai thérapeutique			
55652	ANDREJAK	Michel	15/12/1999	IP-EC	TAKEDA	Essai thérapeutique			
55652	ANDREJAK	Michel	15/12/1999	IP-CF	BOEHRINGER INGELHEIM	Compte rendu congrès européen de cardiologie à Amiens			
55652	ANDREJAK	Michel	15/12/1999	IP-CF	SYNTHELABO	Symposium sur les anti-histaminiques du congrès francais d'allergologie (Grenoble)			
62219	ANNEQUIN	Daniel	30/07/2010	IP-AC	LINDE	revue de la littérature	Rémunération personnelle	12/2009	12/2009
62219	ANNEQUIN	Daniel	30/07/2010	IP-AC	LINDE	Revue bibliographique	Rémunération personnelle	12/2009	12/2009
62219	ANNEQUIN	Daniel	30/07/2010	IP-AC	LINDE INTERNATIONAL	Revue bibliographique	Rémunération personnelle	12/2009	12/2009
62219	ANNEQUIN	Daniel	30/07/2010	EC-INV	PAREXEL POUR MSD	Essai multicentrique rizatriptan	Investigateur principal	01/2010	08/2010
62219	ANNEQUIN	Daniel	03/05/2009	IP-AC	LINDE	Veille bibliographique	Rémunération personnelle	01/2008	01/2009
62219	ANNEQUIN	Daniel	03/05/2009	CF-INT	LINDE	Medicinal gas mixtures in pain management (18/08/09 : Glasgow Congres IASP)	Rémunération personnelle	08/2008	08/2008
62219	ANNEQUIN	Daniel	03/05/2009	CF-INT	LINDE	LIVOPAN zur Schmerztherapie bei Kindern schnell wirksam und sanft (06/02/09) - (Recklinghausen - Germa	Rémunération personnelle	02/2009	02/2009
62219	ANNEQUIN	Daniel	03/05/2009	CF-INT	SANOFI	FMC "la migraine de l'enfant" - Paris 75014	Rémunération personnelle	04/2009	04/2009
62219	ANNEQUIN	Daniel	03/05/2009	CF-AUD	LINDE	Glasgow Congres IASP	Hébergement et transport	08/2008	08/2008
62219	ANNEQUIN	Daniel	03/05/2009	IP-AUT	CANAL 55 POUR LE LABORATOIRE WYETH	Advil : "Monographie sur la douleur de l'enfant"	Rémunération personnelle	06/2008	06/2008
62219	ANNEQUIN	Daniel	13/06/2007	IP-AC	AGA LINDE	Rémunération personnelle		05/2006	03/2007
62219	ANNEQUIN	Daniel	13/06/2007	CF-INT	BOOTS	Conférence " la migraine de l'enfant" - Bordeaux	rémunération personnelle/institution	03/2005	03/2005
62219	ANNEQUIN	Daniel	13/06/2007	CF-INT	BOOTS	Conférence " la migraine de l'enfant" - Paris	Rémunération personnelle/institution	06/2005	06/2005
62219	ANNEQUIN	Daniel	13/06/2007	CF-INT	BOOTS	Conférence " la migraine de l'enfant" - Paris	rémunération personnelle/institution	09/2005	09/2005
62219	ANNEQUIN	Daniel	13/06/2007	CF-AUD	BOOTS	Congrès IHC - Kyoto		07/2006	07/2006
62219	ANNEQUIN	Daniel	15/06/2006	CF-AUD	LABORATOIRE BOOTS HEALTHCARE	Congrès International Headache Society □□Kyoto		10/2005	10/2005
62219	ANNEQUIN	Daniel	15/06/2006	CF-INT	LABORATOIRE BOOTS HEALTHCARE PARIS	Entretiens de Bichat□□Paris Pitié Salpetrière□□"la migraine de l'enfant"	Rémunération personnelle	09/2005	09/2005
62219	ANNEQUIN	Daniel	15/06/2006	CF-INT	LABORATOIRE BOOTS HEALTHCARE PARIS	EPU Paris Hotel Hilton □□"la migraine de l'enfant"	Rémunération personnelle	06/2005	06/2005
62219	ANNEQUIN	Daniel	15/06/2006	CF-INT	LABORATOIRE SERVIER	Institut de recherche Servier □□Issy les Moulineaux□□Conférence "la douleur de l'enfant"□□	Rémunération personnelle	06/2005	06/2005
62219	ANNEQUIN	Daniel	30/09/2003	Néant					
10010	ANTON	Robert	08/03/2010	IP-AC	REVLON	Consultant scientifique ponctuel	rémunération personnelle	01/2008	12/2008
10010	ANTON	Robert	08/03/2010	IP-AC	ROBERTET	Consultant scientifique ponctuel	rémunération personnelle	01/2008	12/2008
10010	ANTON	Robert	08/03/2010	IP-AC	MERCK	Consultant scientifique (Phytothérapie)	rémunération personnelle	01/2009	12/2010
10010	ANTON	Robert	08/03/2010	CF-INT		Conférences diverses avec prise en charge des frais de déplacement uniquement	aucune rémunération		
10010	ANTON	Robert	08/03/2010	VB		Quelques taxes d'apprentissage	Université de Strasbourg		12/2010
10010	ANTON	Robert	08/03/2010	PAR	NATURAL PRODUCT CONSULTING	Directeur	Fils	01/2000	
10010	ANTON	Robert	08/03/2010	PAR	INTERLAC	Directeur	Fils	01/2009	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10010	ANTON	Robert	30/11/2009	IP-AC	BAYER HEALTCARE	Conseil ponctuel	rémunération personnelle	01/2006	12/2006
10010	ANTON	Robert	30/11/2009	IP-AC	REVLON COLOMER	Conseil ponctuel avec accord de l'AFSSAPS	rémunération personnelle	01/2008	12/2008
10010	ANTON	Robert	30/11/2009	IP-AC	ROBERTET	Conseil ponctuel	rémunération personnelle	01/2008	12/2008
10010	ANTON	Robert	30/11/2009	IP-AC	MERCK	Conseil	rémunération personnelle	10/2009	09/2010
10010	ANTON	Robert	30/11/2009	CF-INT		Conférences diverses	aucune rémunération		
10010	ANTON	Robert	30/11/2009	VB		Taxes d'apprentissage	Université de Strasbourg		
10010	ANTON	Robert	30/11/2009	PAR	NATURAL PRODUCT CONSULTING	Directeur	fils (aucune interférence)	01/2000	
10010	ANTON	Robert	01/04/2009	LD-AR		Expert national et européen (instances officielles)	rémunération personnelle		
10010	ANTON	Robert	01/04/2009	LD-AR	AFSASPS - EFSA				
10010	ANTON	Robert	01/04/2009	IP-AC	COLOMER - REVLON	Conseil ponctuel sur un produit cosmétique après avis favorable de l'Afssaps	rémunération personnelle	01/2008	
10010	ANTON	Robert	01/04/2009	CF-INT		Cf liste sur document joint	aucune rémunération	01/2004	12/2009
10010	ANTON	Robert	01/04/2009	VB	Divers	Taxes d'apprentissage	Faculté de pharmacie, Université de Strasbourg exclusivement (chaque année)	01/2008	12/2009
10010	ANTON	Robert	01/04/2009	PAR	NATURAL PRODUCT CONSULTING	Directeur	fils	01/1999	
10010	ANTON	Robert	01/04/2009	LD-AR		Expert national et européen (instances officielle - indemnités)			
10010	ANTON	Robert	01/04/2009	IP-AC	COLOMER-REVLON	Conseil ponduel sur un produit cosmétique après avis favorable de l'AFSSAPS	rémunération personnelle		
10010	ANTON	Robert	01/04/2009	VB	Divers	Taxes d'apprentissage	Faculté de Pharmacie, université de Strasbourg exclusivement		
10010	ANTON	Robert	01/04/2009	PAR	Natural Product Consulting	Directeur	Fils		
10010	ANTON	Robert	20/04/2007	VB	ARKOPHARMA, BAYER SANTE FAMILIALE, BIOPHARMA, BOEHRINGER INGELHEIM, COOPER, DOLISOS, ESTEE LAUDER, LILLY, MERCK SANTE, PHYTO ENERGETIQUE, PIERRE FABRE, PPDH, SANKYO PHARMA	Versement de la taxe d'apprentissage	Université Louis Pasteur	01/2006	12/2006
10010	ANTON	Robert	19/04/2007	IP-AC	BAYER HEALTHCARE	conseil	Rémunération personnelle	01/2007	12/2007
10010	ANTON	Robert	05/09/2006	IF	NATURAL PRODUCTS CONSULTING	actionnaire minoritaire	> 5000s ou > 5% du capital	01/2000	12/2006
10010	ANTON	Robert	05/09/2006	LD-AR	LAB PIERRE FABRE CASTRES	consultant scientifique	rémunération personnelle	01/1990	04/2006
10010	ANTON	Robert	05/09/2006	IP-AC	SERVIER	consultant ponctuel	rémunération personnelle	01/2004	12/2004
10010	ANTON	Robert	05/09/2006	IP-AC	BAYER HEALTH CARE	consultant ponctuel	rémunération personnelle	01/2006	12/2006
10010	ANTON	Robert	05/09/2006	VB	LAB ESTEE LAUDER	contrat de recherche	ULP strasbourg	01/2002	02/2007
10010	ANTON	Robert	05/09/2006	VB	LAB SECMA	contrat de recherche	ULP strasbourg	01/2005	09/2007
10010	ANTON	Robert	05/09/2006	VB		taxes d'apprentissage voir liste 2005 en annexe 2			
10010	ANTON	Robert	05/09/2006	PAR	NATURAL PRODUCTS CONSULTING	directeur	fils	01/2000	
10010	ANTON	Robert	06/06/2006	IF	NATUEAL PRODUCTS CONSULTING	Actionnaire minoritaire	5 % du capital	01/2000	12/2006
10010	ANTON	Robert	06/06/2006	LD-AR	PIERRE FABRE - Castres	consultant scientifique	Rémunération personnelle	01/1990	04/2006
10010	ANTON	Robert	06/06/2006	IP-AC	SERVIER	consultant ponctuel	Rémunération personnelle	01/2004	12/2004
10010	ANTON	Robert	06/06/2006	IP-AC	BAYER HEALTH CARE	Consultant ponctuel (compléments alimentaires)	Rémunération personnelle	01/2005	12/2006
10010	ANTON	Robert	06/06/2006	VB	ESTEE LAUDER	Contrat de recherche	ULP Strasbourg	01/2002	02/2007
10010	ANTON	Robert	06/06/2006	VB	SECMA	Contrat de recherche	ULP Strasbourg	01/2005	09/2007
10010	ANTON	Robert	06/06/2006	VB	ARKOPHARMA,BOEHRINGER,BOIRON,COOPER,DOLISOS, LILLY,LPH,MERCK MEDICATION FAMILIALE,NOVARTIS,PHARDEX,PHARMYGIENE,PHYTO ENERGETIQUE,PIERRE FABRE,PPDH,SERVIER, VETOQUINOL, VICTOR MANE, ESTEE LAUDER	taxe d'apprentissage	Université Louis Pasteur - Strasbourg	01/2005	12/2005
10010	ANTON	Robert	27/05/2005	IF	NATURAL PRODUCTS CONSULTING	Actionnaire			
10010	ANTON	Robert	27/05/2005	IP-RE	SERVIER	Une modification de formulation			
10010	ANTON	Robert	27/05/2005	IP-AC	PIERRE FABRE	Conseil scientifique			
10010	ANTON	Robert	27/05/2005	VB	ESTEE LAUDER	taxes d'apprentissage			
10010	ANTON	Robert	07/03/2005	LD	PIERRE FABRE (Plantes et Médecines)	Consultant depuis 1990			
10010	ANTON	Robert	07/03/2005	IP-RE	SCHAPER ET BRUMMER (Allemagne)	Eperi d'un dossier (2004-2005)			
10010	ANTON	Robert	07/03/2005	IP-RE	SERVIER	Expert d'un dossier (2004-2005)			
10010	ANTON	Robert	07/03/2005	IP-CF		"Qualité des extraits végétaux présents sur le marché et garanties pour les utilisateurs potentiels" - Colloque "La gestion du risque végétal" - mars 2004			
10010	ANTON	Robert	07/03/2005	IP-CF		"Ingrédients naturels : quelles frontières entre alimentaire, pharmacie et cosmétique?" - Colloque "Huiles essentielles arômes et parfums", Vannes, mai 2004			
10010	ANTON	Robert	07/03/2005	IP-CF		"The future development of traditional and medicinal plants as drugs, nutriceuticals and cosmetics : criteria of efficacy assessment and toicological concern in Europe" - Second			
10010	ANTON	Robert	07/03/2005	IP-CF		"Valorisation des matières premières du Pacifique Sud et des savoirs traditionnels : possibilités et contraintes d'un développement éventuel", Assises de la Recherche Française			
10010	ANTON	Robert	07/03/2005	IP-CF		"Compléments alimentaires et cosmétiques : aspects réglementaires", 3ème colloque international sur les plantes aromatiques et médicinales d'outre-mer, Cayenne, Guyane se			
10010	ANTON	Robert	07/03/2005	IP-CF		"Will the new legislation be really helpful?", AESGP Conference "Changing the rules or good supplements and herbal products in Europe", Bruxelles, Belgique, sept. 2004			
10010	ANTON	Robert	07/03/2005	IP-CF		"La cellule végétale laboratoire du vivant", Ecole de l'Herboretum, Saint-Ay, France, janv. 2005			
10010	ANTON	Robert	07/03/2005	IP-CF		Conférences à des congrès et colloques sur invitation : remboursement des frais de déplacement uniquement, sans aucun bénéfice financier proprement dit : liste ci-dessus			
10010	ANTON	Robert	07/03/2005	PAR	NATURAL PRODUCT CONSULTING (NPC)	Fils (poste de responsable)			
10010	ANTON	Robert	07/03/2005	{Autre}		Membre des Académies Nationales de Pharmacie et de Médecine et de diverses associations à but purement scientifique (aucun intérêt financier)			
10010	ANTON	Robert	07/03/2005	VB	AVENTIS, BOEHRINGER INGELHEIM, BOIRON, COOPER, DOLISOS ESTEE LAUDER, FERRIER, GIVAUDAN, INNOTHERA, LILLY France, LPH, MERCK Médication Familiale, NOVARTIS Santé familiale, PHARDE (Biocodex), PHARMYGIENE, PIERRE FABRE MEDICAMENT, PLANTE SYSTEM, PPDH	Liste des laboratoires versant une taxe d'apprentissage au laboratoire de Pharmacognosie dont le Professeur Anton est responsable			
10010	ANTON	Robert	07/03/2005	VB	(suite) VETOQUINOL, VICTOR MANE, WITTWER				
10010	ANTON	Robert	07/03/2005	{Autre}	Centre d'Analyses et de Recherches (Strasbourg-Illkirch)	Membre du Conseil scientifique			
10010	ANTON	Robert	11/06/2004	IP-AC	PIERRE FABRE	Conseil scientifique (Plantes et Méd.)			
10010	ANTON	Robert	11/06/2004	IP-AC	SERVIER	Conseiller scientifique pour un dossier			
10010	ANTON	Robert	11/06/2004	VB	ESTEE LAUDER	Université Louis Pasteur, Strasbourg (contrat de recherche)			
10010	ANTON	Robert	11/06/2004	PAR	NATURAL PRODUCTS CONSULTING (NPC)	Fils			
10010	ANTON	Robert	09/02/2004	IP-AC	PIERRE FABRE (Plantes et méd.))	Conseil scientifique			
10010	ANTON	Robert	09/02/2004	IP-AC	ROCHE- NICHOLAS	Conseil scientifique			
10010	ANTON	Robert	09/02/2004	VB	ESTEE LAUDER	Université Louis Pasteur - Strasbourg (contrat de recherche fondamentale)			
10010	ANTON	Robert	09/02/2004	PAR	NATURAL PRODUCTS CONSULTING	Fils			
10010	ANTON	Robert	18/10/2002	IP-AC	PIERRE FABRE, IRPF, RAMONVILLE	Comité scientifique			
10010	ANTON	Robert	18/10/2002	IP-AC	Els KNORR, UNILEVER - BESTFOODS	Comité de reflexion			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10010	ANTON	Robert	18/10/2002	PAR	NATURAL PRODUCTS CONSULTING (NPC)	Fils			
10010	ANTON	Robert	11/09/2000	IP-AC	PIERRE FABRE	Consultant			
10010	ANTON	Robert	11/09/2000	VB		Contrats de recherche universitaire (Université Louis Pasteur, Strasbourg).			
10010	ANTON	Robert	11/09/2000	(Autre)	Industrie pharmaceutique	Fils			
10010	ANTON	Robert	15/11/1999	IP-EC	PIERRE FABRE	Travaux de recherche scientifique universitaires			
10010	ANTON	Robert	15/11/1999	IP-EC	LEHNING	Travaux de recherche scientifique universitaires			
10010	ANTON	Robert	15/11/1999	IP-EC	ROCHE ; NICHOLAS	Travaux de recherche scientifique universitaires			
10010	ANTON	Robert	15/11/1999	IP-AC	PIERRE FABRE	Activité de conseil			
10010	ANTON	Robert	15/11/1999	(Autre)	CMI (Munich, Allemagne)	Fils.			
60113	ARMAND	Jean-Pierre	23/04/2010	EC-CO	SANOFI	1 essai de phase 1			
60113	ARMAND	Jean-Pierre	23/04/2010	EC-CO	BOEHRINGER	1 essai de phase 1			
60113	ARMAND	Jean-Pierre	16/06/2009	CF-INT	MERCK, SCHERING PLOUGH, ROCHE, BMS, SANOFI....		Rémunération personnelle/institution		
60113	ARMAND	Jean-Pierre	16/06/2009	EC-INV	SANOFI, MERCK,PFIZER, ROCHE, BAYER, SCHERING-PLOUGH, BMS, PHARMAMAR, WIETH, ASTRA ZENECA...	PHASES 1	co-investigateur		
60113	ARMAND	Jean-Pierre	16/06/2009	EC-CO	SANOFI, MERCK, PFIZER, ROCHE, BAYER, J&J, PHARMAMAR, ETC...	Je signe et contracte, en tant que Directeur de l'Institut Claudius Regaud et parfois en tant que co-investigat			
60113	ARMAND	Jean-Pierre	23/11/2007	PAR	DEBIOPHARM		Conjoint licenciement économique en 2007		
60113	ARMAND	Jean-Pierre	23/11/2007	CF-INT	MERCK, SCHERING PLOUGH, ROCHE, PFIZER, SANOFI, BAYER		Aucune rémunération		
60113	ARMAND	Jean-Pierre	23/11/2007	EC-INV	SANOFI, MERCK, PFIZER, ROCHE, BAYER	PHASE 1			
60113	ARMAND	Jean-Pierre	04/01/2006	EC-INV	MERCK, AVENTIS, PFIZER (PHARMACIA, SUGEN...), ABSCIENCE, SCHERING-PLOUGH, BAYER, ROCHE, J&J, BMS, PHARMAMAR, WYETH, OSI, SIGMA TAU, NOVARTIS, NERVIANO, DEBIOPHARM, ASTRA ZENECA, GENCELL, CYCLACEL, SANOFI-AVENTIS	Actuellement ou dans le 5 dernières années, j'ai conduit pour ces laboratoires des essais de phase 1 en car	Cette expertise payée à l'institution s'accompagnait de participations SAB pour le choix d'entrée en phase 1 de nouvelles molécules	01/2001	
60113	ARMAND	Jean-Pierre	04/01/2006	VB	AVENTIS, ASTRA ZENECA, LILLY, BMS, SANOFI, ROCHE	Versement de 4 industries pharmaceutiques sur 5 ans + national cancer institut (USA) workshop annuel ASC	Institution bénéficiaire : FECS (Federation european cancer societies, Bruxelles (Belgique). Je ne suis plus le directeur depuis 2000	01/1996	12/2000
60113	ARMAND	Jean-Pierre	04/01/2006	VB	AVENTIS, AZ, FABRE, BMS, J&J, ROCHE, SERVIER, SANOFI, SCHERING, MERCK, NOVARTIS	Oreganisation annuelle du cours de chimiothérapie de l'IGR depuis 21 ans pendant 15 jours en janvier	Institution bénéficiaire : Institut Gustave Roussy (Villejuif)	01/1985	
60113	ARMAND	Jean-Pierre	04/01/2006	PAR	DEBIOPHARM	Epouse directrice R & D DEBIOCHINE Biotech (pas de rapport avec un produit)		01/1990	
60113	ARMAND	Jean-Pierre	15/06/2003	IF	AVENTIS	Actions > 20 ans			
60113	ARMAND	Jean-Pierre	15/06/2003	IF	SANOFI	Actions > 20 ans			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-EC	NOVARTIS	Phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-EC	PFIZER	Phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-EC	BRISTOL MYERS SQUIBB	Phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-EC	ABSCIENCES Start up	Phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-EC	PHARMAMAR	Phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-AC	PIERRE FABRE	Sélection molécules phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-AC	DSI	Sélection molécules phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-AC	NOVARTIS	Sélection molécules phase I			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-CF	PFIZER	Antiangiogeniques			
60113	ARMAND	Jean-Pierre	15/06/2003	IP-CF	ASTRA ZENECA	Thérapeutiques ciblées			
60113	ARMAND	Jean-Pierre	15/06/2003	VB	PFIZER, ASTRA ZENECA, AVENTIS, PIERRE FABRE, SANOFI	XVI Cours de chimiothérapie de l'Institut Gustave Roussy			
60113	ARMAND	Jean-Pierre	15/06/2003	PAR	DEBIOPHARM	Epouse - Directrice de biochimie			
60113	ARMAND	Jean-Pierre	15/06/2003	(Autre)		Cette déclaration est plus réduite que la précédente car je n'ai rien accepté pendant mon précédent mandat			
60113	ARMAND	Jean-Pierre	20/04/2000	IF	AVENTIS	Actions	depuis la privatisation, peuvent être vendues demain ! (Lettre du 2/10/2000 : réduction d'1/2 du portefeuille AVENTIS)		
60113	ARMAND	Jean-Pierre	20/04/2000	LD	ILEX (USA) Pr.Von Hoff	Conférence téléphonique 1fois/3 mois depuis 3 ans	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	AVENTIS	Phase I, III (IQR)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	ASTRA ZENECA	Phase I, III (IQR)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	PHARMAFARM	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	BOEHRINGER MANNHEIM	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	BRISTOL MYERS SQUIBB	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	ESAI	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	PIERRE FABRE	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	SCHERING	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	WYETH LEDERLE	Phase I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-AC	AVENTIS	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-AC	PHARMAFARM	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-EC	SUGEN	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-AC	BRISTOL MYERS SQUIBB	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-AC	EISAI	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-AC	PIERRE FABRE	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-AC	DEBIOPHARM	Sélection préclinique, options Phases I	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-CF	AVENTIS	Actions de formation, colloques	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-CF	SANOFI	Action de formation, colloques	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-CF	WYETH	Colloque			
60113	ARMAND	Jean-Pierre	20/04/2000	IP-CF	ASTRA ZENECA	Colloque	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	IP-CF	EORTC	Conférence	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	AMGEN	Institut Gustave Roussy (cours de chimiothérapie)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	CHUGAI	Institut Gustave Roussy (cours de chimiothérapie)	(Idem : lettre du 2/10/2000)		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60113	ARMAND	Jean-Pierre	20/04/2000	VB	SMITHKLINE BEECHAM	Institut Gustave Roussy (cours de chimiothérapie)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	AVENTIS	Institut Gustave Roussy (cours de chimiothérapie)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	AVENTIS	Federation European Cancer Societies (Methods in clinical cancer research)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	PHARMACIA	Federation European Cancer Societies (Methods in clinical cancer research)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	ASTRA ZENECA	Federation European Cancer Societies (Methods in clinical cancer research)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	NCI (350 000 US $)	Federation European Cancer Societies (Methods in clinical cancer research)	(Idem : lettre du 2/10/2000)		
60113	ARMAND	Jean-Pierre	20/04/2000	VB	BMS	Federation European Cancer Societies (Methods in clinical cancer research)			
60113	ARMAND	Jean-Pierre	20/04/2000	PAR	DEBIOPHARM	Conjoint (Directrice DEBIOCHINE, R&D, depuis 1994	(Idem : lettre du 2/10/2000)		
61933	ASMAR	Roland	16/10/2001	IF	Institut CardioVasculaire	5% du capital			
61933	ASMAR	Roland	16/10/2001	IP-EC	SEARLE - PHARMACIA	Essai clinique phase III			
61933	ASMAR	Roland	16/10/2001	IP-EC	TAKEDA France	Essai clinique			
61933	ASMAR	Roland	16/10/2001	IP-EC	SERVIER France	Coordination Etudes cliniques			
61933	ASMAR	Roland	16/10/2001	IP-EC	RECORDATI	Formation			
61933	ASMAR	Roland	16/10/2001	IP-AC	RECORDATI - BOUCHARA	Consultant			
61933	ASMAR	Roland	16/10/2001	IP-AC	SERVIER	Consultant			
61933	ASMAR	Roland	16/10/2001	IP-CF	G.S.K.	Kit de formation			
61933	ASMAR	Roland	16/10/2001	IP-CF	SERVIER	Colloques - Conférences			
63387	ASTIER	Alain	18/11/2009	CF-AUD	MERCK LIPHA	Symposium pharmacien cetuximab		06/2009	06/2009
63387	ASTIER	Alain	18/11/2009	CF-INT	TEVA	Barcelone Chairman Symposium Biosimilaires	Rémunération personnelle	03/2009	03/2009
63387	ASTIER	Alain	16/03/2009	CF-AUD	SCHERING PLOUGH	Chicago ASCO		05/2008	06/2009
63387	ASTIER	Alain	16/03/2009	CF-INT	NOVARTIS	Bavène Congrès patients GIST LMC□□Conférence bonne usage inhibiteurs tyrosine kinase	Rémunération personnelle	06/2008	06/2008
63387	ASTIER	Alain	16/03/2009	CF-AUD	ROCHE	Les vaux de Cernay Symposium Pharmaciens cancerologie		03/2008	03/2008
63387	ASTIER	Alain	16/03/2009	CF-INT	TEVA	Maastricht Congrès EAHP Chairman symposium	Aucune rémunération	02/2009	03/2009
63387	ASTIER	Alain	16/03/2009	(Autre)	ATEPS	EPHP (mission pour le directeur général)			01/2008
63387	ASTIER	Alain	16/03/2009	(Autre)	APHP	Conseil scientifique			
63387	ASTIER	Alain	23/11/2005	LD-AR	TEVA	Groupe de reflexion pharmaceutique (niveau européen)	Rémunération personnelle	01/2004	12/2005
63387	ASTIER	Alain	23/11/2005	IP-AC	TEVA	Conseils pharmaceutiques	Rémunération personnelle	01/2004	01/2006
63387	ASTIER	Alain	23/11/2005	CF-AUD	PFIZER	Congrès ACCP / San Francisco		10/2005	10/2005
63387	ASTIER	Alain	23/11/2005	CF-AUD	SERVIER	ESCP / Stockholm		09/2005	09/2005
63387	ASTIER	Alain	23/11/2005	CF-AUD	ROCHE	Journées cancérologie		03/2005	03/2005
63387	ASTIER	Alain	23/11/2005	IP-AUT	APHP	Co-auteur de bBrevet pris par APHP sur nouveaux médicamentx anticancéreux		10/2004	10/2004
63387	ASTIER	Alain	23/11/2005	(Autre)	APHP	Conseil scientifique			
63387	ASTIER	Alain	23/11/2005	(Autre)	ATEPS	EPHP (mission pour le directeur général)			
63387	ASTIER	Alain	23/11/2005	CF-AUD	AMGEN	Symposium		01/2005	01/2005
63387	ASTIER	Alain	27/08/2004	IP-RE	EP-HP (AFEPS)	Rédaction et signature d'expertise pour dossiers Partie II (Morphine sulfate - NP 100)			
63387	ASTIER	Alain	27/08/2004	IP-AC	TEVA PHARMA	Conseils en pharmacie hospitalière (réunion de 4 heures) : 19/02, 15/03, 18/03 (Séville), 23/05			
63387	ASTIER	Alain	27/08/2004	IP-CF	ROCHE	Présidence symposium Neorecormon, Congrès ESCP 28/04/2004 - Conférence sur EPO 15/06/2004 (aspects pharmaceutiques)			
63387	ASTIER	Alain	27/08/2004	IP-AUT	ASTRA ZENECA	Invitation congrès ASCO (New Orleans, 05-09/06)			
63387	ASTIER	Alain	27/08/2004	IP-AUT	ROCHE	Symposium Oncologie, 8-9/04			
63387	ASTIER	Alain	27/08/2004	IP-AUT	BRISTOL MYERS SQUIBB	Congrès ISOPP (Turin, 14-17/04)			
64378	ATKINSON	Jeffrey	17/05/2010	LD-AR	PHARMINE	Recherche en éducation (Pharmacy Education in Europe)	Rémunération personnelle	01/2009	04/2013
64378	ATKINSON	Jeffrey	17/05/2010	RE-AUT	Gouvernement de la République CZECH	Evaluatio de demandes de contrats en recherche médicale	Rémunération personnelle		
64378	ATKINSON	Jeffrey	17/05/2010	RE-AUT	CHINESE UNIVERSITY OF HONG KONG	External Exmainer	Rémunération personnelle		
64378	ATKINSON	Jeffrey	17/05/2010	CF-INT	??	Congrès : recherche cardiovasculaire - recherche en éducation	Aucune rémunération		
64378	ATKINSON	Jeffrey	17/05/2010	IP-AUT	Biocentre for Research in Biomedical Education 6 leeds UK	Membre			
64378	ATKINSON	Jeffrey	17/04/2009	Néant					
64378	ATKINSON	Jeffrey	20/11/2007	IP-AUT	CHINESE UNIVERSITY OF HONG KONG	Examinateur externe		01/2008	10/2020
64378	ATKINSON	Jeffrey	18/04/2006	LD-AR	AFSSA	Membre Commission Nationale de Pharmacovigilance Vétérinaire	Aucune rémunération		
64378	ATKINSON	Jeffrey	18/04/2006	EC-INV	SERVIER PARIS	Evaluation pré-clinique de l'effet cérébroprotecteur d'analogues de la mélatonine		01/2002	12/2005
64378	ATKINSON	Jeffrey	18/04/2006	RE-AUT	COMMISSION EUROPEENNE "CARDIOVASCULAR"	DG Expert et rapporteur 6ème et 7ème PCRPS	Rémunération personnelle	01/2004	12/2009
64378	ATKINSON	Jeffrey	18/04/2006	RE-AUT	COMMISSION INTER UNIVERSITAIRE MES CAMEROUN	Evaluation de projets universitaires	Aucune rémunération	01/2003	12/2008
64378	ATKINSON	Jeffrey	18/04/2006	RE-AUT	CONSEIL REGIONAL CHAMPAGNE ARDENNES	Evaluation de projets pour la Direction de la Recherche	Aucune rémunération	01/2004	12/2006
64378	ATKINSON	Jeffrey	18/04/2006	IP-AC	MEDICAL RESSOURCES COUNCIL PAYS-BAS / IRLANDE	Evaluation de projets de recherche	Rémunération personnelle	01/2004	12/2009
64378	ATKINSON	Jeffrey	18/04/2006	CF-INT	SERVIER PARIS	New Trends in Genatric Prévention - KOS	Aucune rémunération	01/2003	12/2003
64378	ATKINSON	Jeffrey	18/04/2006	CF-INT	SERVIER PARIS	Vème Symposium on Large Arteries - Paris	Aucune rémunération	01/2005	12/2005
64378	ATKINSON	Jeffrey	18/04/2006	VB	BOEHRINGER RIDGWAY CT USA	Evaluation pré-clinique	Université Henri Poincaré - Nancy 1	01/2004	12/2008
64378	ATKINSON	Jeffrey	18/04/2006	EC-INV	BOEHRINGER RIDGWAY CT USA	Evaluation pré-clinique de l'effet cérébroprotecteur d'un nouvel antihypertenseur	investigateur principal	01/2004	12/2008
10016	AUBIER	Michel	25/03/2009	LD-AR	ASTRA ZENECA	Conseil scientifique	Rémunération institution	01/2003	12/2009
10016	AUBIER	Michel	25/03/2009	EC-INV	ASTRA ZENECA	Symbicort - STUART	Investigateur principal	01/2007	12/2009
10016	AUBIER	Michel	25/03/2009	EC-INV	PFIZER	SPIMIVA	Investigateur - coordinateur -	01/2004	12/2008
10016	AUBIER	Michel	25/03/2009	EC-INV	ENCYSIVE / PFIZER	THELIN	investigateur principal	01/2009	12/2011
10016	AUBIER	Michel	25/03/2009	IP-AC	NICONEIL	DAXAS Conseil	Rémunération : institution	01/2009	12/2010
10016	AUBIER	Michel	25/03/2009	IP-AC	MSD	Symbicort: Conseil scientifique	Rémunération : institution	01/2008	12/2010
10016	AUBIER	Michel	25/03/2009	CF-INT	NOVARTIS	CPLF (Lille)		01/2008	
10016	AUBIER	Michel	17/12/2008	LD-AR	ASTRA ZENECA	Conseil scientifique	rémunération institution	01/2002	
10016	AUBIER	Michel	17/12/2008	EC-INV	MSD	Singulair ®	investigateur	01/2004	12/2008
10016	AUBIER	Michel	17/12/2008	EC-INV	NOVARTIS	Xolair ®	investigateur	01/2006	12/2008
10016	AUBIER	Michel	17/12/2008	EC-INV	PFIZER	Sitaxentan (Thelin) co-financement avec l'INSERM	investigateur principal	02/2009	
10016	AUBIER	Michel	17/12/2008	EC-CO	PFIZER	Thelin	rémunération institution	01/2008	
10016	AUBIER	Michel	17/12/2008	IP-AC	PFIZER	Groupe de travail (expert)	rémunération institution	01/2008	01/2008
10016	AUBIER	Michel	17/12/2008	CF-INT	MSD	Asthme - Singulair® - CPLF (Lyon)	rémunération institution	01/2009	
10016	AUBIER	Michel	17/12/2008	CF-INT	NOVARTIS	XOLAIR® - CPLF (Lyon)	INSERM	01/2008	01/2010
10016	AUBIER	Michel	17/12/2008	VB	ASTRA ZENECA	Don pour la recherche	rémunération personnelle / institution	01/1999	
10016	AUBIER	Michel	15/06/2006	LD-AR	GSK	expert	rémunération personnelle / institution	01/2000	
10016	AUBIER	Michel	15/06/2006	LD-AR	ASTRA ZENECA	expert / conseil scientifique			

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10016	AUBIER	Michel	15/06/2006	LD-AR	ALTANA PHARMA		rémunération personnelle / institution	01/2000	12/2003
10016	AUBIER	Michel	15/06/2006	EC-INV	ASTRA ZENECA	Inexium	coordonnateur investigateur	01/2006	12/2008
10016	AUBIER	Michel	15/06/2006	EC-INV	ALTANA PHARMA	Roflumilast	coordonnateur investigateur	01/2006	12/2008
10016	AUBIER	Michel	15/06/2006	EC-CO	WYETH	Enbrel	investigateur	01/2005	12/2006
10016	AUBIER	Michel	15/06/2006	IP-AC	ASTRA ZENECA	conseil scientifique	rémunération institution	01/2001	
10016	AUBIER	Michel	15/06/2006	IP-AC	GSK	conseil scientifique	rémunération institution	01/2000	
10016	AUBIER	Michel	15/06/2006	IP-AC	ALTANA PHARMA	conseil scientifique	rémunération institution	01/2002	12/2006
10016	AUBIER	Michel	15/06/2006	CF-INT	MSD	congrès de Pneumologie de Langue Francaise - Nice	rémunération institution	02/2006	02/2006
10016	AUBIER	Michel	14/02/2006	LD-AR	ASTRA ZENECA	conseil scientifique	rémunération institution	01/2002	
10016	AUBIER	Michel	14/02/2006	LD-AR	NOVARTIS	conseil scientifique	rémunération institution	01/2006	
10016	AUBIER	Michel	14/02/2006	EC-INV	NOVARTIS	CQAB	investigateur principal	01/2002	12/2004
10016	AUBIER	Michel	14/02/2006	EC-INV	ASTRA ZENECA	Inexium		01/2006	
10016	AUBIER	Michel	14/02/2006	EC-CO	WYETH	Etanercept	expérimentateur non principal	01/2004	12/2006
10016	AUBIER	Michel	14/02/2006	CF-INT	MSD	LYON (SPLF) Singulair ®	rémunération personnelle	02/2007	02/2007
10016	AUBIER	Michel	14/02/2006	CF-INT	ASTRA ZENECA	Budapest - Symbicort	rémunération institution	09/2007	09/2007
10016	AUBIER	Michel	28/03/2005	EC-INV	ALTANA PHARMA	Roflumilast	investigateur principal		
10016	AUBIER	Michel	28/03/2005	EC-INV	MSD	Montelukast IV	investigateur principal		
10016	AUBIER	Michel	28/03/2005	EC-INV	NOVARTIS	CQAB	investigateur principal		
10016	AUBIER	Michel	28/03/2005	EC-CO	AZ	Symbicort			
10016	AUBIER	Michel	28/03/2005	EC-CO	GSK	Sérétide			
10016	AUBIER	Michel	28/03/2005	EC-CO	WYETH	etanercept			
10016	AUBIER	Michel	28/03/2005	EC-CO	NOVARTIS	Xolair			
10016	AUBIER	Michel	28/03/2005	IP-CF	ASTRA ZENECA	Symbycort congrès			
10016	AUBIER	Michel	28/03/2005	IP-CF	GSK	Serretide congrès			
10016	AUBIER	Michel	28/03/2005	IP-CF	NOVARTIS	Xolair congrès			
10016	AUBIER	Michel	28/03/2005	CF-INT	ASTRA ZENECA	Symbicort			
10016	AUBIER	Michel	28/03/2005	CF-INT	GSK	Seretide			
10016	AUBIER	Michel	28/03/2005	CF-INT	ALTANA PHARMA	Roflumilast			
10016	AUBIER	Michel	20/02/2004	IP-EC	GLAXO SMITH KLINE				
10016	AUBIER	Michel	20/02/2004	IP-EC	ASTRA ZENECA				
10016	AUBIER	Michel	20/02/2004	IP-EC	AVENTIS				
10016	AUBIER	Michel	20/02/2004	IP-EC	3 M				
10016	AUBIER	Michel	20/02/2004	IP-EC	ALTANA PHARMA				
10016	AUBIER	Michel	20/02/2004	IP-AC	GLAXO SMITHKLINE				
10016	AUBIER	Michel	20/02/2004	IP-AC	ASTRA ZENECA				
10016	AUBIER	Michel	20/02/2004	IP-AC	ALTANA PHARMA				
10016	AUBIER	Michel	20/02/2004	IP-AC	SERVIER				
10016	AUBIER	Michel	20/02/2004	IP-CF	GLAXO SMITHKLINE				
10016	AUBIER	Michel	20/02/2004	IP-CF	ASTRA ZENECA				
10016	AUBIER	Michel	20/02/2004	IP-CF	ALTANA PHARMA				
10016	AUBIER	Michel	20/02/2004	VB	GLAXO SMITHKLINE ; ASTRA ZENECA	Subvention unité INSERM 408			
10016	AUBIER	Michel	08/09/2003	IP-EC	ASTRA ZENECA				
10016	AUBIER	Michel	08/09/2003	IP-AC	GLAXO SMITHKLINE				
10016	AUBIER	Michel	08/09/2003	IP-CF	GLAXO SMITHKLINE, ASTRA ZENECA, BOEHRINGER				
10016	AUBIER	Michel	08/09/2003	VB	ASTRA ZENECA				
10016	AUBIER	Michel	08/09/2003	IP-EC	GLAXO SMITHKLINE				
10016	AUBIER	Michel	08/09/2003	IP-EC	ALTANA PHARMA				
10016	AUBIER	Michel	08/09/2003	IP-AC	ASTRA ZENECA				
10016	AUBIER	Michel	08/09/2003	IP-AC	SERVIER				
10016	AUBIER	Michel	08/09/2003	VB	GLAXO SMITHKLINE				
10016	AUBIER	Michel	28/06/2001	IP-EC	GLAXO, 3M, ASTRA, BOEHRINGER	Essais cliniques			
10016	AUBIER	Michel	28/06/2001	IP-EC	ASTRA ZENECA	Travaux scientifiques			
10016	AUBIER	Michel	28/06/2001	IP-RE	GLAXO, 3M, ASTRA, MSD	Interventions			
10016	AUBIER	Michel	28/06/2001	IP-AC	GLAXO, ASTRA ZENECA	Asthme et BP40			
10016	AUBIER	Michel	28/06/2001	IP-CF	GLAXO, ASTRA ZENECA	Physiopathologie dans l'asthme et le BP40			
10016	AUBIER	Michel	28/06/2001	VB	AIR LIQUIDE	INSERM			
10016	AUBIER	Michel	06/12/2000	IP-EC	GLAXO WELLCOME	Phase II ou III			
10016	AUBIER	Michel	06/12/2000	IP-EC	ASTRA ZENECA	Phase II ou III			
10016	AUBIER	Michel	06/12/2000	IP-EC	BYK France	Phase II ou III			
10016	AUBIER	Michel	06/12/2000	IP-EC	3 M	Phase II ou III			
10016	AUBIER	Michel	06/12/2000	IP-EC	AVENTIS	Phase II ou III			
10016	AUBIER	Michel	06/12/2000	IP-CF	GLAXO WELLCOME, ASTRA ZENECA, 3 M, AVENTIS	Conférences physiopathologie de l'asthme			
10016	AUBIER	Michel	04/05/2000	IP-EC	GLAXO WELLCOME	Essais cliniques			
10016	AUBIER	Michel	04/05/2000	IP-EC	ASTRA ZENECA	Essais cliniques			
10016	AUBIER	Michel	04/05/2000	IP-EC	BYK	Essais cliniques			
10016	AUBIER	Michel	04/05/2000	IP-EC	MSD	Essais cliniques			
10016	AUBIER	Michel	04/05/2000	IP-EC	SKB	Essai clinique			
10016	AUBIER	Michel	04/05/2000	IP-AC	ASTRA ZENECA	Conseil scientifique			
10016	AUBIER	Michel	04/05/2000	IP-AC	GLAXO WELLCOME	Conseil scientifique			
10016	AUBIER	Michel	04/05/2000	IP-AC	SERVIER	conseil scientifique			
10016	AUBIER	Michel	04/05/2000	IP-CF	MSD, GLAXO WELLCOME, UCB, 3 M	Conférences sur la physiopathologie et la prise en charge des maladies bronchiques (asthme, BPCO)			
10016	AUBIER	Michel	04/05/2000	VB	ASTRA ZENECA	Inserm U 408			
10016	AUBIER	Michel	08/03/2000	IP-EC	laboratoire BYK France	1 essai clinique			
10016	AUBIER	Michel	08/03/2000	IP-EC	MSD	1 essai clinique			
10016	AUBIER	Michel	08/03/2000	IP-EC	GLAXO WELLCOME	1 essai clinique			
10016	AUBIER	Michel	08/03/2000	IP-EC	ASTRA	1 essai clinique			
10016	AUBIER	Michel	08/03/2000	IP-EC	3M	1 essai clinique			
10016	AUBIER	Michel	08/03/2000	IP-AC	ASTRA	Participation à un groupe de travail (2 fois/an)			
10016	AUBIER	Michel	08/03/2000	IP-AC	GLAXO WELLCOME	Participation à un groupe de travail (2 fois/an)			
10016	AUBIER	Michel	08/03/2000	IP-CF	MSD	Objectifs du traitement de l'asthme (Congrès de la SPLF)			
10016	AUBIER	Michel	08/03/2000	VB	ZENECA	INSERM			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63152	AUQUIER	Pascal	15/01/2004	IP-EC	SERONO	Développement indicateur de QV			
63152	AUQUIER	Pascal	15/01/2004	IP-EC	LUNDBECK	Développement indicateur de QV			
63152	AUQUIER	Pascal	15/01/2004	IP-EC	SERVIER	Meta-analyse - Enquête épidémiologique de prévalence MP			
63152	AUQUIER	Pascal	15/01/2004	IP-RE	LUNDBECK	Méta-analyse			
63152	AUQUIER	Pascal	15/01/2004	IP-AC	NOVARTIS	Enquête QV patientes cancer du sein et QV			
61298	AUTRET	Alain	21/07/2010	EC-CO	SERVIER	Etude PERFORM arrêtée en décembre 2009	Co-investigateur	12/2009	12/2009
61298	AUTRET	Alain	21/07/2010	CF-INT	MENARINI	Journées Neurologie de Langue Française		04/2009	04/2009
61298	AUTRET	Alain	21/07/2010	CF-INT	MSD	Congress Migraine European ? Society		10/2010	10/2010
61298	AUTRET	Alain	21/07/2010	CF-AUD	MSD	Congrès Migraine - France (Octobre 2009)		10/2009	10/2009
61298	AUTRET	Alain	21/07/2010	CF-AUD	ARAIR	Congrès du sommeil - Marseille (novembre 2009)		11/2009	11/2009
61298	AUTRET	Alain	17/06/2008	EC-CO	IRIS (SERVIER)	co-investigateur terutroban étude PERFORM		01/2006	12/2010
61298	AUTRET	Alain	17/06/2008	EC-CO	PFIZER	Etude FAST		01/2005	12/2006
61298	AUTRET	Alain	17/06/2008	CF-INT	GSK	XXX	rémunération personnelle	01/2007	12/2007
61298	AUTRET	Alain	17/06/2008	CF-AUD	BIOGEN IDEC	American academy of neurology - chicago		01/2008	12/2008
61298	AUTRET	Alain	17/06/2008	CF-AUD	NOVARTIS	American academy of neurology - Boston		01/2007	12/2007
61298	AUTRET	Alain	17/06/2008	CF-AUD	GSK	Université de la migraine - Forges-les-Eaux		01/2007	12/2007
61298	AUTRET	Alain	17/06/2008	VB	ASTRA ZENECA	Subvention	association Tourangelle de recherche neurologique	01/2006	12/2006
61298	AUTRET	Alain	17/06/2008	PAR	ROCHE	Communication	fille	01/2006	06/2008
61298	AUTRET	Alain	12/06/2006	LD-AR	ASTRA ZENECA	co-président d'un groupe d'expertise migraine			
61298	AUTRET	Alain	12/06/2006	LD-AR	SCHWARTZ PHARMA	steering comittee			
61298	AUTRET	Alain	12/06/2006	EC-CO	SERVIER	PERFORM	co-investigateur	01/2006	12/2010
61298	AUTRET	Alain	12/06/2006	EC-CO	GSK	CURE / Parkinson	co-investigateur		12/2004
61298	AUTRET	Alain	12/06/2006	EC-CO	SERVIER	étude PROGRESS	co-investigateur		12/2003
61298	AUTRET	Alain	12/06/2006	EC-CO	SANOFI	DETECT / AVC	co-investigateur		12/2003
61298	AUTRET	Alain	12/06/2006	EC-CO	PHARMAPHARM	CL 43 / migraine	co-investigateur		12/2003
61298	AUTRET	Alain	12/06/2006	CF-INT	GSK	Conférences	rémunération personnelle		
61298	AUTRET	Alain	12/06/2006	CF-INT	JANSSEN	conférences	rémunération personnelle		
61298	AUTRET	Alain	12/06/2006	CF-INT	PFIZER	conférences	rémunération personnelle		
61298	AUTRET	Alain	12/06/2006	CF-INT	LUNDBECK	conférences	rémunération personnelle		
61298	AUTRET	Alain	12/06/2006	CF-INT	LFB	présidence réunion	rémunération personnelle		
61298	AUTRET	Alain	12/06/2006	CF-AUD	GSK	International Headach Society - Kyoto		01/2005	
61298	AUTRET	Alain	12/06/2006	CF-AUD	ASTRA ZENECA	Congrès annuel Journée de neurologie et de langue Française		05/2004	05/2004
61298	AUTRET	Alain	12/06/2006	CF-AUD	LFB / EISAI	American Academy of Neurology - USA		01/2005	12/2005
61298	AUTRET	Alain	12/06/2006	CF-AUD	ALMIRALL	Migraine trust - Londres		01/2005	12/2005
61298	AUTRET	Alain	12/06/2006	PAR	PMS	CDD communication (fin : 2006 ?)	fille	01/2005	
61298	AUTRET	Alain	12/06/2006	VB	JANSSEN CILAG	GAL / Reminyl	Association de recherche neurologique clinique et thérapeutique dont je suis le président		
61298	AUTRET	Alain	12/06/2006	VB	SANOFI SYNTHELABO	Dépakine orale	Association de recherche neurologique clinique et thérapeutique dont je suis le président		12/2006
61298	AUTRET	Alain	12/06/2006	VB	BOEHRINGER		Association de recherche neurologique clinique et thérapeutique dont je suis le président		12/2006
61298	AUTRET	Alain	12/06/2006	VB	GYD INSITUT, SCHERING	Neurocardiologie	Association de recherche neurologique clinique et thérapeutique dont je suis le président		12/2006
61298	AUTRET	Alain	12/06/2006	VB	GSK	CURE Parkinson	Association de recherche neurologique clinique et thérapeutique dont je suis le président		12/2006
61298	AUTRET	Alain	12/06/2006	VB	AVONEX	SEP	Association de recherche neurologique clinique et thérapeutique dont je suis le président		12/2006
61298	AUTRET	Alain	12/06/2006	VB	AVENTIS	AVS	Association de recherche neurologique clinique et thérapeutique dont je suis le président		12/2006
61298	AUTRET	Alain	16/01/2006	LD-AR	ASTRA ZENECA	Président groupe expert migraine	rémunération personnelle		
61298	AUTRET	Alain	16/01/2006	LD-AR	SCHWARTZ PHARMA	Steering Comitte	rémunération personnelle		
61298	AUTRET	Alain	16/01/2006	EC-CO	SERVIER	Progress Ave (2003)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	EC-CO	GSK	CURE Parkinson (2003)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	EC-CO	SANOFI	DETECT AVE (2004)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	EC-CO	PHARMAFARM /ALMIRALL	CL 43 (2003)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	IP-AC	SERVIER	PROGRESS Ave (2003)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	IP-AC	GSK	CURE Parkinson (2003)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	IP-AC	SANOFI	DETECT Ave (2004)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	IP-AC	PHARMAFARM/ALMIRALL	CL 43 (2003)	co-investigateur		
61298	AUTRET	Alain	16/01/2006	IP-CF	GSK	Conférence migraine/ syndrome des jambes sans repos		04/2003	
61298	AUTRET	Alain	16/01/2006	IP-CF	BMS / SANOFI	Présidence symposium (2005)		05/2003	
61298	AUTRET	Alain	16/01/2006	IP-CF	PFIZER	Conférence migraine		05/2004	
61298	AUTRET	Alain	16/01/2006	IP-CF	JANSSEN CILAG	Conférence migraine			
61298	AUTRET	Alain	16/01/2006	IP-CF	LUNDBECK	Conférence migraine (2003)			
61298	AUTRET	Alain	16/01/2006	IP-CF	LFB	Conférence (2004)			
61298	AUTRET	Alain	16/01/2006	CF-AUD	GSK	International Search Society (2005)			
61298	AUTRET	Alain	16/01/2006	CF-AUD	GSK	Université de la migraine		04/2003	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61298 AUTRET		Alain	16/01/2006	CF-AUD	ASTRA ZENECA	Journée de Neurologie de langue Française		04/2003	
61298 AUTRET		Alain	16/01/2006	CF-AUD	LFB	American Academy of Neurolgy (2005)			
61298 AUTRET		Alain	16/01/2006	CF-AUD	JANSSEN CILAG	Journée d'étude céphalées (2004)			
61298 AUTRET		Alain	16/01/2006	CF-AUD	SANOFI	Société Française de Recherche sur le Sommeil (SFRS)			
61298 AUTRET		Alain	16/01/2006	CF-AUD	ALMIRAL	Migraine (2005)			
61298 AUTRET		Alain	16/01/2006	CF-AUD	PFIZER	Société Française d'Etude des migraines et céphalées (2005)			
61298 AUTRET		Alain	16/01/2006	VB	JANSSEN CILAG	GAL (Reminyl)	ATRNCT		
61298 AUTRET		Alain	16/01/2006	VB	SANOFI SYNTHELABO	EFG S286/ALTIMA/ orale			
61298 AUTRET		Alain	16/01/2006	VB	BOEHRINGER	Altéplase 135-132/ orale			
61298 AUTRET		Alain	16/01/2006	VB	GYD INSTITUT	Neurocardiologie	ATRNCT		
61298 AUTRET		Alain	16/01/2006	VB	SCHERING	Neurocardiologie	ATRNCT		
61298 AUTRET		Alain	16/01/2006	VB	GSK	CURE	ATRNCT		
61298 AUTRET		Alain	16/01/2006	VB	BIOGEN	AVONEX traitement de la SEP (Sclérose En Plaques)	ATRNCT		
61298 AUTRET		Alain	16/01/2006	VB	AVENTIS	AVC (Accidents Vasculaires Cérébraux)	ATRNCT		
61298 AUTRET		Alain	16/01/2006	PAR	BMS	communication (2005)	fille		
61298 AUTRET		Alain	14/02/2004	IP-RE			Déclaration identique à celle du 06/10/2003		
61298 AUTRET		Alain	14/02/2004	(Autre)			Déclaration identique à celle du 06/10/2003		
60001 AUTRET-LECA		Elisabeth	29/10/2010	LD-AR	VIDAL	Comité scientifique	Rémunération personnelle		
60001 AUTRET-LECA		Elisabeth	29/10/2010	LD-AR	AFSSAPS	Membre CTPV et COP	Aucune rémunération		
60001 AUTRET-LECA		Elisabeth	29/10/2010	LD-AR	HAS	Commission de la transparence	Rémunération personnelle		
60001 AUTRET-LECA		Elisabeth	29/10/2010	IP-AC	SERVIER	Conseil (produit en développement)	Aucune rémunération	06/2008	06/2008
60001 AUTRET-LECA		Elisabeth	29/10/2010	PAR	ASTRA ZENECA	Directeur Médical	Beau frère	01/2007	
60001 AUTRET-LECA		Elisabeth	25/09/2009	PAR	ASTRAZENECA	Directeur Médical	Beau-frère	01/2007	
60001 AUTRET-LECA		Elisabeth	04/12/2008	IP-AC	SERVIER	Conseil Développement Pédiatrique/Procoralan	Rémunération institution	06/2008	06/2008
60001 AUTRET-LECA		Elisabeth	25/07/2008	IP-AC	SERVIER	conseil/produit en développement	Rémunération institution	06/2008	06/2008
60001 AUTRET-LECA		Elisabeth	25/07/2008	IP-AC	GRIMBERG	conseil/carbosylane	Rémunération institution	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	25/07/2008	IP-AC	BOOTS HEALTHCARE	conseil/ibuprofène	Rémunération institution	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	25/07/2008	EC-INV	BOOTS HEALTHCARE	Ibuprofène	Coordinateur essai clinique	01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	25/07/2008	LD-AR	EDITIONS VIDAL	Membre du Conseil scientifique	Rémunération personnelle	01/1995	
60001 AUTRET-LECA		Elisabeth	03/01/2008	IP-AC	PFIZER	Conseil (réunion groupe experts)	Rémunération institution (ARRPET)	11/2007	12/2007
60001 AUTRET-LECA		Elisabeth	09/03/2007	PAR	BMS	Chef de projet (CDD)	Enfant	01/2006	03/2007
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	ABBOT	Participation Conseil Scientifique	ARRPET	01/2004	12/2004
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	ABBOTT	Expertise Synagis	ARRPET	01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	09/03/2007	CF-INT	ROCHE	Bordeaux - Congrès Société Française de Pharmacologie	Rémunération personnelle	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	09/03/2007	CF-INT	GAMBRO	TOURS - Congrès "Rein et Virus"	Rémunération institution	01/2006	01/2006
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	3 M SANTE	Etude Hémangiome /Imiquimob	Rémunération institution	01/2006	12/2006
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	UCB PHARMA	Conseil	Rémunération institution	01/2006	12/2006
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	NOVARTIS PHARMA	Conseil	Rémunération institution	01/2006	12/2006
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	BOOTS HEALTHCARE	Conseil/ibuprofène	Rémunération institution	01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	GRIMBERG	Etude Carbosylane	Rémunération institution	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	09/03/2007	IP-AC	BOOTS HEALTHCARE	Etude Nureflex	Aucune rémunération	01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	09/03/2007	EC-CO	PROMOTION HOSPITALIERE (PHRC)	Etude épidémiologique / AINS	Co-investigateur	01/2004	12/2006
60001 AUTRET-LECA		Elisabeth	09/03/2007	EC-INV	BOOTS HEALTHCARE	Ibuprofène	Investigateur principal	01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	09/03/2007	LD-ODE	VIDAL	Comité scientifique		01/1995	
60001 AUTRET-LECA		Elisabeth	01/06/2006	LD-AR	EDITION VIDAL	Comité scientifique		01/1995	
60001 AUTRET-LECA		Elisabeth	01/06/2006	EC-INV	BOOTS HEALTHCARE	Coordinateur d'essai clinique/Ibuprofène		01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AUT	ROCHE	Congrès SFP 2005		01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	ABBOTT	Participation Conseil Scientifique	ARRPET	01/2004	12/2004
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	BOOTS HEALTHCARE	Conseil/Ibuprofène	ARRPET	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	ABBOTT	Expertise SYNAGIS®	ARRPET	01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	01/06/2006	VB	GRIMBERG	Etude CARBOSYLANE®	ARRPET	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	BOOTS HEALTHCARE	Etude NUREFLEX®	ARRPET	01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	NOVARTIS	Expertise EXJADE®	ARRPET	01/2006	12/2006
60001 AUTRET-LECA		Elisabeth	01/06/2006	PAR	BMS		Fille	09/2005	03/2007
60001 AUTRET-LECA		Elisabeth	01/06/2006	LD-AR	EDITIONS VIDAL	Comité scientifiques		01/1995	
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-EC	BOOTS HEALTHCARE	Coordinateur d'essai clinique/Nureflex		01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AUT	ROCHE	Congrès SFP 2005		01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	ABBOTT	Participation au conseil scientifique□□Institution bénéficiaire : ARRPET		01/2004	12/2004
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	NOVARTIS	Expertise Exjade RD□Institution bénéficiaire : ARRPET		01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	01/06/2006	IP-AC	3M SANTE	Etude Hémangiome + Imiquimob	Institution bénéficiaire : ARRPET	01/2006	12/2006
60001 AUTRET-LECA		Elisabeth	01/06/2006	PAR	BMS	FILLE		09/2005	03/2007
60001 AUTRET-LECA		Elisabeth	09/02/2006	LD-AR	EDITIONS VIDAL	Comité scientifique (en cours)	Aucune rémunération	01/1995	
60001 AUTRET-LECA		Elisabeth	09/02/2006	EC-INV	BOOTS HEALTHCARE	Essai clinique (en cours)/Nureflex	Coordinateur	01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AUT	ROCHE	Congrès SFP		01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AC	ABBOTT	Participation Conseil scientifique	ARRPET	01/2004	12/2004
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AC	BOOTS HEALTHCARE	Conseil/Nureflex	ARRPET	01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AC	ABBOTT	Expertise Synagis	ARRPET	01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AC	GRIMBERG	Etude Carbosylane	ARRPET	01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AC	BOOTS HEALTHCARE	Etude Nureflex	ARRPET	01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	09/02/2006	IP-AC	3M SANTE	Etude Imiquimod	ARRPET	01/2006	12/2006
60001 AUTRET-LECA		Elisabeth	09/02/2006	PAR	BMS	Fille		09/2005	03/2007
60001 AUTRET-LECA		Elisabeth	12/09/2005	IP-EC	BOOTS	Essai sur Ibuprofene enfant		01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	12/09/2005	IP-AC	ABBOTT	Conseil scientifique étude synagis		01/2004	12/2005
60001 AUTRET-LECA		Elisabeth	12/09/2005	IP-AC	GRIMBERG	Conseil étude carosylane nourrisson		01/2005	01/2005
60001 AUTRET-LECA		Elisabeth	12/09/2005	IP-AC	BOOTS	Conseil Nureflex		01/2005	12/2006
60001 AUTRET-LECA		Elisabeth	12/09/2005	IP-CF	ABBOTT	Participation au comité scientifique d'un projet d'Etude			12/2004
60001 AUTRET-LECA		Elisabeth	12/09/2005	PAR	BMS	Enfant		09/2005	03/2007
60001 AUTRET-LECA		Elisabeth	29/11/2004	IP-EC	BOOTS	Essai clinique Ibuprofène			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60001	AUTRET-LECA	Elisabeth	29/11/2004	IP-AC	ABBOTT	Etude de suivi Synagis		01/2004	12/2005
60001	AUTRET-LECA	Elisabeth	31/03/2004	IP-EC	ABBOTT LABORATOIRE				
60001	AUTRET-LECA	Elisabeth	31/03/2004	IP-CF	BOOTS HEALTHCARE LABORATOIRE				
60001	AUTRET-LECA	Elisabeth	08/09/2003	IP-EC	NOVARTIS	Comité de suivi d'un essai			
60001	AUTRET-LECA	Elisabeth	08/09/2003	IP-AC	MENARINI	Conseil développement en pédiatrie			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-EC	YAMANOUCHI	Coordination essai clinique			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-RE	BOOTS HEALTHCARE	Ibuprofène			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-AC	YAMANOUCHI	Orbénine - Conseil développement pédiatrique			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-AC	3 M SANTE	Conseil pour un essai pédiatrique			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-AC	ZAMBON	Conseil pour un essai pédiatrique			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-AC	MENARINI				
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-CF	GNP Pédiatrique	Coordination de l'ouvrage 2000			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-CF	GNP	Conseil scientifique			
60001	AUTRET-LECA	Elisabeth	04/10/2001	IP-CF	UCB Pharma	Allergie chez la femme enceinte			
60001	AUTRET-LECA	Elisabeth	20/01/2001	IP-AC	YAMANOUCHI	Développement pédiatrique			
60001	AUTRET-LECA	Elisabeth	20/01/2001	IP-AC	BOOTS HEALTHCARE	Dévelopement pédiatrique			
60001	AUTRET-LECA	Elisabeth	20/01/2001	IP-AC	UCB PHARMA	Conseils			
60001	AUTRET-LECA	Elisabeth	22/05/2000	IP-RE	BOOTS HEALTCARE	Ibuprofène Enfant			
60001	AUTRET-LECA	Elisabeth	30/09/1999	IP-EC	THERAPLIX	Essai comparant deux stratégies de traitement de la fièvre de l'enfant			
60001	AUTRET-LECA	Elisabeth	30/09/1999	IP-EC	R.P.R.	Essai antipyrétique enfant.			
60001	AUTRET-LECA	Elisabeth	30/09/1999	IP-RE	BOOTS HEALTHCARE	Ibuprofène enfant			
60001	AUTRET-LECA	Elisabeth	30/09/1999	IP-AC	PHARMA 2000	Pertinence de faire un essai pédiatrique			
60001	AUTRET-LECA	Elisabeth	30/09/1999	IP-AC	SYNTHELABO	Evaluation Aspégic			
60001	AUTRET-LECA	Elisabeth	30/09/1999	IP-AC	DIAMANT	Antibiotique en pédiatrie			
60001	AUTRET-LECA	Elisabeth	10/07/1999	IP-EC	THERAPLIX	Essai comparant deux stratégies de traitement de la fièvre de l'enfant			
60001	AUTRET-LECA	Elisabeth	10/07/1999	IP-EC	R.P.R.	Essai antipyrétique enfant			
60001	AUTRET-LECA	Elisabeth	10/07/1999	IP-RE	BOOTS HEALTHCARE	Ibuprofène enfant			
60001	AUTRET-LECA	Elisabeth	10/07/1999	IP-AC	PHARMA 2000	Pertinence de faire un essai pédiatrique			
60001	AUTRET-LECA	Elisabeth	10/07/1999	IP-AC	SYNTHELABO	Evaluation Aspégic			
60001	AUTRET-LECA	Elisabeth	10/07/1999	IP-AC	DIAMANT	Antibiotique en pédiatrie			
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	SERVIER	Etude comparative Fotemustine VS Dacarbazine	coordonnateur	01/2000	12/2003
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	EORTC	Etude comparative Témozolomide VS Dacarbazine	investigateur non principal	01/2005	
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	P. FABRE	Vaccination anti mélanome +/- P40 / ELA	Investigateur non principal	01/2003	12/2005
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	IDM	vaccination anti mélanome (cellule diacritiques +/- interferon	investigateur non principal	01/2005	12/2006
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	PFIZER	anti CTLA4 (2007)	investigateur non principal		
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	EORTC (SCHERING)	Huit adjuvant avec ou sans PEG intron	investigateur non principal	01/2001	12/2004
60050	AVRIL	Marie-Françoise	29/12/2006	EC-INV	EORTC (BRISTOL MYERS SQUIBB)	huit adjuvant mélanome avec ou sans gangliosides	Investigateur non principal	01/1999	12/2004
60050	AVRIL	Marie-Françoise	29/12/2006	RE-DE	SERVIER	Fotémustine	aucune rémunération	01/2003	12/2003
60050	AVRIL	Marie-Françoise	29/12/2006	IP-AC	AVENTIS PHARMA	genasense oblimersen	aucune rémunération	01/2004	12/2004
60050	AVRIL	Marie-Françoise	29/12/2006	CF-INT	SERVIER	X° entretiens Servier en cancérologie (Paris)	aucune rémunération	04/2002	04/2002
60050	AVRIL	Marie-Françoise	29/12/2006	CF-INT	ITALFARMACO	4° congresso Nationale d'oncologia medica (Milan)	aucune rémunération	09/2002	09/2002
60050	AVRIL	Marie-Françoise	29/12/2006	CF-AUD	AVENTIS PHARMA	- réunion su genasense (New York)		06/2002	06/2002
60050	AVRIL	Marie-Françoise	29/12/2006	CF-AUD	AVENTIS PHARMA	- ASCO La Nouvelle Orleans		06/2004	06/2004
60050	AVRIL	Marie-Françoise	29/12/2006	CF-AUD		- réunion sur les lymphomes (Berlin)		02/2005	02/2005
60050	AVRIL	Marie-Françoise	29/12/2006	CF-AUD	GSK BIO	GSK Symposium (Bruxelles)			
60050	AVRIL	Marie-Françoise	29/12/2006	CF-AUD	SHIRE -France	European Academy Dermatologie (Rhodes)		10/2006	10/2006
60050	AVRIL	Marie-Françoise	29/12/2006	CF-AUD	SCHERING PLOUGH BIODERMA	EPU (dermatologie Paris 15) thème = mélanome - orateur)		06/2006	06/2006
60050	AVRIL	Marie-Françoise	02/04/2002	IP-CF	JANSSEN CILAG	Octobre 2000 - cancers cutanés des malades transplantés			
60050	AVRIL	Marie-Françoise	02/04/2002	IP-CF	SERVIER	2001 - Actualité sur le mélanome			
60050	AVRIL	Marie-Françoise	02/04/2002	VB	SERVIER	Essai randomisé folenustrie vs DMC			
60050	AVRIL	Marie-Françoise	02/04/2002	VB	SCHERING PLOUGH	Essais randomisés (groupe EORTC) - Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	02/04/2002	VB	PROGENIER	Essai EORTC avec gauglosiole : Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	31/07/2000	IP-CF	SCHERING PLOUGH	Congrès à Londres sur le mélanome (19 au 21/03/99)			
60050	AVRIL	Marie-Françoise	31/07/2000	VB	SERVIER	Coordination d'un essai randomisé dans le mélanome (Fotémustine vs OMC) - Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	31/07/2000	VB	PHARMA MAR SA	Participation à un essai de phase II dans le mélanome = ET 743 - Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	31/07/2000	VB	AVENTIS PASTEUR	Participation à un essai de vaccination dans le mélanome (awac-moge) - Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	31/07/2000	VB	BIOTECHNOR THERAPEUTICS	Essai de phase II de vaccination dans le mélanome = lipomel 1 - Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	31/07/2000	VB	ROCHE	Essai de phase II dans le mélanome avec l'interféron alpha - Institut Gustave Roussy			
60050	AVRIL	Marie-Françoise	31/07/2000	VB	SCHERING PLOUGH	Participation à un essai du groupe mélanome de l'EORTC 18952 - traitement adjuvant par l'interféron - Institut Gustave Roussy			
61457	BAILLET-GUFFROY	Arlette	30/03/2010	LD-AR	ADIR	- Consultant CMC -□□- Consultant en enregistrement international□□ contrat 1 an renouvelable	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	30/03/2010	LD-AR	EXPANSCIENCE	- Consultant en analyse et Module 3□□- Consultant en enregistrement international	rémunération personnelle (rémunération régulière)		
61457	BAILLET-GUFFROY	Arlette	30/03/2010	RE-DE	MEDIBRIDGE	Variations Module III	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	30/03/2010	RE-AUT	DOW CORNING	DMF-CEP	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	28/11/2009	LD-AR	EXPANSCIENCE	Consultant enregistrement France	rémunération personnelle (rémunération régulière)		
61457	BAILLET-GUFFROY	Arlette	28/11/2009	LD-AR	SERVIER	Consultant enregistrement international	rémunération personnelle (contrat 1 an renouvelable)		
61457	BAILLET-GUFFROY	Arlette	28/11/2009	RE-AUT	DOW CORNING	CEP	rémunération personnelle	01/2009	12/2009
61457	BAILLET-GUFFROY	Arlette	26/03/2009	LD-AR	ADIR	Conseil en CMC (en cours)	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	26/03/2009	LD-AR	EXPANSCIENCE	Conseil en analyse et module 3 (en cours)	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	26/03/2009	RE-DE	MEDIBRIDGE	Module III (ponctuel)	Rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	26/03/2009	RE-AUT	UNIPEX	DMF -CEP (ponctuel)	rémunération personnelle	01/2006	12/2008
61457	BAILLET-GUFFROY	Arlette	26/03/2009	LD-AR	SERVIER	Consultant CMC (contrat 1 an renouvelable)	Rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	26/03/2009	RE-AUT	DOW CORNING	DMF-CEP	Rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	11/12/2007	LD-AR	ADIR	Conseil en CMC (en cours)	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	11/12/2007	LD-AR	EXPANSCIENNE	Conseil en analyse (en cours)	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	11/12/2007	RE-DE	MEDIBRIDGE	Module III (ponctuel)			
61457	BAILLET-GUFFROY	Arlette	11/12/2007	RE-AUT	UNIPEX	DMF -CEP (ponctuel)	rémunération personnelle		
61457	BAILLET-GUFFROY	Arlette	11/12/2007	IP-AC	IPSEN	Conseil en analyse	rémunération personnelle	12/2007	03/2008
61457	BAILLET-GUFFROY	Arlette	30/09/2006	LD-AR	EXPANSCIENCE		Rémunération régulière		
61457	BAILLET-GUFFROY	Arlette	30/09/2006	LD-AR	SERVIER	Contrat de 1 an renouvelable			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61457	BAILLET-GUFFROY	Arlette	30/09/2006	RE-AUT	INNOTECH	Variations TOT'HEMA (2005)			
61457	BAILLET-GUFFROY	Arlette	30/09/2006	RE-AUT	SUBSTIPHARM	Gabapentine (2006)			
61457	BAILLET-GUFFROY	Arlette	30/09/2006	RE-AUT	DOW CORNING	CEP Simethicone (2006)			
61457	BAILLET-GUFFROY	Arlette	30/09/2006	IP-AC	NOVARTIS	Technico-réglementaire (2006)			
61457	BAILLET-GUFFROY	Arlette	30/09/2006	IP-CF	IFIS	Polymorphisme (2004)			
61457	BAILLET-GUFFROY	Arlette	13/09/2006	LD-AR	EXPANSCIENCE	Conseil	rémunération personnelle / rémunération régulière		
61457	BAILLET-GUFFROY	Arlette	13/09/2006	LD-AR	SERVIER/ADIR	conseil	contrat 1 an renouvelable		
61457	BAILLET-GUFFROY	Arlette	13/09/2006	RE-DE	INNOTECH	TOT' HEMA	rémunération personnelle	01/2004	12/2005
61457	BAILLET-GUFFROY	Arlette	13/09/2006	RE-DE	SUBSTIPHARM	GABAPENTINE	rémunération personnelle	01/2003	12/2006
61457	BAILLET-GUFFROY	Arlette	13/09/2006	RE-DE	DOW CORNING	CEP Simethicone	rémunération personnelle	01/2004	12/2006
61457	BAILLET-GUFFROY	Arlette	13/09/2006	IP-AC	NOVARTIS		rémunération personnelle	05/2006	06/2006
61457	BAILLET-GUFFROY	Arlette	13/09/2006	IP-AC	3 M SANTE	Flécaïnide	rémunération personnelle	01/2006	12/2006
61457	BAILLET-GUFFROY	Arlette	13/09/2006	CF-INT	IFIS	Polymorphisme	rémunération personnelle	01/2004	12/2004
61457	BAILLET-GUFFROY	Arlette	31/01/2006	Néant					
61457	BAILLET-GUFFROY	Arlette	05/10/2003	LD	EXPANSCIENCE	Rémunération régulière			
61457	BAILLET-GUFFROY	Arlette	05/10/2003	LD	ADIV/SERVIER	Contrat 1 an renouvelable			
61457	BAILLET-GUFFROY	Arlette	05/10/2003	IP-RE	NOVARTIS				
61457	BAILLET-GUFFROY	Arlette	05/10/2003	IP-AC	DOW CORNING				
61457	BAILLET-GUFFROY	Arlette	12/09/2002	LD	SERVIER-ADIR	Consultant			
61457	BAILLET-GUFFROY	Arlette	12/09/2002	LD	EXPANSCIENCE	Consultant			
61457	BAILLET-GUFFROY	Arlette	12/09/2002	IP-RE	NOVARTIS	Transfert de sites industriels			
61457	BAILLET-GUFFROY	Arlette	12/09/2002	IP-RE	INTERCHEMICAL	DMF			
61457	BAILLET-GUFFROY	Arlette	12/09/2002	IP-CF	IFIS	Polymorphisme			
60478	BAILLIART	Olivier	25/06/2010	EC-CO	SERVIER	Antiarythmique CL2-44121-005	co-investigateur	06/2010	09/2010
60478	BAILLIART	Olivier	25/06/2010	PAR	SERVIER	Directeur informatique	fils	01/2004	
60478	BAILLIART	Olivier	04/09/2009	PAR	SERVIER	Directeur ingénieur informatique	fils	01/2004	
60478	BAILLIART	Olivier	04/09/2009	PAR	SERVIER	Directeur ingénieur informatique	fils	01/2004	
60478	BAILLIART	Olivier	14/03/2008	EC-INV	ABBOTT			01/2005	12/2005
60478	BAILLIART	Olivier	14/03/2008	EC-INV	AVENTIS			01/2005	12/2005
60478	BAILLIART	Olivier	14/03/2008	CF-INT	MSD	Facteurs de risques cardio-vasculaires - AVC	rémunération personnelle	06/2006	06/2006
60478	BAILLIART	Olivier	14/03/2008	CF-INT	MSD	Facteurs de risques cardio-vasculaires - AVC	rémunération personnelle	09/2006	09/2006
60478	BAILLIART	Olivier	14/03/2008	PAR	SERVIER	Ingénieur informatique	Fils	01/2004	
60478	BAILLIART	Olivier	12/03/2007	RE-DE	AFSSAPS	Commission de contrôle de la publicité en faveur des objets, appareils et méthodes	Président titulaire expert		
60478	BAILLIART	Olivier	12/03/2007	IP-EC	ABBOTT	essais cliniques			
60478	BAILLIART	Olivier	12/03/2007	IP-EC	AVENTIS	essais cliniques			
60478	BAILLIART	Olivier	12/03/2007	IP-CF	MSD	prévenir l'AVC			
60478	BAILLIART	Olivier	12/03/2007	PAR	SERVIER	ingénieur informatique	fils		
60478	BAILLIART	Olivier	09/11/2005	EC-CO	AVENTIS	Echo doppler (étude en cours)	réalisation d'écho doppler veineux		05/2006
60478	BAILLIART	Olivier	09/11/2005	EC-CO	SANOFI SYNTHELABO	Echo doppler (étude en cours)	réalisation d'écho doppler veineux		
60478	BAILLIART	Olivier	09/11/2005	EC-CO	BAYER	Inhibiteur anti xa	réalisation d'écho doppler	07/2005	08/2005
60478	BAILLIART	Olivier	09/11/2005	RE-AUT	BETEM (BUREAU D'ETUDE DE L'AP)	Voz Max, ECG d'effort, Echographie	aucune rémunération		
60478	BAILLIART	Olivier	09/11/2005	CF-INT	MSD	Actions de formations	rémunération personnelle	06/2005	09/2005
60478	BAILLIART	Olivier	09/11/2005	PAR	SERVIER	Enfant (depuis 2003- en cours)	responsable des réseaux informatiques		
60478	BAILLIART	Olivier	08/03/2003	IP-EC	AVENTIS	Essais cliniques			
60478	BAILLIART	Olivier	08/03/2003	IP-EC	PHARMACIA	Essais cliniques			
60478	BAILLIART	Olivier	08/03/2003	IP-RE	B.E.T.E.M. (Bureau d'étude de l'AP)	Rapports E.C.G. d'effort ; rapports appareils à effet Doppler			
60478	BAILLIART	Olivier	08/03/2003	IP-CF	Industrie pharmaceutique	Physiopathologie cardio-vasculaire			
60478	BAILLIART	Olivier	08/03/2003	PAR	SERVIER	Enfant			
60478	BAILLIART	Olivier	30/11/1999	LD	Hôpital Lariboisière	Activité libérale			
60478	BAILLIART	Olivier	30/11/1999	VB	CNES - BORDEAUX II	Contrat vols paraboliques			
60285	BAKCHINE	Serge	16/12/2009	IP-AC	SERVIER	conseil scientifique étude CL2-38093-005, phase IIb (Alzheimer)	Rémunération personnelle	01/2009	12/2009
60285	BAKCHINE	Serge	16/12/2009	IP-AC	BIOGEN	participation à 1 advisory board (activité troubles cognitifs et SEP)	Aucune rémunération	01/2009	12/2009
60285	BAKCHINE	Serge	16/12/2009	IP-AC	FONDATION LUNDBECK	participation à 1 advisory board (activités démence)	Rémunération personnelle	01/2000	12/2009
60285	BAKCHINE	Serge	16/12/2009	IP-AC	WYETH	Conseil méthodologique (tests neuropsychologie) études alzheimer	Rémunération personnelle	01/2009	12/2009
60285	BAKCHINE	Serge	16/12/2009	EC-CO	PIERRE FABRE	PARKINSON (fatigue) /Etude DC0158 AM 401 1B prolongation de l'inclusion	co-investigateur	12/2009	06/2010
60285	BAKCHINE	Serge	16/12/2009	EC-CO	WYETH	ALZHEIMER/étude 31333K1-bapizumab (reprise étude suspendue)	co-investigateur	09/2009	09/2012
60285	BAKCHINE	Serge	16/12/2009	EC-CO	IRIS-SERVIER	ALZHEIMER/CL2-38093-005, phase IIb	co-investigateur et conseiller scientifique pour l'étude	11/2009	06/2010
60285	BAKCHINE	Serge	25/11/2008	EC-INV	SANOFI AVENTIS	Traitement symptomatique Maladie Alzheimer (produit abandonné - problème de sécurité en phase II)	investigateur principal phase III	01/2008	12/2008
60285	BAKCHINE	Serge	25/11/2008	EC-INV	NOVARTIS	Patch Exelon - étude phase IV nationale	coordonnateur	01/2008	12/2009
60285	BAKCHINE	Serge	25/11/2008	EC-CO	WYETH	Démence / Bapineuzumab (étude suspendue à ce jour)	co-investigateur	01/2008	12/2010
60285	BAKCHINE	Serge	25/11/2008	EC-CO	EISAI	MCI / Donépezil	co-investigateur	01/2008	12/2009
60285	BAKCHINE	Serge	25/11/2008	EC-CO	PIERRE FABRE	DCO 158 sur la fatigue dans la maladie de Parkinson	co-investigateur	01/2008	12/2009
60285	BAKCHINE	Serge	25/11/2008	IP-AC	JANSSEN CILAG	Groupe de réflexion sur exposition imagerie des démences	rémunération personnelle	01/2008	12/2008
60285	BAKCHINE	Serge	25/11/2008	IP-AC	ROCHE	Groupe de réflexion sur phases précoces de la Maladie d'Alzheimer	rémunération personnelle	01/2008	12/2008
60285	BAKCHINE	Serge	25/11/2008	IP-AC	LUNDBECK	Stratégies thérapeutiques dans la Maladie d'Alzheimer	rémunération personnelle	01/2007	12/2008
60285	BAKCHINE	Serge	25/11/2008	IP-AC	SERVIER	Développement précoce d'un traitement symptomatique dans la Maladie d'Alzheimer	rémunération personnelle	01/2008	12/2009
60285	BAKCHINE	Serge	25/11/2008	CF-INT	LUNDBECK	ECNP Conférence / Mémantine - analyse globale d'efficacité - Vienne	rémunération personnelle	10/2007	10/2007
60285	BAKCHINE	Serge	25/11/2008	CF-INT	LUNDBECK	Springfield Conférence en AD - Mémantine - specific benefit analysis	rémunération personnelle	04/2006	04/2006
60285	BAKCHINE	Serge	25/11/2008	CF-AUD	BIOGEN	American Academy of Neurology - Chicago		07/2008	07/2008
60285	BAKCHINE	Serge	25/11/2008	CF-AUD	JANSSEN CILAG	Springfield Conférence - Hong Kong		02/2008	02/2008
60285	BAKCHINE	Serge	25/11/2008	CF-AUD	BIOGEN	ECTRIMS - Prague		10/2007	10/2007
60285	BAKCHINE	Serge	25/11/2008	CF-AUD	BIOGEN	American Academy of Neurology - Boston		05/2007	05/2007
60285	BAKCHINE	Serge	25/11/2008	CF-AUD	LUNDBECK	ADRDA - Madrid		07/2006	07/2006
60285	BAKCHINE	Serge	25/11/2008	VB	BIOGEN	Développement d'une batterie socio cognitive informatisée	ARINCA	01/2007	12/2008
60285	BAKCHINE	Serge	25/11/2008	VB	SERONO	Recrutement d'un psychologue pour prise en charge de patients atteints de SEP	CHU de Reims	01/2007	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60285	BAKCHINE	Serge	28/05/2006	LD-AR	EISAI,PFIZER,LUNDBECK,JANSSEN,AVENTIS,NOVARTI S,SERVIER,..	Participation épisodique à des groupes d'experts (Advisory Board) ou avis individuels avec la majorité des c	rémunération personnelle		
60285	BAKCHINE	Serge	28/05/2006	EC-INV	LUNDBECK	Etude 99679 / Mémantine + extension 3 ans	investigateur principal	01/2001	12/2006
60285	BAKCHINE	Serge	28/05/2006	EC-INV	EISAI	Observatoire des pratiques de traitement de la Maladie Alzheimer	membre du conseil scientifique	01/2004	12/2005
60285	BAKCHINE	Serge	28/05/2006	EC-INV	JANSSEN	Observatoire des pratiques de traitement de la Maladie Alzheimer	membre du conseil scientifique	01/2004	12/2004
60285	BAKCHINE	Serge	28/05/2006	CF-INT	EISAI,PFIZER,LUNDBECK,JANSSEN,AVENTIS,NOVARTI S,SERVIER etc.	6 ou 7 interventions annuelles à des symposiums sur les démences organisées ou sponsorisées par les con	aucune rémunération / rémunération personnelle selon les cas		
60285	BAKCHINE	Serge	28/05/2006	CF-AUD	BIOGEN	American Academy of Neurology / San Diego		04/2006	04/2006
60285	BAKCHINE	Serge	05/01/2006	EC-INV	LUNDBECK SA	maladie d'Alzheimer - Mémantine	investigateur principal - étude internationale 99679	01/2002	12/2005
60285	BAKCHINE	Serge	05/01/2006	EC-CO	NOVARTIS	Alzheimer - Exelon	co-investigateur	01/2003	12/2004
60285	BAKCHINE	Serge	05/01/2006	EC-CO	EISAI	Alzheimer - Aricept	conseiller scientifique - étude observationnelle	01/2004	12/2005
60285	BAKCHINE	Serge	05/01/2006	EC-CO	JANSSEN-CILAG	Alzheimer - Reminyl	Conseiller scientifique - étude épidémiologique	01/2004	12/2005
60285	BAKCHINE	Serge	05/01/2006	RE-DE	LUNDBECK	En vue d'une commission CHMP - Alzheimer dans les formes modérées et sévères - Mémantine (2005)	rémunération personnelle/institution		
60285	BAKCHINE	Serge	05/01/2006	IP-AC	LUNDBECK, JANSSEN CILAG, NOVARTIS, JOHNSON & JONSON, PFIZER, SERVIER, BOEHRINGER	Produits anti-démence - activités ponctuelles de conseil (entre 2003 et 2005)	rémunération personnelle/institution		
60285	BAKCHINE	Serge	05/01/2006	CF-INT	LUNDBECK, JANSSEN CILAG, PFIZER, SERVIER, EISAI	Intervention à des symposiums ou congrès à l'invitation des laboratoires - conférence sur les traitements de	rémunération personnelles		
60285	BAKCHINE	Serge	05/01/2006	CF-AUD	NOVARTIS	World Congres of Neurology - Sydney		11/2005	
60285	BAKCHINE	Serge	05/01/2006	IP-AUT	ESAI, PFIZER, LUNDBECK, JANSSEN CILAG, INNOGENETICS	Interventions de FMC ou de formation spécialisée sponsorisées par ces laboratoires (de 2003 à 2005)			
60285	BAKCHINE	Serge	05/01/2006	VB	SERONO, NOVARTIS, SCHERRING, JANSSEN CILAG, ESAI	versements de subventions diverses de petits montants, pour des actions de formations ou colloques , mont	ARINCA : Association Loi 1901 dont je suis Président		
60285	BAKCHINE	Serge	03/05/2003	IP-EC	EISAI - PFIZER	Essai clinique Alzheimer			
60285	BAKCHINE	Serge	03/05/2003	IP-EC	JANSSEN CILAG	Etude épidémiologique Alzheimer			
60285	BAKCHINE	Serge	03/05/2003	IP-EC	NOVARTIS	Essai clinique SLA			
60285	BAKCHINE	Serge	03/05/2003	IP-EC	LUNDBECK	Essai clinique Alzheimer			
60285	BAKCHINE	Serge	03/05/2003	IP-EC	IPSEN - PHARMA	Essai clinique SEP cognition			
60285	BAKCHINE	Serge	03/05/2003	IP-AC	BIOGEN	SEP et cognition			
60285	BAKCHINE	Serge	03/05/2003	IP-AC	PFIZER	Démences vasculaires			
60285	BAKCHINE	Serge	03/05/2003	IP-CF	JANSSEN CILAG	Action de formation (FMC) Alzheimer			
60285	BAKCHINE	Serge	03/05/2003	IP-CF	EISAI - PFIZER	Action de formation (FMC) Alzheimer			
60285	BAKCHINE	Serge	03/05/2003	IP-CF	LUNDBECK - EISAI - JANSSEN	Alzheimer, démences vasculaires			
60285	BAKCHINE	Serge	03/05/2003	IP-CF	AVENTIS	Démences rares, troubles du comportement émotionnel, etc.			
60285	BAKCHINE	Serge	03/05/2003	(Autre)		Reçu des subventions diverses à une association de recherche (ARINCA) dont je suis président. Montant limité (< 14 000 €/an au total en moyenne) - Utilisation pour recherche/			
60165	BALANSARD	Guy	17/03/2009	EC-INV	BOIRON	Travaux réalisés dans le service	coordonnateur	01/2002	05/2009
60165	BALANSARD	Guy	10/04/2008	EC-INV	BOIRON	Mises au point analytiques	Coordonnateur	01/2002	05/2009
60165	BALANSARD	Guy	23/05/2006	EC-INV	BOIRON	Mise au point analytique	travaux réalisés dans le laboratoire que je dirige	01/2002	12/2006
60165	BALANSARD	Guy	23/05/2006	RE-DE	CRID PHARMA		Rémunération versée à une institution	01/2003	12/2003
60165	BALANSARD	Guy	23/05/2006	RE-DE	CRID PHARMA		Rémunération versée à une institution	01/2004	12/2004
60165	BALANSARD	Guy	23/05/2006	VB	BOIRON	mise au point analytique	Université de la Méditerranée (Protisvalor) pour faculté de pharmacie (année 2004, 2005, 2006)		
60165	BALANSARD	Guy	23/05/2006	EC-INV	SEVENE	Mise au point analytique	Travaux réalisés dans le laboratoire que je dirige	01/2005	12/2006
60165	BALANSARD	Guy	23/05/2006	VB	SEVENE	Mise au point analytique	Université de la Méditerranée (Protisvalor) pour faculté de pharmacie (année 2004, 2005, 2006)	01/2005	12/2006
60165	BALANSARD	Guy	23/05/2006	VB	SEVENE	Mise au point analytique	Université de la Méditerranée (Protisvalor) pour faculté de pharmacie (année 2004, 2005, 2006)	01/2006	12/2006
60165	BALANSARD	Guy	23/05/2006	VB	ARKOPHARMA, ASTRA ZENECA, BAYER PHARMA, BOIRON, BROTHIER, DEB ARMA, DOLISOS, FERRIER, HAUTES SYNERGIE, ICC, IFORA, PFIZER SAS, PHARMACIE DU ROCHER, PIERRE FABRE, SANOFI SYNTHELABO	taxes d'apprentissage		01/2005	12/2005
60165	BALANSARD	Guy	23/02/2005	IP-RE	CRID PHARMA	2003/2004			
60165	BALANSARD	Guy	23/02/2005	VB	BOIRON	2002-2003-2004-2005, financement > du budget			
60165	BALANSARD	Guy	23/02/2005	VB	ARKOPHARMA	Financements < 15% du budget du service, travaux de recherche ponctuels (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	ASTRA ZENECA	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	BAYER PHARMA	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	BOIRON	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	BROTHIER	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	DEB ARMA	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	DOLISOS	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	FERRIER	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	HAUTES SYNERGIE	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	ICC	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	IFORA	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	PFIZER SAS	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60165	BALANSARD	Guy	23/02/2005	VB	PHARMACIE DU ROCHER	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	PIERRE FABRE	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	VB	SANOFI SYNTHELABO	Financements < 15% du budget du service, taxes d'apprentissage, (2004)			
60165	BALANSARD	Guy	23/02/2005	IP-CF	LEHNING FERRIER	Participation à congrès			
60165	BALANSARD	Guy	23/02/2005	IP-CF	BOIRON WELEDA	Participation à congrès			
60165	BALANSARD	Guy	23/02/2005	IP-CF	DOLISOS	Participation à congrès			
60165	BALANSARD	Guy	23/02/2005	IP-AUT	SNPHPU	Aucun intérêt			
60165	BALANSARD	Guy	23/02/2005	IP-AUT	SFE	Aucun intérêt			
60165	BALANSARD	Guy	23/02/2005	IP-AUT	AFERP	Aucun intérêt			
60165	BALANSARD	Guy	10/06/2004	IP-EC	ARKOPHARMA				
60165	BALANSARD	Guy	10/06/2004	IP-EC	FABRE				
60165	BALANSARD	Guy	10/06/2004	IP-EC	BOIRON				
60165	BALANSARD	Guy	10/06/2004	IP-RE	CRID PHARMA				
60165	BALANSARD	Guy	10/06/2004	IP-AUT	SANOFI	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	PFIZER	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	FABRE	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	BOIRON	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	SERVIER	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	ASTRA	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	ARKOPHARMA	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	TISANE PROVENCALE	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	FRESENIUS	Taxes			
60165	BALANSARD	Guy	10/06/2004	IP-AUT	SCRAS	Taxes			
60165	BALANSARD	Guy	10/06/2004	VB	BOIRON				
60165	BALANSARD	Guy	08/09/2003	IP-EC	BOIRON				
60165	BALANSARD	Guy	08/09/2003	IP-RE	DBF ETHYPHARM				
60165	BALANSARD	Guy	08/09/2003	VB	BOIRON				
60165	BALANSARD	Guy	08/09/2003	IP-EC	DBF ETHYPHARM				
60165	BALANSARD	Guy	08/09/2003	IP-EC	ARKOPHARMA				
60165	BALANSARD	Guy	08/09/2003	IP-EC	TISANE PROVENCALE				
60165	BALANSARD	Guy	08/09/2003	IP-RE	TISANE PROVENCALE				
60165	BALANSARD	Guy	08/09/2003	IP-RE	CRID PHARMA				
60165	BALANSARD	Guy	22/08/2000	VB	INSTITUT DE RECHERCHE PIERRE FABRE	ESUS (Université de la Méditerranée)			
60165	BALANSARD	Guy	22/08/2000	VB	BOIRON	ESUS (Université de la Méditerranée)			
60165	BALANSARD	Guy	22/08/2000	VB	CHEFARO ARDERAL	Association - Enseignants pharmacognosistes Marseille			
60165	BALANSARD	Guy	22/08/2000	VB	CRID	Association - Enseignants pharmacognosistes Marseille			
60165	BALANSARD	Guy	22/08/2000	VB	LABORATOIRE TISANE PROVENCALE	Association Enseignant pharmacognosistes Marseille			
60165	BALANSARD	Guy	22/08/2000	VB	IPSEN BEAUFOUR	Association Enseignants pharmacognosistes Marseille			
55657	BARDIN	Thomas	11/02/2010	LD-AR	IPSEN MENARINI	Board Fébuxostat (travail sur l'environnement du produit : mise en place d'un enseignement sur la goutte) =	Rémunération personnelle	01/2005	
55657	BARDIN	Thomas	11/02/2010	EC-INV	ROCHE	Coordinateur d'une étude sur le tocilizumab		01/2006	12/2008
55657	BARDIN	Thomas	11/02/2010	EC-INV	TRB CHEMIDICA SOCIETE SPRIT	Coordonnateur national d'une étude comparative Ostényl vs Synvisc		01/2008	12/2009
55657	BARDIN	Thomas	11/02/2010	EC-CO	EXPANSCIENCE	Coordonnateur régional/piasclédine		01/2002	12/2008
55657	BARDIN	Thomas	11/02/2010	IP-AC	CEPHALON	Conseil sur PEG uricase (entretiens fin 2007 et janvier 2008)	Rémunération personnelle	12/2008	01/2008
55657	BARDIN	Thomas	11/02/2010	IP-AC	PROCTER GAMBLE	Conseil sur PEG uricase (1 réunion en 2008)	Rémunération personnelle		12/2008
55657	BARDIN	Thomas	11/02/2010	IP-AC	SANOFI AVENTIS	Inhibiteurs de l'IL1 et goutte-Thérapeutique de la PR (1 réunion en 2008)	Rémunération personnelle		12/2008
55657	BARDIN	Thomas	11/02/2010	IP-AC	GRUNENTHAL	Tapendol (1 réunion en 2009)	Rémunération personnelle		12/2009
55657	BARDIN	Thomas	11/02/2010	IP-AC	ROCHE, BMS	Participation à des registres de patients traités par bithérapie (Rituximab, Orencia), visant à évaluer leur tolé	Aucune rémunération	01/2005	
55657	BARDIN	Thomas	11/02/2010	CF-INT	ROCHE	Modérateur symposium : déc. 2007, 1 et 2 fév. 2008 (congrès SFR), 2010 (Journées de Viggo)	Rémunération personnelle		
55657	BARDIN	Thomas	11/02/2010	CF-INT	IPSEN/MENARINI	Modérateur/orateur symposiums : EULAR 2008 et 2010 ; SFR 2008, 2009, 2010 ; J. Viggo 2010	Rémunération personnelle		
55657	BARDIN	Thomas	11/02/2010	CF-INT	BMS	Modérateur symposium (Journées de Viggo), 2006 et 2007			12/2007
55657	BARDIN	Thomas	11/02/2010	IP-AC	PFIZER	Comité de suivi des effets indésirables de l'inhibiteur JAK 3 dans la PR (2 réunions/an)	Rémunération personnelle	01/2008	
55657	BARDIN	Thomas	16/03/2009	LD-AR	IPSEN	International advisory board Febuxostat	rémunération personnelle	01/2005	
55657	BARDIN	Thomas	16/03/2009	LD-AR	PFIZER	Comité de suivi des effets indésirables de l'inhibiteur JAK 3 dans la PR	rémunération partagée personnelle/institution	01/2005	
55657	BARDIN	Thomas	16/03/2009	LD-AR	ROCHE	Membre du comité scientifique air PR (suivi du rituximab), au titre de représentant de la société française de	aucune rémunération	01/2007	
55657	BARDIN	Thomas	16/03/2009	LD-AR	BMS	Membre du comité scientifique au titre de représentant de la SFR du registre de patients traités par ORENCI	aucune rémunération	01/2007	
55657	BARDIN	Thomas	16/03/2009	EC-INV	ROCHE	Coordinateur d'une étude sur le tocilizumab		01/2006	12/2008
55657	BARDIN	Thomas	16/03/2009	EC-INV	TRB CHEMIDICA SOCIETE SPRIT	Coordonnateur national d'une étude comparative Ostényl vs Synvisc	date de fin : 2009 ou 2010 selon rythme des inclusions	01/2008	12/2009
55657	BARDIN	Thomas	16/03/2009	EC-CO	EXPANSCIENCE	Piasclédine	coordonnateur régional	01/2002	12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AC	CEPHALON	Conseil sur PEG uricase - entretiens fin 2007 et janvier 2008	rémunération personnelle		12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AC	PROCTER AND GAMBLE	Conseil sur PEG Uricase	1 réunion en 2008	01/2008	12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AC	SANOFI AVENTIS	Inhibiteurs de l'IL 1 et goutte thérapeutique de la PR	1 réunion en 2008	01/2008	12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AC	IPSEN	Fébuxostat	3 réunions en 2008	01/2008	12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AC	GRUNENTHAL	Tapentadol	1 réunion en 2009	01/2009	12/2009
55657	BARDIN	Thomas	16/03/2009	IP-AC	FONDATION SOPHIA	Conseil d'administration	rémunération institution	01/2005	12/2006
55657	BARDIN	Thomas	16/03/2009	IP-AC	NOVARTIS	Inhibiteur IL 1 et goutte - 1 réunion en 2008	rémunération personnelle	01/2008	12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AC	PROCTER AND GAMBLE	Conseil sur PEG uricase - 1 entretien en septembre 2007	rémunération personnelle	09/2007	09/2007
55657	BARDIN	Thomas	16/03/2009	CF-INT	ROCHE	Modérateur symposium (congrès SFR)	rémunération personnelle	12/2007	12/2007
55657	BARDIN	Thomas	16/03/2009	CF-INT	IPSEN	Modérateur symposium (EULAR 2008)	rémunération personnelle	02/2008	02/2008
55657	BARDIN	Thomas	16/03/2009	CF-INT	BMS	Modérateur symposium	rémunération personnelle	03/2008	03/2008
55657	BARDIN	Thomas	16/03/2009	CF-INT	IPSEN	Modérateur symposium SFR 2008	rémunération personnelle	06/2008	06/2008
55657	BARDIN	Thomas	16/03/2009	CF-INT	PFIZER	Présentation de cas clinique	rémunération personnelle	01/2006	12/2006
55657	BARDIN	Thomas	16/03/2009	CF-INT	ALMIRALL	Orateur au symposium des journées nationales de rhumatologie , modérateur enseignement maladie de Du	rémunération personnelle	01/2006	12/2007
55657	BARDIN	Thomas	16/03/2009	CF-INT	MVS	Modérateur " les temps forts de l'ACR" présentés au congrès de la SFR - financé par Negma	rémunération personnelle	01/2006	12/2008
55657	BARDIN	Thomas	16/03/2009	CF-AUD	BMS	Congrès de l'EULAR - Copenhague		01/2009	12/2009
55657	BARDIN	Thomas	16/03/2009	IP-AUT	EXPANSCIENCE	Réalisation de 3 DVD sur la rhumatologie interventionnelle à la main		01/2007	12/2008
55657	BARDIN	Thomas	16/03/2009	IP-AUT	ALMIRALL	DVD information des patients : Dupuytren, prothèses		01/2006	12/2007
55657	BARDIN	Thomas	16/03/2009	IP-AUT	GENZYME	Rédaction d'un article scientifique pour la revue de la firme		01/2007	
55657	BARDIN	Thomas	06/02/2008	LD-AR	IPSEN	Advisory board Febuxostat (international)		01/2005	
55657	BARDIN	Thomas	06/02/2008	LD-AR	ALMIRALL	advisory board - cortex		01/2004	12/2006
55657	BARDIN	Thomas	06/02/2008	LD-AR	NOVARTIS	board Lumiracoxib (international)		01/2007	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
55657	BARDIN	Thomas	06/02/2008	LD-AR	ROCHE	comité scientifique AIR PR (registre Rituximab) au titre de représentant de la société française de rhumatologie		01/2007	
55657	BARDIN	Thomas	06/02/2008	IP-EC	ROCHE	Coordinateur de l'étude sur tocilizumab	coordonateur	01/2006	12/2008
55657	BARDIN	Thomas	06/02/2008	IP-EC	TRB CHEMIDICA	Coordinateur de l'essai Ostényl (dispositif médical)		01/2008	
55657	BARDIN	Thomas	06/02/2008	EC-CO	EXPANSCIENCE	Coordinateur régional		01/2002	12/2008
55657	BARDIN	Thomas	06/02/2008	IP-AC	CEPHALON	Consultation sur la goutte	rémunération personnelle	01/2008	
55657	BARDIN	Thomas	06/02/2008	IP-AC	PROCTER AND GAMBLE	Uricase oxydase en vue achat licence	rémunération personnelle	01/2007	
55657	BARDIN	Thomas	06/02/2008	IP-AC	FONDATION SOPHIA	Membre du conseil d'administration	rémunération institution	01/2005	12/2006
55657	BARDIN	Thomas	06/02/2008	IP-CF	ROCHE	Modérateur symposium, Jorgen Viggo (mars 2007) , SFR (décembre 2007), Paris Janvier 2008 - Polyarthrite	rémunération personnelle		
55657	BARDIN	Thomas	06/02/2008	IP-CF	TAKEDA	2005-2007 bon usage des AINS - médecins généralistes	rémunération personnelle		
55657	BARDIN	Thomas	06/02/2008	IP-CF	EXPANSCIENCE	2005 symposium congrès russe - exposé pathophyciology of Osteoarthritis - Paris			
55657	BARDIN	Thomas	06/02/2008	IP-CF	IPSEN	Modérateur symposium EULAR		01/2008	12/2008
55657	BARDIN	Thomas	06/02/2008	IP-CF	PFIZER	2006 cas cliniques radio rhumato (avec XXX), siège Pfizer, 2005 journée AIDA pathologie de la main, Paris (Pfizer)2004 congrès à Athènes (président)			
55657	BARDIN	Thomas	06/02/2008	IP-CF	ALMIRALL	Symposium SFR : 2006 + symposium Barcelone, cours d'enseignements Dupuytren			
55657	BARDIN	Thomas	06/02/2008	IP-CF	MSD	2005			
55657	BARDIN	Thomas	06/02/2008	IP-AUT	GENZYME	Rédaction d'un article scientifique dans la revue de la firme		01/2007	
55657	BARDIN	Thomas	06/02/2008	IP-AUT	EXPANSCIENCE	DVD enseignement post universitaire		01/2006	
55657	BARDIN	Thomas	06/02/2008	IP-AUT	ALMIRALL	DVD informations des patients - Enseignement : l'aiguille		01/2005	12/2007
55657	BARDIN	Thomas	06/02/2008	IP-AUT	LCA	Rédaction d'un poster sur l'essai clinique		01/2005	
55657	BARDIN	Thomas	06/02/2008	IP-CF	EXPANSCIENCE	2004 exposé pathophysiology of Osteoarthritis - Paris			
55657	BARDIN	Thomas	08/12/2006	IP-AC	ALMIRALL	Conseil post lancement Cartrex - 2 réunions par an	Rémunération personnelle	01/2004	
55657	BARDIN	Thomas	08/12/2006	(Autre)	EXPANSCIENCE	Participation à la réalisation d'un DVD d'enseignement des techniques d'infiltration			
55657	BARDIN	Thomas	08/12/2006	EC-INV	IPSEN	Febuxostat (à venir) - Coordinateur européen			
55657	BARDIN	Thomas	04/08/2005	EC-INV	ROCHE	étude MRA anti récepteur IL 6	coordinateur national - investigateur d'une autre étude	01/2005	
55657	BARDIN	Thomas	04/08/2005	EC-INV	SEARLE	étude CELEBREX		01/2000	12/2001
55657	BARDIN	Thomas	04/08/2005	EC-CO	MERCK	Etorocoxib	investigateur (théorique)	01/2203	
55657	BARDIN	Thomas	04/08/2005	IP-AC	ROCHE	Conseil développement Rituximab	rémunération personnelle	01/2005	
55657	BARDIN	Thomas	04/08/2005	IP-AC	ALMIRALL	conseil post lancement Cartrex	rémunération personnelle	01/2004	
55657	BARDIN	Thomas	04/08/2005	IP-AC	GRUNENTHAL	conseil post lancement Zaldiar	rémunération personnelle	01/2000	12/2004
55657	BARDIN	Thomas	04/08/2005	IP-AC	NOVARTIS	board Lumiracoxib (international)	rémunération personnelle	01/2003	
55657	BARDIN	Thomas	04/08/2005	IP-AC	IPSEN	board Febuxostat (international)	rémunération personnelle	01/2005	
55657	BARDIN	Thomas	04/08/2005	CF-INT	PFIZER	symposium à Athènes (président) ; journée d'enseignement AIDA	rémunération personnelle	01/2003	12/2004
55657	BARDIN	Thomas	04/08/2005	CF-INT	TAKEDA	symposium pour des généralistes / Athènes/Budapest	rémunération personnelle	01/2003	12/2005
55657	BARDIN	Thomas	04/08/2005	IP-CF	GRUNENTHAL	Symposia satellites congrès SFR (société française de rhumatologie) ou EULAR (European League Against	rémunération personnelle	01/2003	12/2004
55657	BARDIN	Thomas	04/08/2005	CF-INT	EXPANSCIENCE	Symposium satellite congrès russe, conférence Paris	rémunération personnelle	01/2004	12/2005
55657	BARDIN	Thomas	04/08/2005	CF-INT	WYETH	exposés PRISME / Paris	rémunération personnelle	01/2004	12/2005
55657	BARDIN	Thomas	04/08/2005	CF-AUD	BRISTOL MYERS SQUIBB	EULAR / Vienne		06/2005	
55657	BARDIN	Thomas	04/08/2005	CF-AUD	SERVIER	congrès de la Société Française de Rhumatologie (SFR) / Paris			
55657	BARDIN	Thomas	04/08/2005	IP-AUT	LCA	rédaction d'abstracts sur études		01/2004	
55657	BARDIN	Thomas	04/08/2005	VB	Association Rhumatisme et Travail	L'association Rhumatisme et Travail dont je suis le président organise tous les ans deux journées dans lesquelles une cinquantaine de laboratoires prennent des stands et 1			
55657	BARDIN	Thomas	04/08/2005	EC-CO	ABBOTT	Adalimumab	Investigateur (théorique)	01/2005	
55657	BARDIN	Thomas	04/08/2005	CF-INT	TAKEDA	symposium pour des généralistes / Athènes/Budapest	rémunération personnelle	01/2005	
55657	BARDIN	Thomas	04/08/2005	CF-INT	EXPANSCIENCE	Symposium satellite congrès russe - conférence Paris	Rémunération personnelle	01/2005	
55657	BARDIN	Thomas	04/08/2005	EC-INV	IPSEN	Febuxostat (à venir)	coordinateur européen		
55657	BARDIN	Thomas	04/08/2005	EC-CO	ABBOTT	Humira	investigateur théorique		
55657	BARDIN	Thomas	05/03/2005	IP-AC	NOVARTIS	activité de conseil sur Prexige			
55657	BARDIN	Thomas	05/03/2005	IP-AC	ALMIRALL	activité de conseil sur Cartrex			
55657	BARDIN	Thomas	05/03/2005	IP-AC	GRUNENTHAL	activité de conseil sur Zaldiar			
55657	BARDIN	Thomas	05/03/2005	IP-EC	ROCHE	en qualité d'investigateur principal sur MRA			
55657	BARDIN	Thomas	05/03/2005	IP-EC	ROCHE	co-investigateur sur MRA			
55657	BARDIN	Thomas	05/03/2005	IP-CF	TAKEDA, GRUNENTHAL	conférences			
55657	BARDIN	Thomas	05/03/2005	CF-AUD	PHARMASCIENCE, PFIZER, TAKEDA, MSD	conférences			
55657	BARDIN	Thomas	05/03/2005	VB	MERCK				
55657	BARDIN	Thomas	05/03/2005	PAR	Société française de rhumatologie	Je suis membre de la Société Française de Rhumatologie dont la majorité des ressources proviennent de l'industrie notamment pour le congrès français de rhumatologie. Je sui			
55657	BARDIN	Thomas	05/03/2005	IP-EC	PROCTER & GAMBLE PHARM	Actonel et arthrose			
55657	BARDIN	Thomas	18/08/2003	IP-EC	PHARMACIA	Essai clinique - coordination			
55657	BARDIN	Thomas	18/08/2003	IP-EC	PHARMASCIENCE	Essai clinique - coordination			
55657	BARDIN	Thomas	18/08/2003	IP-AC	GRUNENTHAL				
55657	BARDIN	Thomas	18/08/2003	IP-AC	NOVARTIS				
55657	BARDIN	Thomas	18/08/2003	IP-CF	PFIZER	Actuel			
55657	BARDIN	Thomas	18/08/2003	IP-CF	MSD	Passé			
55657	BARDIN	Thomas	18/08/2003	IP-CF	GRUNENTHAL	Actuel			
55657	BARDIN	Thomas	18/08/2003	IP-CF	PHARMASCIENCE	Passé			
55657	BARDIN	Thomas	18/08/2003	IP-CF	TAKEDA	Actuel			
55657	BARDIN	Thomas	18/08/2003	IP-CF	GENZYNE	Actuel			
55657	BARDIN	Thomas	18/08/2003	VB	ABBOTT	Essai clinique			
55657	BARDIN	Thomas	18/08/2003	VB	GRUNENTHAL	Essai clinique			
55657	BARDIN	Thomas	18/08/2003	VB	PROCTER & GAMBLE	Essai clinique			
55657	BARDIN	Thomas	18/08/2003	VB	MSD	Essai clinique			
55657	BARDIN	Thomas	26/09/2001	IP-EC	AMGEN	Essai clinique			
55657	BARDIN	Thomas	26/09/2001	IP-EC	PHARMACIA	Essai clinique			
55657	BARDIN	Thomas	26/09/2001	IP-EC	SCHERING-PLOUGH	Essai clinique			
55657	BARDIN	Thomas	26/09/2001	IP-AC	GRUNENTHAL	Comité de pilotage radiar			
55657	BARDIN	Thomas	26/09/2001	IP-CF	MERK	COXIBs			
55657	BARDIN	Thomas	26/09/2001	IP-CF	PHARMACIA	COXIBs			
55657	BARDIN	Thomas	26/09/2001	IP-CF	PHARMASCIENCE	Antiarthrosiques d'action lente			
55657	BARDIN	Thomas	26/09/2001	VB	PHARMACIA, SCHERING-PLOUGH	Laboratoire européen de génétique polyarthrite rhumatoïde (Evry Génopole) F Cornilis			
55657	BARDIN	Thomas	15/01/2001	IP-EC	PHARMACIA				
55657	BARDIN	Thomas	15/01/2001	IP-EC	PROCTER GAMBLE				
55657	BARDIN	Thomas	15/01/2001	IP-EC	PHARMASCIENCE				
55657	BARDIN	Thomas	15/01/2001	IP-EC	GENEVRIER				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
55657	BARDIN	Thomas	15/01/2001	IP-CF	PHARMACIA				
55657	BARDIN	Thomas	15/01/2001	IP-CF	MSD				
55657	BARDIN	Thomas	15/01/2001	IP-CF	PHARMASCIENCE				
55657	BARDIN	Thomas	15/01/2001	VB	AVENTIS				
55657	BARDIN	Thomas	15/01/2001	VB	PHARMACIA				
55657	BARDIN	Thomas	26/06/2000	IP-EC	SEARLE				
55657	BARDIN	Thomas	26/06/2000	IP-EC	MERCK SHARP & DOHME				
55657	BARDIN	Thomas	26/06/2000	IP-EC	TAKEDA				
55657	BARDIN	Thomas	26/06/2000	IP-EC	PROCTER & GAMBLE				
55657	BARDIN	Thomas	26/06/2000	IP-EC	PHARMASCIENCE				
55657	BARDIN	Thomas	26/06/2000	IP-EC	GENEVRIER				
55657	BARDIN	Thomas	26/06/2000	IP-CF	MERCK SHARP & DOHME				
55657	BARDIN	Thomas	26/06/2000	IP-CF	SEARLE				
55657	BARDIN	Thomas	26/06/2000	VB	SEARLE				
55657	BARDIN	Thomas	26/06/2000	VB	ROCHE				
55657	BARDIN	Thomas	26/06/2000	VB	SCHERING PLOUGH				
55657	BARDIN	Thomas	22/06/1999	IP-EC	TAKEDA	Coordination d'essais			
55657	BARDIN	Thomas	22/06/1999	IP-EC	PROCTER-GAMBLE	Investigateur			
55657	BARDIN	Thomas	22/06/1999	IP-EC	PHARMASCIENCE	Investigateur			
55657	BARDIN	Thomas	22/06/1999	IP-EC	BOEHRINGER INGELHEIM	Investigateur			
55657	BARDIN	Thomas	22/06/1999	IP-CF	SEARLE	EPU			
55657	BARDIN	Thomas	22/06/1999	VB	PFIZER	Subvention de recherche (laboratoire)			
55657	BARDIN	Thomas	22/06/1999	IP-AUT	PFIZER	Déplacement congrès			
55657	BARDIN	Thomas	22/06/1999	IP-AUT	SEARLE	Déplacement congrès			
10028	BARRE	Jérôme	14/09/2010	Néant					
10028	BARRE	Jérôme	18/12/2009	IP-AC	SANOFI AVENTIS	Consultation pharmacocinétique □□association antituberculeux	Rémunération personnelle	06/2009	06/2009
10028	BARRE	Jérôme	05/01/2009	IP-AC	SANOFI AVENTIS	Conseils pharmacocinétiques association antituberculeux	Rémunération personnelle	11/2008	11/2008
10028	BARRE	Jérôme	07/01/2008	IP-AC	STEBA FRANCE	Conseils pharmacocinétiques □□produits photodynamiques	Rémunération personnelle	06/2007	12/2007
10028	BARRE	Jérôme	07/01/2008	IP-AC	SANOFI AVENTIS	Conseils pharmacocinétiques association antituberculeux	Rémunération personnelle	06/2007	12/2007
10028	BARRE	Jérôme	07/01/2008	IP-AC	ETHYPHARM	Conseil générique ventafaxine	Rémunération personnelle	07/2007	07/2007
10028	BARRE	Jérôme	16/07/2007	IP-AC	MERCK	Conseils études pharmacocinétiques Acamprosate	Rémunération personnelle	02/2007	02/2007
10028	BARRE	Jérôme	16/07/2007	IP-AC	MERCK	Conseils nouvelles formulations Metformine	Rémunération personnelle	06/2007	06/2007
10028	BARRE	Jérôme	16/07/2007	IP-AC	SANDOZ	Conseil générique Tramadol	Rémunération personnelle	05/2007	05/2007
10028	BARRE	Jérôme	26/01/2007	IP-AC	NEGMA LERADS	Conseils pharmacocinétiques Ténatoprazole et produit utilisés en photothérapie dynamique	Rémunération institution	02/2006	07/2006
10028	BARRE	Jérôme	26/01/2007	CF-INT	ANDRE REY CONSULTANTS	Génériques en France : état des lieux (séminaire - Paris)	Rémunération personnelle	07/2006	07/2006
10028	BARRE	Jérôme	26/01/2007	CF-INT	ANDRE REY CONSULTANTS	Génériques questions d'actualité : bioéquivalence et impuretés génotoxiques (mini séminaire - Paris)	Rémunération personnelle	10/2006	10/2006
10028	BARRE	Jérôme	26/01/2007	IP-AC	SANOFI AVENTIS	Conseils pharmacocinétiques Artésunate et Amodiaquine	Rémunération personnelle	01/2006	11/2006
10028	BARRE	Jérôme	26/01/2007	RE-DE	SANDOZ	Bioéquivalence Tramadol LP	Rémunération personnelle	05/2006	05/2006
10028	BARRE	Jérôme	26/01/2007	RE-DE	SANDOZ	Bioéquivalence Trimébuline	Rémunération personnelle	06/2006	06/2006
10028	BARRE	Jérôme	26/01/2007	IP-AC	NOVARTIS SANTE FAMILIALE	Conseils pharmacocinétiques fluorure de sodium	Rémunération personnelle	06/2006	06/2006
10028	BARRE	Jérôme	04/05/2006	IP-AC	SANOFI-AVENTIS	Conseil pharmacocinétique : association Ramipril/Pravastatine	Rémunération personnelle	01/2006	01/2006
10028	BARRE	Jérôme	04/05/2006	IP-AC	MERCK SANTE	Conseil pharmacocinétique : Metformine	Rémunération personnelle	03/2006	03/2006
10028	BARRE	Jérôme	05/01/2006	IP-AC	NOVARTIS SANTE FAMILIALE	Conseils pharmacocinétiques forme galénique fluor	Rémunération personnelle	07/2005	07/2005
10028	BARRE	Jérôme	05/01/2006	IP-AC	GLAXO SMITHKLINE	Conseils pharmacocinétiques Sumatriptan	Rémunération personnelle	03/2005	03/2005
10028	BARRE	Jérôme	05/01/2006	IP-AC	GLAXO SMITHKLINE	Conseils pharmacocinétiques Naratriptan	Rémunération personnelle	06/2005	06/2005
10028	BARRE	Jérôme	05/01/2006	IP-AC	BESINS INTERNATIONAL	Conseils pharmacocinétques anti-œstrogène	Rémunération personnelle	09/2005	09/2005
10028	BARRE	Jérôme	05/01/2006	RE-DE	SANDOZ	Bioéquivalence Ramipril	Rémunération personnelle	10/2005	10/2005
10028	BARRE	Jérôme	05/01/2006	IP-AC	MERCK SANTE	Conseils pharmacocinétqiues Acamprosate	Rémunération personnelle	10/2005	10/2005
10028	BARRE	Jérôme	05/01/2006	IP-AC	SANOFI SYNTHELABO GROUPE	Conseils pharmacocinétiques Artésunate et Amodiaquine	Rémunération personnelle	01/2005	12/2005
10028	BARRE	Jérôme	05/01/2006	IP-AC	NEGMA LERADS	Conseils pharmacocinétiques Ténatoprazole	Rémunération = association loi 1901	03/2005	12/2005
10028	BARRE	Jérôme	11/02/2005	IP-AC	NEGMA LERADS	Diacerheine, Tenatoprazole	rémunération versée à une association	01/2003	12/2004
10028	BARRE	Jérôme	11/02/2005	IP-AC	SANOFI-AVENTIS	Artésunate	rémunération versée à une association	01/2004	12/2004
10028	BARRE	Jérôme	11/02/2005	IP-RE	PHARMA 2000	Doxycyline		01/2000	12/2000
10028	BARRE	Jérôme	11/02/2005	IP-RE	NEGMA LERADS	Buprenorphine		01/2001	12/2001
10028	BARRE	Jérôme	11/02/2005	IP-RE	NEGMA LERADS	Diacerheine		01/2004	12/2004
10028	BARRE	Jérôme	11/02/2005	IP-RE	IPSOR	Ticlopidine		01/2002	12/2002
10028	BARRE	Jérôme	11/02/2005	IP-RE	MEDIBRIDGE	Meloxicam		01/2002	12/2002
10028	BARRE	Jérôme	11/02/2005	IP-RE	GNR PHARMA	Amox/ac. Clav.		01/2003	12/2003
10028	BARRE	Jérôme	11/02/2005	IP-RE	GNR PHARMA	Ibuprofene		01/2003	12/2003
10028	BARRE	Jérôme	11/02/2005	IP-RE	GNR PHARMA	Cetirizine		01/2003	12/2003
10028	BARRE	Jérôme	11/02/2005	IP-RE	BESINS INTERNATIONAL	Oestrodose		01/2003	12/2003
10028	BARRE	Jérôme	11/02/2005	IP-RE	BESINS INTERNATIONAL	Progesterone		01/2004	12/2004
10028	BARRE	Jérôme	11/02/2005	CF-INT	BAYER	Symposium Fluoroquinoles - caractéristiques pharmacocinétiques des nouvelles fluoroquinolones		01/2000	01/2000
10028	BARRE	Jérôme	11/02/2005	PAR	SANOFI-AVENTIS	Conjoint, responsable du service information scientifique		10/1976	
10028	BARRE	Jérôme	28/08/2004	IP-CF	ANDRE REY CONSULTANTS	Activités Scientifique et Réglementaires			
10028	BARRE	Jérôme	28/08/2004	IP-CF	BAYER PHARMA	Pharmacocinétique nouvelles fluoroquinilones			
10028	BARRE	Jérôme	28/08/2004	IP-CF	SANOFI SYNTHELABO	Pharmacocinétique : exigences réglementaire			
10028	BARRE	Jérôme	28/08/2004	IP-CF	SERVIER	Pharmacocinétique : fixation proteine			
10028	BARRE	Jérôme	28/08/2004	IP-CF	MEDIBRIDGE	Médicaments génériques			
10028	BARRE	Jérôme	28/08/2004	IP-RE	NEGMA LERADS	Buprenorphine	année 2001		
10028	BARRE	Jérôme	28/08/2004	IP-RE	NEGMA LERADS	Diacerheine	année 2004		
10028	BARRE	Jérôme	28/08/2004	IP-RE	IPSOR	Ticlopidine	année 2002		
10028	BARRE	Jérôme	28/08/2004	IP-RE	MEDIBRIDGE	MELOXICAM	année 2002		
10028	BARRE	Jérôme	28/08/2004	IP-RE	GNR PHARMA	AMOX / AC.CLAV - IBUPROFENE - CETIRIZINE	année 2003		
10028	BARRE	Jérôme	28/08/2004	IP-CF	BESINS INTERNATIONAL	OESTRODOSE	année 2003		
10028	BARRE	Jérôme	28/08/2004	IP-RE	BESINS INTERNATIONAL	PROGESTERONE	année 2004		
10028	BARRE	Jérôme	28/08/2004	IP-AC	ETHYPHARM	DILTIAZEM LP	année 2001		
10028	BARRE	Jérôme	28/08/2004	IP-AC	NOVARTIS CONSUMER HEALTH	NICOTINELL (2001) - DICLOFENAC (2002) - VITAMINE D (2004)			
10028	BARRE	Jérôme	28/08/2004	IP-AC	GSK	AZANTAC - SALBUMOL (2001) - ZINNAT- AUGMENTIN SR (2002)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10028	BARRE	Jérôme	28/08/2004	IP-AC	GSK GRAND PUBLIC	PARACETAMOL	année 2002-2004		
10028	BARRE	Jérôme	28/08/2004	IP-AC	BOEHRINGER INGEILHEIM	BACITRACINE	année 2002		
10028	BARRE	Jérôme	28/08/2004	IP-AC	BOOTS HEALTHCARE	IBUPROFENE	année 2002		
10028	BARRE	Jérôme	28/08/2004	IP-AC	ABBOTT France	CLARITHROMYCINE	année 2002-2004		
10028	BARRE	Jérôme	28/08/2004	IP-AC	LAFON	MODIODAL	année 2002		
10028	BARRE	Jérôme	28/08/2004	IP-AC	MERCK SANTE	AC. ACETYLSALICYLIQUE (2002) - METFORMINE (2003)			
10028	BARRE	Jérôme	28/08/2004	IP-AC	MEDIBRIDGE	SIMVASTATINE	année 2003		
10028	BARRE	Jérôme	28/08/2004	IP-AC	CEMAX	RAMIPRIL	année 2003		
10028	BARRE	Jérôme	28/08/2004	IP-AC	SANDOZ	RAMIPRIL	année 2004		
10028	BARRE	Jérôme	28/08/2004	VB	THERAPHARM RECHERCHE : Membre Conseil Scientifique	Association JURIPHARM 2000-2004			
10028	BARRE	Jérôme	28/08/2004	VB	NEGMA LERADS : Conseils méthodologie Pharmacocinétique	Association JURIPHARM 2000-2004			
10028	BARRE	Jérôme	28/08/2004	PAR	SANOFI SYNTHELABO	Conjoint		10/1976	
10028	BARRE	Jérôme	10/04/2003	IP-RE	NEGMA-LERADS	Bioéquivalence			
10028	BARRE	Jérôme	10/04/2003	IP-RE	GNR - PHARMA	Bioéquivalence			
10028	BARRE	Jérôme	10/04/2003	IP-RE	BESINS INTERNATIONAL	Bioéquivalence			
10028	BARRE	Jérôme	10/04/2003	IP-AC	GLAXO WELLCOME	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	GLAXO SMITHKLINE	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	ABBOTT France	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	NOVARTIS Santé Familiale	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	ETHYPHARM	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	NEGMA-LERADS	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	LAFON	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	BOOTS HEALTHCARE	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	BOEHRINGER INGELHEIM	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-AC	MERCK SANTE	Conseils pharmacocinétiques - Analyses d'études, élaboration de protocoles			
10028	BARRE	Jérôme	10/04/2003	IP-CF	ANDRE REY CONSULTANTS	Médicaments génériques			
10028	BARRE	Jérôme	10/04/2003	VB	NEGMA-LERADS	Association			
10028	BARRE	Jérôme	10/04/2003	VB	NOVARTIS Santé Familiale	Association			
10028	BARRE	Jérôme	10/04/2003	VB	THERAPHARM	Association			
10028	BARRE	Jérôme	10/04/2003	PAR	SANOFI SYNTHELABO	Conjoint			
10028	BARRE	Jérôme	21/08/2000	IP-EC	SERVIER	Etudes pharmacocinétiques de molécules en développement préclinique			
10028	BARRE	Jérôme	21/08/2000	IP-RE	SERVIER	Pharmacocinétique d'une forme LP de Trimétazidine			
10028	BARRE	Jérôme	21/08/2000	IP-RE	MEDIBRIDGE	Etude de bioéquivalence : Méloxicam			
10028	BARRE	Jérôme	21/08/2000	IP-RE	IPSOR	Etudes de bioéquivalence : Ticlopidine, Molsidomine			
10028	BARRE	Jérôme	21/08/2000	IP-RE	NEGMA, PHARMA 2000	Etudes de bioéquivalence : Doxycycline, Diacérheine			
10028	BARRE	Jérôme	21/08/2000	IP-AC	SMITHKLINE BEECHAM, SERVIER, GLAXO WELLCOME, NOVARTIS, AVENTIS, PIERRE FABRE, PHARMA 2000	Conseils pour études pharmacocinétiques			
10028	BARRE	Jérôme	21/08/2000	IP-CF	ARC	Médicaments génériques			
10028	BARRE	Jérôme	21/08/2000	IP-CF	BAYER PHARMA	Pharmacocinétique des nouvelles fluoroquinolones			
10028	BARRE	Jérôme	21/08/2000	VB	SERVIER	Etablissement hospitalier et association			
10028	BARRE	Jérôme	21/08/2000	VB	THERAPHARM	Association			
10028	BARRE	Jérôme	21/08/2000	PAR	SANOFI-SYNTHELABO	Conjoint			
60772	BARTOLI	Jean-Michel	20/11/2009	EC-CO	EVASCAN	Coroscanner - PHRC National	collaborateur	01/2007	12/2009
60772	BARTOLI	Jean-Michel	20/11/2009	IP-RE	AFSSAPS	Endoprothèse aortique	aucune rémunération	01/2001	12/2003
60772	BARTOLI	Jean-Michel	20/11/2009	IP-RE	AFSSAPS	Endoprothèse aortique (révision du rapport)	aucune rémunération	01/2007	12/2008
60772	BARTOLI	Jean-Michel	20/11/2009	IP-AC	CORDIS	Groupe de réflexion	aucune rémunération	01/2005	12/2006
60772	BARTOLI	Jean-Michel	20/11/2009	PAR	ASTRA ZENECA	PDG (en cours)	Soeur	01/2005	
60772	BARTOLI	Jean-Michel	04/02/2009	EC-CO	PHRC NATIONAL	EVASCAN - Corescan (en cours)	co-investigateur	01/2008	
60772	BARTOLI	Jean-Michel	04/02/2009	RE-DE	AFSSAPS		aucune rémunération	01/2000	12/2004
60772	BARTOLI	Jean-Michel	04/02/2009	RE-DE	AFSSAPS	Endoprothèse aortique	aucune rémunération	01/2007	12/2008
60772	BARTOLI	Jean-Michel	04/02/2009	PAR	ASTRA ZENECA Belgique	Directeur général (en cours)	sœur	01/2005	
60772	BARTOLI	Jean-Michel	19/09/2007	PAR	ASTRAZENECA	Directeur général Belgique Luxembourg	Soeur	01/2007	
60772	BARTOLI	Jean-Michel	19/09/2007	IP-AC	CORDIS FRANCE	Membre du BOARD Consultant	Rémunération personnelle	09/2007	
60772	BARTOLI	Jean-Michel	25/09/2006	EC-INV			investigateur	01/2005	12/2006
60772	BARTOLI	Jean-Michel	25/09/2006	EC-INV	EVASCAN	Coloscanner	investigateur	01/2006	
60772	BARTOLI	Jean-Michel	25/09/2006	CF-AUD	GUERBET	Journées Francophones de Radiologie□□JFR 04 et JFR 05		10/2004	10/2005
60772	BARTOLI	Jean-Michel	25/09/2006	PAR	ASTRA-ZENECA BELGIQUE	P.D.G.	sœur	01/2005	
60772	BARTOLI	Jean-Michel	21/06/2004	IP-RE		Dans le cadre de la commission des dispositifs médicaux			
60772	BARTOLI	Jean-Michel	21/06/2004	VB	Laboratoire d'Hémodynamique et de Mécanique Cardio-Vasculaire	salaire de l'AP-HM, et de l'université de la méditerranée			
60772	BARTOLI	Jean-Michel	18/10/2003	VB	SERVIER, SCHERING, GUERBET, BSC, GORE	Essais cliniques - Université de la Méditéranée, AP-HM - ADEREM - PHBC National			
60772	BARTOLI	Jean-Michel	18/10/2003	VB	GORE, GLAXO SMITHKLINE, BSG	Conférences, colloques, formations - ADEREM			
60772	BARTOLI	Jean-Michel	18/10/2003	PAR	ASTRAZENECA	sœur			
60772	BARTOLI	Jean-Michel	30/07/2002	IP-EC	GORE	Etude européenne multicentrique randomisée - prothèse hemiehain			
60772	BARTOLI	Jean-Michel	30/07/2002	IP-CF	Société Française de Radiologie	Journées Française de Radiologie			
60772	BARTOLI	Jean-Michel	30/07/2002	IP-CF	Société Française d'imagerie Cardio-vasculaire	Réunion de Printemps			
60772	BARTOLI	Jean-Michel	30/07/2002	IP-CF	FORIME D-PACA	1 réunion scientifique annuelle			
60772	BARTOLI	Jean-Michel	30/07/2002	VB	GUERBET	ADEREM/lecteur			
60772	BARTOLI	Jean-Michel	30/07/2002	VB	EPIX	AP-HM (CPCET)			
60772	BARTOLI	Jean-Michel	30/07/2002	PAR	ASTRAZENECA	Sœur			
60772	BARTOLI	Jean-Michel	12/05/2000	PAR	ASTRAZENECA	Sœur			
60772	BARTOLI	Jean-Michel	12/05/2000	VB	PMR	Essais multicentriques - ADEREM			
60772	BARTOLI	Jean-Michel	12/05/2000	VB	BSC, GORE	Conférences, colloques, formations - ADEREM			
10029	BASDEVANT	Arnaud	24/10/2007	EC-CO	ABBOTT	Sibutramine	co-investigateur	01/2005	12/2009
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	LILLY	Exenatide	rémunération personnelle	01/2007	
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	NOVO NORDISK	Liraglutide	rémunération personnelle	01/2007	
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	MERCK	Liraglutide	rémunération personnelle	01/2005	
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	BMS	Liraglutide	rémunération personnelle	01/2006	
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	MSD	Liraglutide	rémunération personnelle	01/2005	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	ROCHE				
10029	BASDEVANT	Arnaud	24/10/2007	IP-AC	DANONE				
10029	BASDEVANT	Arnaud	24/10/2007	CF-INT	JANSSEN SANTE ANIMALE	Symposium obésité - Paris	rémunération personnelle	01/2007	12/2007
10029	BASDEVANT	Arnaud	24/10/2007	CF-INT	SANOFI AVENTIS	Symposium diabétologie	rémunération personnelle	01/2007	12/2007
10029	BASDEVANT	Arnaud	24/10/2007	CF-INT	NOVO NORDISK			01/2006	12/2006
10029	BASDEVANT	Arnaud	24/10/2007	VB	ROCHE, SANOFI	soutien recherche	AAID	01/2003	12/2007
10029	BASDEVANT	Arnaud	24/10/2007	(Autre)	CNAM , DHOS				
10029	BASDEVANT	Arnaud	20/07/2006	EC-INV	MSD	Etude clinique (fin 2008)	Investigateur	01/2004	
10029	BASDEVANT	Arnaud	20/07/2006	EC-INV	ROCHE	Etude épidémiologique	Investigateur	01/2004	
10029	BASDEVANT	Arnaud	20/07/2006	EC-INV	KNOLL	Etude clinique	Investigateur	01/2004	
10029	BASDEVANT	Arnaud	20/07/2006	IP-AC	DANONE/LU	Groupe de travail	Rémunération personnelle et institution		
10029	BASDEVANT	Arnaud	20/07/2006	IP-AC	ROCHE, KOBE	Groupe de réflexion	Rémunération personnelle et institution		
10029	BASDEVANT	Arnaud	20/07/2006	CF-INT	ROCHE	Sairo	Rémunération personnelle		
10029	BASDEVANT	Arnaud	20/07/2006	CF-INT	SANOFI	Membre de jury de prix	Rémunération personnelle		
10029	BASDEVANT	Arnaud	20/07/2006	CF-INT	FONDATION BENJAMIN DELESERT	Journée annuelle de nutrition et diététique	Aucune rémunération		
10029	BASDEVANT	Arnaud	20/07/2006	VB	ROCHE, SANOFI	Soutien Recherches	AAID	01/2002	12/2006
10029	BASDEVANT	Arnaud	20/07/2006	VB	SERVIER	Conseil scientifique	AAID		
10029	BASDEVANT	Arnaud	03/09/2003	IP-EC	ROCHE				
10029	BASDEVANT	Arnaud	03/09/2003	IP-EC	ABBOTT				
10029	BASDEVANT	Arnaud	03/09/2003	IP-EC	SANOFI				
10029	BASDEVANT	Arnaud	03/09/2003	IP-EC	SERVIER				
10029	BASDEVANT	Arnaud	03/09/2003	IP-CF	ROCHE				
10029	BASDEVANT	Arnaud	03/09/2003	IP-CF	ABBOTT				
10029	BASDEVANT	Arnaud	03/09/2003	IP-CF	SANOFI				
10029	BASDEVANT	Arnaud	03/09/2003	VB	ROCHE				
10029	BASDEVANT	Arnaud	03/09/2003	VB	SERVIER				
10029	BASDEVANT	Arnaud	10/10/2002	IP-EC	SANOFI	Essais cliniques			
10029	BASDEVANT	Arnaud	10/10/2002	IP-EC	ROCHE	Essais cliniques			
10029	BASDEVANT	Arnaud	10/10/2002	IP-EC	SERVIER	Travaux scientifiques			
10029	BASDEVANT	Arnaud	10/10/2002	IP-EC	ABBOTT	Essais cliniques			
10029	BASDEVANT	Arnaud	10/10/2002	IP-CF	SERVIER	Colloques, conférences			
10029	BASDEVANT	Arnaud	10/10/2002	IP-CF	ROCHE	Conférence			
10029	BASDEVANT	Arnaud	10/10/2002	VB	ROCHE	AAID			
10029	BASDEVANT	Arnaud	10/10/2002	VB	SERVIER	AAID			
10029	BASDEVANT	Arnaud	17/01/2000	IP-EC	SERVIER				
10029	BASDEVANT	Arnaud	17/01/2000	IP-EC	NOVARTIS				
10029	BASDEVANT	Arnaud	17/01/2000	IP-CF	ROCHE				
10029	BASDEVANT	Arnaud	01/01/1999	LD	Ardix ; activité régulière de conseil pour la réalisation de documents pédagogiques; de réunions de Formation médicale, de diapositives d'enseignement.				
10029	BASDEVANT	Arnaud	01/01/1999	IP-EC	Roche				
10029	BASDEVANT	Arnaud	01/01/1999	IP-EC	Organon				
10029	BASDEVANT	Arnaud	01/01/1999	IP-EC	Sanofi				
10029	BASDEVANT	Arnaud	01/01/1999	IP-EC	Theramex				
10029	BASDEVANT	Arnaud	01/01/1999	IP-EC	Novo				
10029	BASDEVANT	Arnaud	01/01/1999	IP-AC	Novartis				
10029	BASDEVANT	Arnaud	01/01/1999	IP-CF	Novartis				
10029	BASDEVANT	Arnaud	01/01/1999	IP-CF	Knoll				
10029	BASDEVANT	Arnaud	01/01/1999	IP-CF	Ardix				
10029	BASDEVANT	Arnaud	02/01/1998	IP-AUT	Novo				
10029	BASDEVANT	Arnaud	02/01/1998	IP-AUT	Organon				
10029	BASDEVANT	Arnaud	01/01/1998	IP-AUT	Cassenne				
10029	BASDEVANT	Arnaud	01/01/1998	IP-AUT	Ardix Médical				
10029	BASDEVANT	Arnaud	01/01/1998	IP-AUT	Hoechst				
10029	BASDEVANT	Arnaud	01/01/1998	IP-AUT	Roche				
63418	BEBEAR	Jean-Pierre	22/05/2004	IP-EC	SERVIER, AVENTIS, etc.	Essais cliniques			
63418	BEBEAR	Jean-Pierre	22/05/2004	IP-RE	Tribunal , Sécurité Sociale , assurances	peu de rapports par an			
63418	BEBEAR	Jean-Pierre	22/05/2004	IP-CF		Nombreuses sur le plan scientifique dans le cadre classique de la fonction hospitalo-universitaire			
60216	BELEGAUD	Jacques	24/09/2010	Néant					
60216	BELEGAUD	Jacques	18/12/2009	RE-DE	GENEVRIER	Cardioral (NCO)	rémunération personnelle	07/2009	07/2009
60216	BELEGAUD	Jacques	18/12/2009	RE-AUT	GENEVRIER	Flector tissugel héparine (IP-RE)	rémunération personnelle	05/2008	05/2008
60216	BELEGAUD	Jacques	18/12/2009	RE-AUT	GENEVRIER	Tissugel Genévrier (IP-RE)	rémunération personnelle	02/2006	03/2006
60216	BELEGAUD	Jacques	18/12/2009	RE-AUT	PIERRE FABRE	Primalan (IP-RE)	rémunération personnelle	05/2006	12/2006
60216	BELEGAUD	Jacques	18/12/2009	IP-AC	PIERRE FABRE	Conseils sur énantiomère méquitazine	rémunération personnelle	02/2009	06/2009
60216	BELEGAUD	Jacques	18/12/2009	IP-AC	GIULIANI	Conseils phase I GED (PPAR gamma)	rémunération personnelle	07/2009	09/2009
60216	BELEGAUD	Jacques	19/01/2009	RE-DE	GENEVRIER	Flector tissugel héparine	Rémunération personnelle	05/2008	06/2008
60216	BELEGAUD	Jacques	26/05/2008	RE-DE	GENEVRIER	Flector Tissugel Heparine	Rémunération personnelle	04/2008	05/2008
60216	BELEGAUD	Jacques	07/05/2007	RE-DE	GENEVRIER	Tissugel Genevrier (RE)	Rémunération personnelle	02/2006	03/2006
60216	BELEGAUD	Jacques	07/05/2007	RE-DE	PIERRE FABRE	Primalan (RE)	Rémunération personnelle	05/2006	12/2006
60216	BELEGAUD	Jacques	30/01/2006	IP-AC	GALDERMA	Ivermectine		04/2005	04/2005
60216	BELEGAUD	Jacques	10/03/2005	IP-RE	PIERRE FABRE	Méquitazine (2002)			
60216	BELEGAUD	Jacques	10/03/2005	IP-RE	MENARINI	Ketum			
60216	BELEGAUD	Jacques	10/03/2005	IP-RE	GENEVRIER	Fostimon - Flector (2004)			
60216	BELEGAUD	Jacques	28/04/2003	LD	Ministère Agriculture (DGAL)	Occasionnel - Evaluation dossiers phytosanitaires			
60216	BELEGAUD	Jacques	28/04/2003	IP-RE	GENEVRIER (IP)	Rapport expert Flector Tissugel			
60216	BELEGAUD	Jacques	28/04/2003	IP-RE	Service Santé Armées	Rapport expert DTPA			
60216	BELEGAUD	Jacques	28/04/2003	IP-AC	ETHYPHARM (IP)	Expertise d'un excipient			
60216	BELEGAUD	Jacques	28/04/2003	IP-AC	BIOCODEX (IP)	Réponse EMEA Stiripentol			
60216	BELEGAUD	Jacques	28/04/2003	IP-CF	IFIS	Conférence - Le dossier CTD toxicologique			
60216	BELEGAUD	Jacques	28/04/2003	IP-CF	ANDRE REY CONSULTANTS	Conférence - Actualités en toxicologie			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
					SERVIER, GLAXO SMITHKLINE, BOEHRINGER				
60216	BELEGAUD	Jacques	28/04/2003	VB	INGELHEIM, BAYER PHYTO	Taxe apprentissage versee a l'agent comptable de l'Université Picardie			
60216	BELEGAUD	Jacques	02/04/2001	IP-RE	LABCATAL	Rubozirec			
60216	BELEGAUD	Jacques	02/04/2001	IP-RE	BIOCODEX	Stiripentol			
60216	BELEGAUD	Jacques	02/04/2001	IP-RE	PIERRE FABRE	Conseils en développement			
60216	BELEGAUD	Jacques	02/04/2001	IP-RE	SERB	Infracyanins			
60216	BELEGAUD	Jacques	02/04/2001	IP-AC	SERVIER	Conseil en développement			
60216	BELEGAUD	Jacques	02/04/2001	IP-CF	IFIP	Le dossier préclinique			
60216	BELEGAUD	Jacques	02/04/2001	IP-CF	A.R.C.	Evaluation impuretés			
60216	BELEGAUD	Jacques	24/05/2000	IP-RE	SERVIER	Rapport expertise préclinique Diamicron et Muphoran			
60216	BELEGAUD	Jacques	24/05/2000	IP-RE	SERB	Rapport d'expertise ATU Infracyonine			
60216	BELEGAUD	Jacques	24/05/2000	IP-AC	NOVARTIS PHARMA	Conseils en toxicologie			
60216	BELEGAUD	Jacques	24/05/2000	IP-AC	INNOTHERA	Attestation toxicologique CCPRB			
60216	BELEGAUD	Jacques	24/05/2000	IP-CF	IFIP	Développement préclinique			
61172	BENICHOU	Jacques	02/09/2009	EC-CO	SERVIER	étude pharmacoépidémiologique : cohorte prospective chez les patients prenant du Valdoxan	Membre du Comité scientifique	01/2009	
61172	BENICHOU	Jacques	02/09/2009	EC-CO	NOVARTIS	étude épidémiologique sur la prescription de vitamine D (quel que soit le produit) chez le nourrisson et le jeu	Membre du Comité scientifique	01/2008	
61172	BENICHOU	Jacques	01/03/2006	Néant					
61172	BENICHOU	Jacques	07/06/2004	(Autre)	DGS	Etude de type pharmaco-épidémiologique sur le vaccin Prévenar (WYETH) ayant pour but de décrire les utilisateurs du vaccin ainsi que les éventuels effets secondaires et l'effi			
61172	BENICHOU	Jacques	07/06/2004	IP-EC	AVENTIS	Essai randomisé de phase III évaluant de façon comparative deux chimiothérapies dans le traitement du cancer du sein opéré - Membre du comité de surveillance de cette étud			
61172	BENICHOU	Jacques	07/06/2004	(Autre)	DGS (suite)	Cette étude commanditée par la DGS (confiée à équipe Inserm - Pr G. Bréart). Participation au Comité scientifique de cette étude - Participation non rémunérée. Etude en cours			
61172	BENICHOU	Jacques	07/06/2004	IP-EC	AVENTIS (suite)	Instance indépendante du laboratoire et des équipes de cliniciens et de méthodologistes qui mènent cette étude (essai en cours)			
61172	BENICHOU	Jacques	07/06/2004	IP-AC	MERCK SHARP & DOHME, CHIBRET	En 2003, consultation ponctuelle pour la planification d'une étude de type pharmaco-épidémiologique (but : description des biphosphonates et du raloxifène dans la prise en che			
61172	BENICHOU	Jacques	07/06/2004	IP-AC	BEAUFOUR IPSEN PHARMA	Consultation ponctuelle en 2004 concernant l'analyse d'une étude sur le produit Bedelix et le possibilité de publication scientifique de ses résultats			
61172	BENICHOU	Jacques	29/01/2004	IP-EC	SCHERING	Essai de phase II, leucémie lymphoïde chronique, expertise méthodologique et statistique (en cours)			
61172	BENICHOU	Jacques	29/01/2004	IP-EC	MERCK	Etude post AMM, ostéoporose			
61172	BENICHOU	Jacques	29/01/2004	IP-RE	AVENTIS	Essai de phase III, cancer du sein, participation au comité de surveillance de l'essai (en cour)			
61172	BENICHOU	Jacques	08/07/2002	IP-EC	SCHERING	Analyse statistique et aide à la planification : un essai de phase II en hémato-oncologie (2001-2002)			
61172	BENICHOU	Jacques	06/09/2000	IP-EC	SCHERING	Essai phase II - Biostatisticien de cet essi commencé en 1999			
61172	BENICHOU	Jacques	06/09/2000	IP-AC	RHONE POULENC RORER	Journée de formation sur analyse séquentielle groupée en 1999			
62508	BENSMAN	Albert	22/06/2010	EC-CO	ROCHE	Etude sur la mircera dans l'anemie - NH 19707 - Dolphin (en cours)	co-investigateur	10/2009	
62508	BENSMAN	Albert	11/06/2009	EC-INV	AMGEN	Darbépoétine alfa - Registre prospectif chez les enfants avec insuffisance renale chronique	Investigateur coordinnateur	03/2009	
62508	BENSMAN	Albert	11/06/2009	EC-INV	ROCHE	- Etude Dolphin □□- Mircera ® dans l'insuffisance renale de l'enfant	investigateur coordinnateur	01/2009	
62508	BENSMAN	Albert	24/12/2007	EC-CO	ROCHE	Cell Cept - Son intérêt dans le syndrome néphrotique corticodépendant	collaborateur à l'étude	01/2003	11/2006
62508	BENSMAN	Albert	24/12/2007	EC-CO	AVENTIS	Oroken - Son intérêt dans le traitement des pyélonéphrites aiguës	collaborateur à l'étude	01/2003	
62508	BENSMAN	Albert	24/12/2007	RE-DE		Traitement de l'infection urinaire de l'enfant	aucune rémunération	01/2005	12/2006
62508	BENSMAN	Albert	24/12/2007	CF-AUD	ROCHE	American Society of Nephrology - San Diego		09/2006	09/2006
62508	BENSMAN	Albert	24/12/2007	CF-AUD	SANDOZ	Société Francophone de Pédiatrie - Marrakech		04/2007	04/2007
62508	BENSMAN	Albert	24/12/2007	VB	Société de Néphrologie Pédiatrique	Président			
62508	BENSMAN	Albert	24/12/2007	VB	ROCHE	Bourses permettant à 6 jeunes médecins à participer à un congrès international	Société de néphrologie pédiatrique	01/2006	12/2006
62508	BENSMAN	Albert	24/12/2007	VB	ROCHE	Bourses permettant à 6 jeunes médecins à participer à un congrès international	Société de néphrologie pédiatrique	01/2007	12/2007
62508	BENSMAN	Albert	24/12/2007	VB	NOVARTIS	Bourses permettant à 15 jeunes médecins à participer à un congrès international	Société de néphrologie pédiatrique	01/2005	12/2005
62508	BENSMAN	Albert	24/12/2007	VB	NOVARTIS	Bourses permettant à 15 jeunes médecins à participer à un congrès international	Société de néphrologie pédiatrique	01/2006	12/2006
62508	BENSMAN	Albert	24/12/2007	VB	NOVARTIS	Bourses permettant à 15 jeunes médecins à participer à un congrès international	Société de néphrologie pédiatrique	01/2007	12/2007
62508	BENSMAN	Albert	24/12/2007	VB	AMGEN	Bourses permettant à 6 jeunes médecins à participer à un congrès international	Société de néphrologie pédiatrique	01/2008	12/2008
62508	BENSMAN	Albert	16/03/2006	EC-CO	SERVIER	Perin (étude chez l'enfant hypertendu 2-11 ans)	Co-investigateur	01/2003	12/2005
62508	BENSMAN	Albert	16/03/2006	IP-AC	AFSSAPS	Prise en charge de l'infection urinaire de l'enfant	rémunération personnelle	01/2005	12/2006
62508	BENSMAN	Albert	16/03/2006	IP-AC	AFSSAPS	Rapport du dossier PP 528	rémunération personnelle	01/2006	
62508	BENSMAN	Albert	16/03/2006	CF-AUD	AMGEN	Congrès européen Nephologie Pédiatrique Istanbul (Turquie)		09/2005	09/2005
62508	BENSMAN	Albert	16/03/2006	CF-AUD	ROCHE	Congres societe Nephologie Pédiatrique Amsterdam		11/2005	11/2005
62508	BENSMAN	Albert	22/06/2004	Néant					
62508	BENSMAN	Albert	03/05/2004	Néant					
60397	BERENBAUM	Francis	23/08/2005	LD	NOVARTIS	Advisory Board / Lumiracoxib (2002)			
60397	BERENBAUM	Francis	23/08/2005	LD	PFIZER	Articulum (2002)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	TAKEDA	réunions de consensus IPP (2005)			
60397	BERENBAUM	Francis	23/08/2005	LD	ASTRA ZENECA	Advisory Board / NO-AINS (2001-2002)			
60397	BERENBAUM	Francis	23/08/2005	LD	ASTRA ZENECA	Advisory Board /IPP (2003-2004)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	GSK	GW406381/ Investigateur principal (2005)		01/2005	12/2005
60397	BERENBAUM	Francis	23/08/2005	IP-EC	EXPANSCIENCE	Piascledine		01/2003	12/2004
60397	BERENBAUM	Francis	23/08/2005	IP-EC	PFIZER	Investigateur / Celebrex co-investigateur (2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	ROCHE	MRA / co-investigateur (2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	BMS	Abatacept / co-investigateur (2004-2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	AMGEN	Kineret / co-investigateur (2002)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	ABBOTT	Humira / co-investigateur (2003)			
60397	BERENBAUM	Francis	23/08/2005	IP-EC	SERVIER	Ranelate de strontium / co-investigateur (2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-AC	ASTRA ZENECA	Conseils sur traitements de la polyarthrite (2003-2004)			
60397	BERENBAUM	Francis	23/08/2005	IP-CF	PFIZER, MSD,NOVARTIS, ASTRA ZENECA	2002-2005			
60397	BERENBAUM	Francis	23/08/2005	IP-CF	ABBOTT	Prise en charge de déplacement en congrès : EULAR (2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-CF	MSD	Prise en charge de déplacement en congrès : EULAR (2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-CF	MSD	Prise en charge de déplacement en congrès : ACR (2004)			
60397	BERENBAUM	Francis	23/08/2005	IP-CF	PFIZER	Prise en charge de déplacement en congrès : ACR (2005)			
60397	BERENBAUM	Francis	23/08/2005	IP-AUT	EXPANSCIENCE	Consultant régulier pour le site web "arthrolink" sponsorisé par les laboratoires Expanscience (2003)			
60397	BERENBAUM	Francis	01/01/2000	IF	MONSANTO	Actions (100)	DPI non datée et non signée		
60397	BERENBAUM	Francis	01/01/2000	LD	WYETH	Consultant			
60397	BERENBAUM	Francis	01/01/2000	IP-EC	BOEHRINGER INGELHEIM	Une étude expérimentales sur des cellules en culture (1998)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60397	BERENBAUM	Francis	01/01/2000	IP-RE	ROD-LINE (Agence de Marketing)	Aceclofenac			
60397	BERENBAUM	Francis	01/01/2000	IP-AC	MONSANTO SEARLE / PFIZER	Stratégie, Advisory Board			
60397	BERENBAUM	Francis	01/01/2000	IP-AC	NOVARTIS	Advisory Board			
60397	BERENBAUM	Francis	01/01/2000	IP-AC	UPSA	Advisory Board			
60397	BERENBAUM	Francis	01/01/2000	IP-CF	WYETH	Actions de formation - Organisation d'un symposium			
60397	BERENBAUM	Francis	01/01/2000	IP-CF	BOEHRINGER INGELHEIM	Conférences (Inhibiteurs spécifiques COX2)			
60397	BERENBAUM	Francis	01/01/2000	IP-CF	MONSANTO SEARLE / PFIZER	Conférences (Inhibiteurs spécifiques COX2)			
60397	BERENBAUM	Francis	01/01/2000	IP-CF	THERABEL	Conférences (Inhibiteurs spécifiques COX2)			
60397	BERENBAUM	Francis	01/01/2000	IP-CF	MERCK	Conférences (Inhibiteurs spécifiques COX2) + corrections d'actions de formation			
62400	BERGERON	Christine	26/03/2009	EC-CO	MTM LABORATOIRES AG	Evaluation du kit cytologique CIN tec® pour la détection de la P 16 dans les frottis en milieu liquide	co-investigateur	04/2007	
62400	BERGERON	Christine	26/03/2009	IP-AC	GSK	" Independent Data Monitoring Committee " (IDMC) sur les vaccins contre le HPV - vaccin cervarix	rémunération personnelle	06/2004	06/2009
62400	BERGERON	Christine	26/03/2009	IP-AC	SANOFI PASTEUR MSD	Comité scientifique : étude impact vaccination et lésions CIN 2/3 dossier DGS	rémunération personnelle	10/2007	
62400	BERGERON	Christine	20/12/2007	IP-AC	SANOFI PASTEUR MSD	Réflexions du groupe d'experts sur la phase d'une vaccination contre le HPV en France - Vaccin Gardasil	Rémunération personnelle	01/2005	12/2006
62400	BERGERON	Christine	20/12/2007	IP-AC	SANOFI PASTEUR MSD	Comité scientifique : Etude Impact Vaccination et lésions CIN2/3 dossier DGS	Rémunération personnelle	09/2007	
62400	BERGERON	Christine	20/12/2007	CF-INT	MTM LABORATORIES AG	Congrès EUROGIN, Monaco, Symposium protéine p16 : présentation sur la p16	Rémunération personnelle	10/2007	10/2007
62400	BERGERON	Christine	20/12/2007	EC-CO	ARKOPHARMA	Etude PHYTOSOYA	Co-investigateur	01/2004	09/2008
62400	BERGERON	Christine	20/12/2007	IP-AC	LABORATOIRE GLAXOSMITHKLINE BIOLOGICALS, BRUXELLES	Réflexions du "Independent Data Monitoring Committee (IDMC)" sur les vaccins contre les Papillomavirus H	Rémunération personnelle	06/2004	06/2009
62400	BERGERON	Christine	14/06/2006	CF-INT	SANOFI PASTEUR MSD	Congrès EUROGIN, Paris, Participation au Symposium et à la conférence de Presse (Vaccin HPV)	Rémunération personnelle	04/2006	04/2006
62400	BERGERON	Christine	14/06/2006	RE-DE	LABORATOIRE GLAXOSMITHKLINE BIOLOGICALS, BRUXELLES	Réflexions du "Independent Data Monitoring Committee (IDMC)" sur les vaccins contre les Papillomavirus H	Rémunération personnelle	06/2004	06/2009
62400	BERGERON	Christine	14/06/2006	RE-DE	LABORATOIRE SANOFI-PASTEUR MSD	Réflexions d'un Groupe d'Experts sur la phase d'une vaccination contre les Papillomavirus Humains en Fran	Rémunération personnelle	01/2005	12/2006
62400	BERGERON	Christine	14/06/2006	EC-CO	IRIS-SERVIER	Biopsie d'endomètre - Produit : Norethisterone continuously combined with a fixed dose of 17B estradiol for	Co-investigateur	01/2000	12/2003
62400	BERGERON	Christine	14/06/2006	EC-CO	THERAMEX	Biopsie d'endomètre - Produit : 17B estradiol+ nomegestrol acetate + NUVELLE	Co-investigateur	01/2000	12/2004
62400	BERGERON	Christine	14/06/2006	EC-CO	ARKOPHARMA	Biopsie d'endomètre - produit :PHYTOSOYA.	Co-investigateur	01/2004	
62400	BERGERON	Christine	15/04/2005	IP-AC	SERVIER	Aérodiol, rémunération personnelle (année 2003-2004)		01/2003	12/2004
62914	BERNARD	Sophie	08/06/2006	EC-CO	TAKEDA, LILLY	Etude internationale multicentrique PROACTIVE (Pioglitazone)	co-investigateur	01/2002	06/2006
62914	BERNARD	Sophie	08/06/2006	CF-INT	FOURNIER,NOVO,MSD,TAKEDA,ASTRA	EPU régulières dans le domaine du diabète, dystipidémie, prévention cardiovasculaire□□2 à 3 fois /an pas (	rémunération personnelle et institution	01/2005	12/2006
62914	BERNARD	Sophie	08/06/2006	CF-AUD	ASTRA, SERVIER, PFIZER	Environ 2 à 3 invitations/an sans laboratoire privilégié		01/2005	12/2006
62914	BERNARD	Sophie	08/06/2006	VB	ASTRA ZENECA	bourse de recherche cardiovasculaire 2005□□Lauréat : Dr S.Bernard	Association Loi 1901 GELAGE		
62914	BERNARD	Sophie	10/03/2006	EC-CO	TAKEDA	essai Proactive (Pioglitazone)	co-investigateur		06/2005
62914	BERNARD	Sophie	10/03/2006	EC-CO	SERVIER	essai S18886 (molécule en développement)	co-investigateur		
62914	BERNARD	Sophie	10/03/2006	CF-INT	PAS DE LABORATOIRE DE PRéDILECTION	EPU pour la FMC des médecins	Aucune rémunération		
62914	BERNARD	Sophie	10/03/2006	CF-AUD	PAS DE LABORATOIRE DE PRéDILECTION		Association GELAGE		
62914	BERNARD	Sophie	10/03/2006	VB	ASTRA-ZENECA	Bourse de recherche cardiovasculaire□□(15000 euros) pour l'achat de consommables pour dosages biologi	(Président Pr Philippe Moulin)		
62914	BERNARD	Sophie	07/04/2005	EC-CO	TAKEDA	Essais cliniques comme co-investigateur au sein de l'équipe du Pr Moulin (Proactive avec Pioglitazone)			
62914	BERNARD	Sophie	07/04/2005	EC-CO	SERVIER	Essais cliniques comme co-investigateur au sein de l'équipe du Pr Moulin (médicament en développement)			
62914	BERNARD	Sophie	07/04/2005	CF-INT	EPU	Université ou médecins libéraux spécialistes ou généralistes de labo de "prédilection"			
62914	BERNARD	Sophie	07/04/2005	IP-AUT		Financement pour le congrès médical (transport, hébergement, inscription)			
62914	BERNARD	Sophie	03/03/2005	EC-CO	SERVIER	Etude S18882	Co-investigateur		
62914	BERNARD	Sophie	03/03/2005	IP-CF		Prise en charge des frais d'inscription, hébergement et transport pour différents congrès pour différents labo			
62914	BERNARD	Sophie	14/11/2003	IP-AUT	PFIZER	Financement congrès - Journées européennes SF Cardio Paris 2003			
62914	BERNARD	Sophie	14/11/2003	IP-AUT	FOURNIER	Financement congrès DALM New York, septembre 2001			
62914	BERNARD	Sophie	14/11/2003	IP-AUT	PARKE DAVIS	Financement congrès Risk CV Venise 1999			
62914	BERNARD	Sophie	14/11/2003	IP-AUT	NOVARTIS	Financement congrès SFE Tours 2002			
62914	BERNARD	Sophie	14/11/2003	IP-AUT	ASTRA ZENECA	Financement congrès EFES Lyon 2003			
62914	BERNARD	Sophie	14/11/2003	VB	SERVIER	Achat d'un échographe pour étude dysfonctionnement paroi vasculaire - Association GELAGE (Loi 1901 Pr	Moulin - Pr Berthezene)		
62914	BERNARD	Sophie	14/11/2003	VB	IPSEN	Bourse SFE 1998 - Association GELAGE, Financement d'un projet de recherche			
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	ROCHE	Formation en immunologie	rémunération personnelle de 400 Euros	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	SERVIER	Douleurs fessières de causes rares ou originales.	Rémunération personnelle de 400 Euros	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-AUD	ABBOTT	Congrès américain de Rhumatologie□□Boston 2007		01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	BMS	Role du lymphocyte T dans la pathogénie des polyarthrites rhumatoïdes. Pas de rémunération à ce jour.	Aucune rémunération	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	LFB	Rhumatisme des hypogammaglibulinémies. Non rémunéré à ce jour.	Aucune rémunération	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	BMS	Role du lymphocyte T dans la pathogénie des polyarthrites rhumatoïdes. pas de rémunération à ce jour.	Aucune rémunération	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	ROCHE	Cours de mise à niveau en immunologie : cellule dendritique, lymphocyte T, lymphocyte B□□rémunération d	Rémunération personnelle	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	LD-AR	SANOFI-AVENTIS	Membre du groupe STPR : recherche clinique sur la mesure de l'activité des polyarthrites rhumatoïdes.	Rémunération personnelle de 400 Euros pour les déplacements bi-annuels à Paris.	01/2008	01/2009
63845	BERTHELOT	Jean-Marie	24/01/2008	EC-CO	ABBOTT	Etude réalisée : suivi à long terme de la tolérance de l'adalimumab dans les polyarthrites rhumatoïdes	Co-investigateur, mas pas de rémunération personnelle: compte de recherche ANPIR géré par le CHU de Nantes	01/2003	12/2009
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	SERVIER	Douleurs fessières d'étiologies rares ou méconnues. (déplacement de 300 kms).	Rémunération personnelle de 400 Euros	11/2007	11/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-AUD	ABBOTT	Congrès américain de Rhumatologie (ACR) à Boston, Novembre 2007		11/2007	11/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	BMS	Role du lymphocyte T dans la pathogénie des polyarthrites rhumatoïdes. Pas de rémunération à ce jour.	Aucune rémunération	12/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	CF-INT	ROCHE	Mise à niveau en Immunologie □□Lymphocytes T et cellules dendritiques□□Lymphocytes B□□Rémunérati	Rémunération personnelle	01/2007	12/2007
63845	BERTHELOT	Jean-Marie	24/01/2008	EC-CO	NOVARTIS	Anticorps anti-IL-1 dans le traitement du syndrome de Muckle-Wells	Co-investigateur, mais pas de rémunération personnelle : compte de recherche ANPIR géré par le CHU de Nantes	09/2007	09/2008
63845	BERTHELOT	Jean-Marie	30/01/2007	LD-AR	AVENTIS	Groupe STPR (conseil sur le choix des traitements des polyarthrites débutants selon leur activité)	aucune rémunération	01/2001	12/2007
63845	BERTHELOT	Jean-Marie	30/01/2007	EC-INV	CHU de Nantes + ABBOTT		investigateur principal	01/2004	12/2007
63845	BERTHELOT	Jean-Marie	30/01/2007	EC-INV	CHU de Nantes	étude rétrospective : évaluation de l'efficacité des anti TNF-alpha chez les SPA (spondylarthrite ankylosante	investigateur principal	01/2006	12/2007
63845	BERTHELOT	Jean-Marie	30/01/2007	EC-CO	Groupement REES/ALCIMED	Etude TC2 : étude sur la prescription de médicaments anti TNF-alpha	collaborateur à l'étude	03/2006	05/2006
63845	BERTHELOT	Jean-Marie	30/01/2007	CF-INT	WYETH	Réunion PRISME - Rennes	aucune rémunération	01/2007	01/2007

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63845	BERTHELOT	Jean-Marie	30/01/2007	CF-INT	ABBOTT	Séminaire post ACR 2006 - Nantes	aucune rémunération		
63845	BERTHELOT	Jean-Marie	30/01/2007	CF-INT	ABBOTT	Séminaires sur lésions structurelles de Polyarthrite Rhumatoïde	Rémunération de 300 euros		
63845	BERTHELOT	Jean-Marie	30/01/2007	CF-INT	ROCHE	3 animations sur le thème de l'immunopathologie de la polyarthrite rhumatoïde (+ mise à niveau)	rémunération de 300€ par réunions	09/2006	01/2007
63845	BERTHELOT	Jean-Marie	30/01/2007	CF-AUD	PFIZER	Congrès Français de Rhumatologie ,		12/2006	12/2006
63845	BERTHELOT	Jean-Marie	10/12/2005	CF-AUD	CF CHAPITRE 2.6 (ERREUR DE CHAPITRE)	Divers congrès de Rhumatologie□□internationaux (et rarement nationaux)		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	EC-CO		Pas de rémunération personnelle : tous dédomagements versés sur le comptede recherche du service de rh		01/1995	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	RE-DE		Toujours fait "gracieusement" jusqu'à ce jour		01/2000	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AC		Idem : pas de rémunération personnelle : tous dédommagements versés sur le compte ANPIR	Investigateur - principal	01/2004	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AC	AVENTIS	Molécule "ARAVA" dans le cadre du groupe de réflexion "GESPER"	Aucune rémunération	01/2002	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	CF-INT	WYETH	Une rémunération acceptée l'an dernier pour un colloque + diaporama sur les modifications dans les polyarth	Rémunération personnelle	02/2005	02/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	PFIZER	3 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	AVENTIS	4 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	NOVARTIS	2 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	ABBOTT	1 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	PHARMASCIENCE	1 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	MERCK	2 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	SEARLE	1 fois		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	ACR	Depuis environ 15 ans : congrès à l'étranger : American Congres of Rhumatology		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-AUT	EULAR	EULAR : European League against rhumatism		01/1990	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	VB	ABBOTT	travail de recherche fondamentale sur le répertoire des lymphocytes et régulateurs dans le contexte des pol	CHU de Nantes	01/2004	01/2004
63845	BERTHELOT	Jean-Marie	20/05/2005	(Autre)	AVENTIS	Groupe d'expert "GESPER" déjà mentionné (molécule : Léflunomide : Arava) pas de compensation financière		01/2002	12/2005
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-EC	CHU Nantes	Etude : évaluation de l'efficacité à la des anti- des SPA avec ou sans critères de		01/2006	12/2007
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-EC	Groupement /ALCIMED	TC2 : étude de la de la prescription de traitements anti-T.N.F.-Alpha		03/2006	05/2006
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-CF	WYETH	Réunion "Prisma" à Rennes		01/2007	
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-CF	ABBOTT	Réunion		01/2007	
63845	BERTHELOT	Jean-Marie	20/05/2005	IP-CF	PFIZER	Congrès français de rhumatologie		12/2006	12/2006
10046	BERTHEZENE	François	04/05/2004	IP-AC	ASTRA ZENECA	Statines (année 2002)			
10046	BERTHEZENE	François	04/05/2004	IP-AC	MERCK-LIPHA	Association fixe d'antidiabétiques (2002-2003)			
10046	BERTHEZENE	François	04/05/2004	IP-AC	SERVIER	Conseils scientifiques (2002-2003)			
10046	BERTHEZENE	François	04/05/2004	IP-AC	PFIZER	Jury de bourses (2003-2004)			
10046	BERTHEZENE	François	04/05/2004	IP-CF	LILLY	Orateur dans des colloques (1999)			
10046	BERTHEZENE	François	04/05/2004	IP-CF	MSD	Orateurs dans des colloques (1999 / 2003)			
10046	BERTHEZENE	François	04/05/2004	IP-CF	TAKEDA	Orateur dans des colloques (2001/2004)			
10046	BERTHEZENE	François	04/05/2004	IP-CF	BAYER	Orateur dans des colloques (2003)			
10046	BERTHEZENE	François	04/05/2004	IP-CF	SERVIER	Orateur dans des colloques (2003/2004)			
10046	BERTHEZENE	François	04/05/2004	IP-CF	NOVO	Orateur dans des colloques (2003)			
10046	BERTHEZENE	François	04/05/2004	IP-AUT	TAKEDA (participation à des congrès)	International endocrinologie (2001/2003)			
10046	BERTHEZENE	François	04/05/2004	IP-AUT	SERVIER (participation à des congrès)	Endocrinologie (2003)			
10046	BERTHEZENE	François	04/05/2004	IP-AUT	PFIZER (depuis 5 ans) participation à des congrès	AHA			
10046	BERTHEZENE	François	04/05/2004	IP-AUT	SERVIER	Achat de matériel pour le service (2003)			
10046	BERTHEZENE	François	04/05/2004	VB	LILLY	Association Claude Bernard	Tous les comptes ne sont plus sous mon nom mais du Pr MOULIN		
10046	BERTHEZENE	François	04/05/2004	VB	NOVO	EZUS Lyon 1	Tous les comptes ne sont plus sous mon nom mais du Pr MOULIN		
10046	BERTHEZENE	François	04/05/2004	VB	MERCK	Naturalia et Biologia	Tous les comptes ne sont plus sous mon nom mais du Pr MOULIN		
10046	BERTHEZENE	François	04/05/2004	VB	SCHERING-PLOUGH, TAKEDA	EZUS Lyon 1	Tous les comptes ne sont plus sous mon nom mais du Pr MOULIN		
10046	BERTHEZENE	François	04/05/2004	VB	BAYER, NOVARTIS,GSK	EZUS Lyon 1	Tous les comptes ne sont plus sous mon nom mais du Pr MOULIN		
10046	BERTHEZENE	François	04/05/2004	(Autre)	MERCK LIPHA, NOVO	Aide à un réseau de prise en charge du diabète de type 2 que je préside			
10046	BERTHEZENE	François	04/05/2004	IP-AUT	FOURNIER (participation à des congrès)	PPAR (2003)			
10046	BERTHEZENE	François	01/09/2003	IP-AC	MERCK-LIPHA	Association fixe d'antidiabétiques (2002- 2003)			
10046	BERTHEZENE	François	01/09/2003	IP-AC	SERVIER	Conseils scientifiques (2002 - sept. 2003)			
10046	BERTHEZENE	François	01/09/2003	IP-AC	PFIZER	Jury de bourse - jusqu'en déc. 2003			
10046	BERTHEZENE	François	01/09/2003	IP-AC	ASTRA ZENECA	Statines - 2002			
10046	BERTHEZENE	François	01/09/2003	IP-CF	TAKEDA	Dyolipidémie diabétique - 2001			
10046	BERTHEZENE	François	01/09/2003	IP-CF	BAYER	Prévention du diabète - 2003			
10046	BERTHEZENE	François	01/09/2003	IP-CF	SERVIER	Traitement du diabète - 2003			
10046	BERTHEZENE	François	01/09/2003	IP-CF	NOVO	L'hormone de croissance chez l'adulte			
10046	BERTHEZENE	François	01/09/2003	IP-CF	MERCK SHARP & DOHME	Traitement dyolopidémies - 2000 (?)			
10046	BERTHEZENE	François	01/09/2003	IP-CF	LILLY	Ménopause et diabète - 1999 (?)			
10046	BERTHEZENE	François	01/09/2003	IP-AUT	PFIZER	Congrès AHA (Rapport Lettre Cardiologues) - depuis 4 ans			
10046	BERTHEZENE	François	01/09/2003	IP-AUT	TAKEDA	Congrès d'endocrinologie - 2001			
10046	BERTHEZENE	François	01/09/2003	IP-AUT	SERVIER	Congrès d'endocrinologie - 2003			
10046	BERTHEZENE	François	01/09/2003	IP-AUT	SERVIER	Achat d'équipement pour le service			
10046	BERTHEZENE	François	01/09/2003	VB	LILLY	Association Claude Bernard			
10046	BERTHEZENE	François	01/09/2003	VB	NOVO	EZUS Lyon 1			
10046	BERTHEZENE	François	01/09/2003	VB	MERCK LIPHA	Naturalia-Biologia			
10046	BERTHEZENE	François	01/09/2003	VB	SCHERING-PLOUGH	EZUS Lyon 1			
10046	BERTHEZENE	François	01/09/2003	VB	BAYER	EZUS Lyon 1			
10046	BERTHEZENE	François	01/09/2003	VB	NOVARTIS	EZUS Lyon 1			
10046	BERTHEZENE	François	18/10/2002	IP-EC	MERCK-LIPHA	Essais de phase II ou III			
10046	BERTHEZENE	François	18/10/2002	IP-AC	SERVIER	Développement produits			
10046	BERTHEZENE	François	18/10/2002	IP-AC	MERCK LIPHA	Intérêt association médicaments			
10046	BERTHEZENE	François	18/10/2002	IP-AC	MSD	Développement produits			

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					ASTRA ZENECA, MSD, PFIZER, GLAXO SMITHKLINE,				
10046	BERTHEZENE	François	18/10/2002	IP-CF	NOVO NORDISK	Endocrinology, lipides, métabolisme			
10046	BERTHEZENE	François	18/10/2002	IP-EC	TAKEDA	Essais de phase II ou III			
10046	BERTHEZENE	François	18/10/2002	IP-EC	LILLY	Essais de phase II ou III			
10046	BERTHEZENE	François	18/10/2002	IP-EC	NOVO NORDISK	Essais de phase II ou III			
10046	BERTHEZENE	François	18/10/2002	IP-EC	KNOLL	Essais de phase II ou III			
10046	BERTHEZENE	François	18/10/2002	IP-EC	MERCK-LIFFA, TAKEDA, LILLY, NOVO-NORDISK, KNOLL	Essais de phase 2 ou 3			
10046	BERTHEZENE	François	18/10/2002	IP-RE			Rien cette année		
10046	BERTHEZENE	François	18/10/2002	IP-AC	SERVIER	Développement produits			
10046	BERTHEZENE	François	18/10/2002	IP-AC	MERCK-LIFFA	Intérêt association médicament			
10046	BERTHEZENE	François	18/10/2002	IP-AC	MSD	Développement produits			
10046	BERTHEZENE	François	18/10/2002	IP-CF	ASTRA ZENECA, MSD, PFIZER, GSK, NOVO-NORDISK	Endocrinology - lipides, métabolisme			
10046	BERTHEZENE	François	19/07/2000	IP-EC	NOVO NORDISK, SHERING PLOUGH, NEGMA, GLAXO, LILLY, ASTRA ZENECA	Nombreux essais - les derniers :			
10046	BERTHEZENE	François	19/07/2000	IP-RE	MSD	Changement RCP pour le Zour			
10046	BERTHEZENE	François	19/07/2000	IP-AC	TAKEDA				
10046	BERTHEZENE	François	19/07/2000	IP-CF		Nombreuses : 3 à 6/an			
63444	BLACHER	Jacques	27/01/2008	CF-INT	INTERVENANT à DE NOMBREUX SYMPOSIUMS DONNANT LIEU PARFIS à DES HONORAIRES DE LA MAJORITé DES INDUSTRIELS COMMERCIALISANT DES ANTIHYPERTENSEURS ET AUTRES DROGUES DE PRéVENTION CARDIOVASCULAIRE	en moyenne, 2 interventions par mois	Rémunération personnelle		
63444	BLACHER	Jacques	27/01/2008	EC-CO	NOVARTIS	ALISKIREN essai thérapeutique ALTITUDE	Co-investigateur	01/2008	
63444	BLACHER	Jacques	22/03/2007	EC-INV	BMS - SANOFI	PLAVIX - étude épidémiologique ATTEST	Investigateur/coordinateur	01/2005	12/2006
63444	BLACHER	Jacques	22/03/2007	EC-CO	INSERM	Vitamines B + Oméga 3 = Sufolom3	Co-investigateur	01/2004	
63444	BLACHER	Jacques	22/03/2007	IP-RE	AFSSAPS	EPLERENONE	Rémunération personnelle	01/2006	
63444	BLACHER	Jacques	22/03/2007	RE-AUT	DRC-PHRC	3 expertises en 2007	Aucune rémunération	01/2007	
63444	BLACHER	Jacques	22/03/2007	CF-AUD	SERVIER	ESH 2006		01/2006	12/2006
63444	BLACHER	Jacques	22/03/2007	CF-AUD	NOVARTIS	ASH 2007		01/2007	
63444	BLACHER	Jacques	22/03/2007	PAR	NOVARTIS	Controleur de gestion - aucun rapport direct avec les produits	Sœur	01/1995	
63444	BLACHER	Jacques	22/03/2007	CF-INT		Nombreuses interventions ces 3 dernières années avec une douzaine d'industriels commercialisant des ant rémunération personnelle			
63444	BLACHER	Jacques	11/10/2004	IP-EC	SANOFI	Conseil scientifique étude attest aprouver			
63444	BLACHER	Jacques	11/10/2004	IP-EC	BMS	Conseil scientifique étude attest aprouver			
63444	BLACHER	Jacques	11/10/2004	IP-CF	SANOFI	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	BMS	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	PFIZER	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	ABBOTT	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	GLAXO WELLCOME	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	AVENTIS	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	BOEHRINGER	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	ASTRA ZENECA	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	SERVIER	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	IP-CF	MENARINI	HTA - Risque cardio vasculaire			
63444	BLACHER	Jacques	11/10/2004	PAR	NOVARTIS	Sœur			
10053	BLAYAC	Jean-Pierre	06/01/2009	Néant					
10053	BLAYAC	Jean-Pierre	25/12/2007	Néant					
10053	BLAYAC	Jean-Pierre	14/12/2006	Néant					
10053	BLAYAC	Jean-Pierre	28/06/2005	IP-RE	SERVIER	Expertise judiciaire / Dexfenfluramine			
10053	BLAYAC	Jean-Pierre	24/05/2004	LD	UNIVERSITE MONTPELLIER III	Chargé de cours, responsable de l'enseignement - Musicothérapie, Département musique			
10053	BLAYAC	Jean-Pierre	24/05/2004	IP-RE		Expertise judiciaire exceptionnellement			
10053	BLAYAC	Jean-Pierre	14/02/2003	Néant					
10053	BLAYAC	Jean-Pierre	22/01/2000	IP-RE	NOVARTIS	Un rapport d'expertise sur 1 cas de pharmacovigilance			
10053	BLAYAC	Jean-Pierre	22/01/2000	IP-CF	LEO	Une conférence : action de formation sur les HBPM			
61323	BLIN	Olivier	13/12/2010	CF-AUD	IMS HEALTH	Advisory board du 16 novembre à Londres		12/2010	12/2010
61323	BLIN	Olivier	13/12/2010	IP-AC	PHARNEXT	Advisory board à juin à Paris	Rémunération personnelle	06/2010	12/2010
61323	BLIN	Olivier	13/12/2010	RE-AUT	HERON HEALTH	Lu AA21004	Rémunération personnelle		
61323	BLIN	Olivier	13/12/2010	RE-AUT	CRCI PACA	Dossier 07-013-c-0207	Rémunération personnelle	06/2010	10/2010
61323	BLIN	Olivier	13/12/2010	EC-CO	CYTHERIS	Hépatite C	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	MITSUBISHI	2 études	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	FERRING	Degarelix	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	GSK	Mélanome	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	MERTCK	Glioblastomeb avec méthylation	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	ASTRA ZENECA	Glioblastome	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	EXILIXIS	K thyroide	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	TEVA	Alstar	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	TROPHOS	Mitotarget	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	MERCK	Vaccin anti K, K bronchopulmonaire non à petites cellules	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	ROCHE	K bronchique non à petites cellules avec métastases cérébrales	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	PFIZER	K poumon non à petites cellules autre que adenoK avec CP751.871	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	BMS	Ipilimumab dans le IK bronchique Phase 2	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	MILLENIUM-QUINTILES	Crohn	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	ALLERGAN_BOTOX	Incontinence vésicale neurogène	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	MERCK	K oesogastrique	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	LILLY	K colorectal métastatique	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	AMGEN	K colorectal	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	BAYER	K hépatocellulaire	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	IPSEN	Etude entéropancréatiques	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	GSK	K du sein	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	AB SCIENCE	Résistances au Glivec	Aide logistique		
61323	BLIN	Olivier	13/12/2010	EC-CO	ARIAD	Sarcome	Aide logistique		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61323 BLIN		Olivier	13/12/2010	EC-CO	PFIZER	Neuroendocrines	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	SCHERING PLOUGH	Sarcome	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	BIOPROJET	Etude neuro	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	SYNOSIA	Etude neuro	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	ARCADIA	Parkinson et démense	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	NEUROSEARCH	Chorée de Huntington	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	AMGEN	Evolve	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	ROCHE	Ostéosarcome	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	BIOCODEX	Etude Modage	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	WYETH	Etude Alzheimer	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	IRIS SERVIER		Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	EISAI	Hyppocampe	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	TEVA		Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	BIOGEN	Extension étude 101 MS	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	SANOFI AVENTIS	LTS 6049	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	PPD/NOVARTIS	Extension étude 2301	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-CO	NOVARTIS	Extension étude 2302- Extension étude 2201	Aide logistique		
61323 BLIN		Olivier	13/12/2010	EC-INV	AVANTAGE NUTRITION/FORTE PHARMA	Etude surpoids et hypercholestérolémie	Investigateur Principal	10/2010	
61323 BLIN		Olivier	13/12/2010	EC-INV	DANONE	Croissance et risque cardiovasculaire	Investigateur Principal	09/2010	
61323 BLIN		Olivier	13/12/2010	IF	LFB	< 5% du capital	<5000 € ou <5% du capital		
61323 BLIN		Olivier	13/12/2010	IF	MEDISCAN	1%	<5000 € ou <5% du capital		
61323 BLIN		Olivier	13/12/2010	IF	EPIDEMIUM	< 5% du capital	<5000 € ou <5% du capital		
61323 BLIN		Olivier	13/12/2010	IF	BIOPHARMED	< 5% du capital	<5000 € ou <5% du capital		
61323 BLIN		Olivier	13/12/2010	IF	QUALISSIMA	Loi innovation - Avis favorable de la Commission de déontologie	<5000 € ou <5% du capital		
61323 BLIN		Olivier	13/12/2010	EC-INV	MAYOLI-SPENDLER	Etude nouvelle lipase MS1819	Investigateur Principal	10/2010	
61323 BLIN		Olivier	17/04/2009	CF-AUD	SERVIER	Congrès européen de Neurologie à Barcelone			
61323 BLIN		Olivier	17/04/2009	RE-DE	UCB PHARMA		Rémunération personnelle		
61323 BLIN		Olivier	17/04/2009	EC-CO	TROPHOS		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	TAHO		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	SERVIER		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	SCHERING		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	SCHERING PLOUGH		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	QUINTILES		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	KENDLE		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	PFIZER		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	NEUROSEARCH ACADIA		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	MUNDI PHARMA		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	MERCK		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	LILLY		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	KENDLE		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	IPSEN		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	EISAI		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	EXILIS		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	BMS		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	BIOPROJET		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	ROCHE		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	BAYER		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	AVANTAGE NUTRITION		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	ASTRA ZENECA		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	ARIAD		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	AMGEN		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	ALLERGAN		Aide logistique		
61323 BLIN		Olivier	17/04/2009	EC-CO	ABSCIENCE		Aide logistique		
61323 BLIN		Olivier	03/03/2009	CF-AUD	SERVIER	Congrès des Pharmacologues du Sud-Est à Montpellier			
61323 BLIN		Olivier	03/03/2009	CF-AUD	PFIZER	Journées Interdisciplinaires à Monaco			
61323 BLIN		Olivier	03/03/2009	CF-AUD	EUTHERAPIE	APA à Washington			
61323 BLIN		Olivier	03/03/2009	CF-INT	SANOFI-AVENTIS	Sarudant à Paris	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	CF-INT	SERVIER	Congrès européen de Barcelone (Valdoxan)□□P2T à clermont-Ferrand	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	CF-INT	BMS	Valence (France)□□Ponte Delgada (Açores)(Ü□Nimes (France)□□Uzès (Franco)	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	IP-AC	UCB	Seglor	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	IP-AC	MAYOLI-SPINDLER	Météoplasmine□□Mégamag	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	IP-AC	PIERRE FABRE	V0191□□Debrumyl	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	RE-AUT	CRCI PACA	Dossiers : 06-013-C0109□□07-013-C-0079□□08-013-C-0034□□	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	RE-DE	CEPHALON	Armolafinil	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	RE-DE	AP-HP	Résilience	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	RE-DE	GW PHARMA	Sativex	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	RE-DE	WYETH	Bapineuzumab	Rémunération personnelle		
61323 BLIN		Olivier	03/03/2009	EC-CO	BIOCODEX		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	WYETH		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	PIERRE FABRE		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	PEPTIMUME		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	GSK		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	TEVA		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	BIOGEN		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	SANOFI-AVENTIS		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-CO	NOVARTIS		Aide logistique		
61323 BLIN		Olivier	03/03/2009	EC-INV	DANONE	Croissance et risques cardiovasculaires	Investigateur Principal		
61323 BLIN		Olivier	03/03/2009	EC-INV	BIOCODEX	Moclobémide	Investigateur Principal		12/2010
61323 BLIN		Olivier	03/03/2009	IF	LFB		<5000 euros ou <5% du capital		
61323 BLIN		Olivier	03/03/2009	IF	EPIDEMIUM	1%	<5000 euros ou <5% du capital		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61323	BLIN	Olivier	03/03/2009	IF	BIOPHARMED	1%	<5000 euros ou <5% du capital		
61323	BLIN	Olivier	03/03/2009	IF	MEDISCAN	1%	<5000 euros ou <5% du capital		
61323	BLIN	Olivier	03/03/2009	IF	QUALISSIMA	Loi innovation - Avis favorable de la Commission de Déontologie	<5000 euros ou <5% du capital		
61323	BLIN	Olivier	03/03/2009	EC-INV	AVANTAGE NUTRITION	Etude de nutrition avec calorimétrie indirecte	Investigateur principal		09/2010
61323	BLIN	Olivier	29/10/2008	IP-AC	SANOFI AVENTIS	SR58611 et Sanudant	Rémunération personnelle	01/2008	01/2008
61323	BLIN	Olivier	29/10/2008	IP-AC	TROPHOS	Aide sur dossiers en cours	Rémunération personnelle	01/2008	01/2008
61323	BLIN	Olivier	29/10/2008	IP-AC	BIOCODEX	Exposé et aide à la rédaction d'article	Rémunération personnelle	01/2008	04/2008
61323	BLIN	Olivier	29/10/2008	IP-AC	EISAI	Assistance scientifique	Rémunération personnelle	06/2008	06/2008
61323	BLIN	Olivier	29/10/2008	RE-AUT	CRCI PACA	DOSSIER 07-013-C-0079	Rémunération personnelle	01/2008	04/2009
61323	BLIN	Olivier	29/10/2008	CF-INT	LEEM RECHERCHE	Ecole du Leem Recherche, Vaux de Cernay	Aucune rémunération	09/2008	09/2008
61323	BLIN	Olivier	29/10/2008	CF-INT	BMS	Abilify no Mundo de Esquizofrenia, à Ponta Delgada (Azores)	Rémunération personnelle	03/2008	03/2008
61323	BLIN	Olivier	29/10/2008	CF-INT	SERVIER	Valdoxan speaker training session, Barcelone	Rémunération personnelle	08/2008	09/2008
61323	BLIN	Olivier	29/10/2008	EC-CO	BIOCODEX		Aide Logistique		
61323	BLIN	Olivier	29/10/2008	EC-INV	DANONE	croissance et risques cardiovasculaires	Investigateur principal	10/2008	12/2012
61323	BLIN	Olivier	29/10/2008	EC-INV	BIOCODEX	Moclobémide	Investigateur Principal	10/2008	12/2009
61323	BLIN	Olivier	29/10/2008	EC-CO	WYETH		Aide Logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	TROPHOS		Aide logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	PIERRE FABRE		Aide Logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	PEPTIMUME		Aide Logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	GLAXOSMITHKLINE		Aide logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	TEVA		Aide logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	BIOGEN		Aide Logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	NOVARTIS		Aide logistique		
61323	BLIN	Olivier	29/10/2008	EC-CO	SANOFI AVENTIS		Aide Logistique		
61323	BLIN	Olivier	29/10/2008	IF	LABORATOIRE FRANCAIS DU FRACTIONNEMENT		<5000 € ou <5% du capital		
61323	BLIN	Olivier	29/10/2008	IF	EPIDEMIUM	1%	<5000 € ou <5% du capital		
61323	BLIN	Olivier	29/10/2008	IF	BIOPHARMED	1%	<5000 € ou <5% du capital		
61323	BLIN	Olivier	29/10/2008	IF	MEDISCAN	1%	<5000 € ou <5% du capital		
61323	BLIN	Olivier	29/10/2008	IF	QUALISSIMA	Loi Innovation-Avis favorable de la commission de Déontologie	<5000 € ou <5% du capital		
61323	BLIN	Olivier	29/10/2008	EC-INV	SANOFI AVENTIS	Kétamine, SSR103800	Investigateur Principal	09/2008	12/2008
61323	BLIN	Olivier	31/10/2007	CF-AUD	VEDIM PHARMA	6ème symposium du CREA - Paris			
61323	BLIN	Olivier	31/10/2007	CF-INT	VEDIM PHARMA	6ème symposium du CREA - Paris	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	RE-AUT	FHF	Formation recherche clinique	Aucune rémunération		
61323	BLIN	Olivier	31/10/2007	RE-AUT	HAS	Psychotropes et sujets agés	Aucune rémunération		
61323	BLIN	Olivier	31/10/2007	EC-INV	MINISTERE DES ARMEES	N2O	Investigateur Principal		
61323	BLIN	Olivier	31/10/2007	CF-INT	SERVIER	APA - San Diego, post APA - Paris	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	CF-INT	BIOCODEX	Etifoxine - Vérone	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	CF-INT	QUATORZEBIS	Acutalités dans la prise en charge au long cours des schizophrénies - Montpellier	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	CF-AUD	SERVIER	APA - San Diego, post APA - Paris			
61323	BLIN	Olivier	31/10/2007	CF-AUD	BIOCODEX	Etifoxine - Vérone			
61323	BLIN	Olivier	31/10/2007	CF-AUD	QUATORZEBIS	Acutalités dans la prise en charge au long cours des schizophrénies - Montpellier			
61323	BLIN	Olivier	31/10/2007	RE-AUT	UCB PHARMA	Seglor	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	EC-INV	MINISTERE DES TRANSPORTS	THC	Investigateur Principal		
61323	BLIN	Olivier	31/10/2007	IP-AC	SERVIER	APA, post APA	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	IP-AC	BIOCODEX	Stresam, Etifoxine	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	IP-AC	MAYOLI SPINDLER	Comité scientifique	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	IP-AC	BOEHRINGER INGELHEIM	Comité scientifique SIFROL	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	IP-AC	SANOFI-AVENTIS	Steering Committee	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	IP-AC	LUNDBECK	Rasagiline	Rémunération personnelle		
61323	BLIN	Olivier	31/10/2007	EC-CO	ASTRA ZENECA		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	TROPHOS		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	WYETH		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	ABBOTT		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	BAYER		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	PFIZER		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	GSK		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	TEVA		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	EISAI		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	IPSEN		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	BIOGEN		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	SANOFI-AVENTIS		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-CO	NOVARTIS		Aide logistique		
61323	BLIN	Olivier	31/10/2007	EC-INV	SERVIER	Piribédil orodispersible, SC-90049-003 - Parkopi	Investigateur principal		
61323	BLIN	Olivier	31/10/2007	EC-INV	SANOFI-AVENTIS	Zolpidem, Eplivanserin, Etude INT6078, level of bone turnover markers	Investigateur principal		
61323	BLIN	Olivier	31/10/2007	EC-INV	BIOCODEX	ETILOR	Investigateur principal		
61323	BLIN	Olivier	31/10/2007	EC-INV	AVANTAGE NUTRITION	Scalime Lactalis	Investigateur Proncipal		
61323	BLIN	Olivier	31/10/2007	EC-INV	INSTITUT DE RECHERCHE PIERRE FABRE	DEANOL, F14679 Oral solution 0.02, 0.05, 0.12, 0.3 and 0.6 mg, L0014 IN (500 mg, 2x500 mg), L00023 GE	Investigateur principal		
61323	BLIN	Olivier	31/10/2007	EC-INV	MERCK-LIPHA	SPIRID-O	investigateur principal		
61323	BLIN	Olivier	31/10/2007	IF	LABORATOIRE FRANCAIS DU FRACTIONNEMENT		<5000 € ou <5% du capital		
61323	BLIN	Olivier	31/10/2007	IF	MEDISCAN	1%	<5000 € ou <5% du capital		
61323	BLIN	Olivier	31/10/2007	IF	BIOPHARMED		<5000 € ou <5% du capital		
61323	BLIN	Olivier	31/10/2007	IF	QUALISSIMA	Loi Innovation	<5000 € ou <5% du capital		
61323	BLIN	Olivier	31/10/2007	IF	EPIDEMIUM		<5000 € ou <5% du capital		
61323	BLIN	Olivier	13/06/2006	(Autre)		Président AFPB, Membre du cabinet du Ministre de la santé et de la protection sociale		06/2004	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61323	BLIN	Olivier	13/06/2006	VB	MERCK LIPHA, PIERRE FABRE, SERVIER, IMMUNOTECH, SANOFI-AVENTIS, MERISTEM, BIOCODEX, DGA, GSK, LFB, BMS, SCHERING-PLOUGH, CHIESI, UCB PHARMA, NOVARTIS, BAYER, ELEKTA, PPD, CRID, ONO, TEVA, KSB, IPSEN, PFIZER, JANSSEN-CILAG, ROCHE-NICHOLAS, BIOPROJET, SERON				
61323	BLIN	Olivier	13/06/2006	IP-AUT	LILLY	Rédaction d'articles scientifiques			
61323	BLIN	Olivier	13/06/2006	IP-AUT	LUNDBECK	Rédaction d'articles scientifiques			
61323	BLIN	Olivier	13/06/2006	IP-AUT	BIOCODEX	Rédaction d'articles scientifiques			
61323	BLIN	Olivier	13/06/2006	IP-CF	BIOCODEX	Spécificités de la dépression chez le sujet âgé			
61323	BLIN	Olivier	13/06/2006	IP-CF	SERVIER	Journées neurologiques de la langue française			
61323	BLIN	Olivier	13/06/2006	IP-CF	BRISTOL MYERS SQUIBB	Schizophrénie & Dopamine			
61323	BLIN	Olivier	13/06/2006	IP-CF	UCB PHARMA	Tardive Dyskinesia			
61323	BLIN	Olivier	13/06/2006	IP-AC	QUALISSIMA	Recueil téléphonique de données			
61323	BLIN	Olivier	13/06/2006	IP-AC	CHIESI	Paroxetine			
61323	BLIN	Olivier	13/06/2006	IP-AC	BRISTOL MYERS SQUIBB	Aripiprazol			
61323	BLIN	Olivier	13/06/2006	IP-AC	PIERRE FABRE	Divers			
61323	BLIN	Olivier	13/06/2006	IP-AC	BIOCODEX	Moclobémide			
61323	BLIN	Olivier	13/06/2006	IP-RE	TROPHOS	Expertise			
61323	BLIN	Olivier	13/06/2006	IP-RE	ANVAR PACA	Expertise			
61323	BLIN	Olivier	13/06/2006	IP-RE	UCB PHARMA	Expertise			
61323	BLIN	Olivier	13/06/2006	IP-EC	MERCK	Essai clinique			
61323	BLIN	Olivier	13/06/2006	IP-EC	BIOCODEX	Travaux scientifiques ponctuels			
61323	BLIN	Olivier	13/06/2006	IP-EC	SCHERING-PLOUGH	Essai clinique			
61323	BLIN	Olivier	13/06/2006	IP-EC	SERVIER	Essai clinique			
61323	BLIN	Olivier	13/06/2006	IF	MEDISCAN	1%			
61323	BLIN	Olivier	13/06/2006	IF	SUD CONSULTING (SARL)	Cession de la totalité des parts			
61323	BLIN	Olivier	13/06/2006	IF	QUALISSIMA (SARL)	Loi Innovation-Avis favorable de la Comm. Déontologie			
61323	BLIN	Olivier	13/01/2005	IF	QUALISSIMA (SARL)	Loi Innovation-Avis favorable de la Comm. Déontologie			
61323	BLIN	Olivier	13/01/2005	IF	SUD CONSULTING (SARL)	Cession de la totalité des parts			
61323	BLIN	Olivier	13/01/2005	IF	MEDISCAN	1%			
61323	BLIN	Olivier	13/01/2005	IP-EC	SERVIER	Essai clinique			
61323	BLIN	Olivier	13/01/2005	IP-EC	SCHERING-PLOUGH	Essai clinique			
61323	BLIN	Olivier	13/01/2005	IP-EC	BIOCODEX	Travaux scientifiques ponctuels			
61323	BLIN	Olivier	13/01/2005	IP-EC	MERCK	Essai clinique			
61323	BLIN	Olivier	13/01/2005	IP-RE	UCB PHARMA	Expertise			
61323	BLIN	Olivier	13/01/2005	IP-RE	ANVAR PACA	Expertise			
61323	BLIN	Olivier	13/01/2005	IP-RE	TROPHOS	Expertise			
61323	BLIN	Olivier	13/01/2005	IP-AC	BIOCODEX	Moclobémide			
61323	BLIN	Olivier	13/01/2005	IP-AC	PIERRE FABRE	Divers			
61323	BLIN	Olivier	13/01/2005	IP-AC	BRISTOL MYERS SQUIBB	Aripiprazol			
61323	BLIN	Olivier	13/01/2005	IP-AC	CHIESI	Paroxetine			
61323	BLIN	Olivier	13/01/2005	IP-AC	QUALISSIMA	Recueil téléphonique de données			
61323	BLIN	Olivier	13/01/2005	IP-CF	UCB PHARMA	Tardive Dyskinesia			
61323	BLIN	Olivier	13/01/2005	IP-CF	BRISTOL MYERS SQUIBB	Schizophrénie & Dopamine			
61323	BLIN	Olivier	13/01/2005	IP-CF	SERVIER	Journées neurologiques de la langue française			
61323	BLIN	Olivier	13/01/2005	IP-CF	BIOCODEX	Spécificités de la dépression chez le sujet âgé			
61323	BLIN	Olivier	13/01/2005	IP-AUT	BIOCODEX	Rédaction d'articles scientifiques			
61323	BLIN	Olivier	13/01/2005	IP-AUT	LUNDBECK	Rédaction d'articles scientifiques			
61323	BLIN	Olivier	13/01/2005	IP-AUT	LILLY	Rédaction d'articles scientifiques			
61323	BLIN	Olivier	13/01/2005	VB	MERCK LIPHA, PIERRE FABRE, SERVIER, IMMUNOTECH, SANOFI-AVENTIS, MERISTEM, BIOCODEX, DGA, GSK, LFB, BMS, SCHERING-PLOUGH, CHIESI, UCB PHARMA, NOVARTIS, BAYER, ELEKTA, PPD, CRID, ONO, TEVA, KSB, IPSEN, PFIZER, JANSSEN-CILAG, ROCHE-NICHOLAS, BIOPROJET, SERON				
61323	BLIN	Olivier	13/01/2005	(Autre)		Président AFPB, Membre du cabinet du Ministre de la santé et de la protection sociale	06/2004		
61323	BLIN	Olivier	12/10/2002	IF	QUALISSIMA	Propo valorisation loi Allègre			
61323	BLIN	Olivier	12/10/2002	IP-EC	LUNDBECK, SANOFI, SERVIER, PIERRE FABRE, ROCHE, NOVARTIS, BIO CODEX, MERCK, TEVA, LILLY				
61323	BLIN	Olivier	12/10/2002	IP-RE	ROCHE, NOVARTIS, MEDISEN, BIOCODEX, MERCK				
61323	BLIN	Olivier	12/10/2002	IP-AC	JANSSEN, LUNDBECK, OTL PHARMA, MERCK, UCB, LILLY, GSK, CHIESI				
61323	BLIN	Olivier	12/10/2002	IP-CF	LUNDBECK, JANSSEN, GLAXO SMITHKLINE				
61323	BLIN	Olivier	12/10/2002	VB	SANOFI, LUNDBECK, JANSSEN				
61323	BLIN	Olivier	06/02/2002	IP-EC	PIERRE FABRE, UCB, JANSSEN, AVENTIS, NOVARTIS				
61323	BLIN	Olivier	06/02/2002	IP-EC	SERVIER, LILLY, GSK, SANOFI-SYNTHELABO, IPSEN				
61323	BLIN	Olivier	06/02/2002	IP-RE	JANSSEN, GSK, SERVIER, PHARMACIA UPJOHN, BIOCODEX, ROCHE				
61323	BLIN	Olivier	06/02/2002	IP-AC	GSK, UCB, PFIZER, JANSSEN, BIOCODEX, ROCHE, LILLY				
61323	BLIN	Olivier	06/02/2002	IP-CF	JANSSEN CILAG, PFIZER, LILY, GSK				
61323	BLIN	Olivier	06/02/2002	VB	PIERRE FABRE, UCB, JANSSEN, LILLY, ROCHE, AVENTIS, NOVARTIS, MERCK, GSK, SERVIER	AP-HM			
61323	BLIN	Olivier	10/01/2001	IF	SUD Consulting (SARL)				
61323	BLIN	Olivier	10/01/2001	IP-EC	PIERRE FABRE				
61323	BLIN	Olivier	10/01/2001	IP-RE	BIOCODEX				
61323	BLIN	Olivier	10/01/2001	IP-AC	ROCHE				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61323	BLIN	Olivier	10/01/2001	IP-CF	Glaxo, Pfizer, SB, Pharmacia, Sanofi Synthelabo, Janssen, SB				
61323	BLIN	Olivier	10/01/2001	VB	Pharmacia - Ipsen, Aventis - Janssen, Biocodex - Laphal, Biogen - Lilly, Servier, Sumitomo, Teva, Solvay, Ipsor				
61323	BLIN	Olivier	10/01/2001	IF	QUALISSIMA (SARL)				
61323	BLIN	Olivier	10/01/2001	IP-EC	PHARMACIA UPJOHN				
61323	BLIN	Olivier	10/01/2001	IP-EC	JANSSEN CILAG				
61323	BLIN	Olivier	10/01/2001	IP-EC	AVENTIS				
61323	BLIN	Olivier	10/01/2001	IP-EC	TEVA				
61323	BLIN	Olivier	10/01/2001	IP-RE	JANSSEN CILAG				
61323	BLIN	Olivier	10/01/2001	IP-RE	PHARMACIA UPJOHN				
61323	BLIN	Olivier	10/01/2001	IP-RE	SYNTHELABO				
61323	BLIN	Olivier	10/01/2001	IP-AC	SERVIER				
61323	BLIN	Olivier	10/01/2001	IP-AC	PIERRE FABRE				
61323	BLIN	Olivier	10/01/2001	IP-AC	JANSSEN CILAG				
61323	BLIN	Olivier	10/01/2001	IP-AC	LILLY				
61323	BLIN	Olivier	10/01/2001	IP-AC	SB				
61323	BLIN	Olivier	10/01/2001	IP-AC	NOVARTIS				
61323	BLIN	Olivier	10/01/2001	IP-AC	SOLVAY				
61323	BLIN	Olivier	10/01/2001	IP-AC	BIOCODEX				
61323	BLIN	Olivier	10/01/2001	IP-AC	PFIZER				
61207	BLOTMAN	Francis	28/06/2009	LD-AR	CHAINE THERMALE DU SOLEIL	Conférences d'information	rémunération personnelle	01/2004	
61207	BLOTMAN	Francis	28/06/2009	EC-INV	ROCHE GSK	Ostéoporose - Bonviva - étude épidémiologiques - Ostepi et Postepi	comité scientifique	01/2004	12/2009
61207	BLOTMAN	Francis	28/06/2009	EC-CO	SERVIER	Protelos	expérimentateur	01/2001	12/2005
61207	BLOTMAN	Francis	28/06/2009	EC-CO	SERVIER	Protelos - suivi épidémiologique	expérimentateur	01/2008	
61207	BLOTMAN	Francis	28/06/2009	EC-CO	PFIZER	Pregabaline	expérimentateur	01/2006	12/2008
61207	BLOTMAN	Francis	28/06/2009	EC-CO	ROCHE GSK	Bonviva	expérimentateur	01/2008	12/2009
61207	BLOTMAN	Francis	28/06/2009	IP-AC	PIERRE FABRE	Groupes de travail "entretiens du Carla"	rémunération personnelle	01/2004	12/2007
61207	BLOTMAN	Francis	28/06/2009	CF-INT	ROCHE	Société de rhumatologie - Bonviva - symposium satellite - Paris	aucune rémunération	01/2007	12/2007
61207	BLOTMAN	Francis	28/06/2009	CF-INT	IPSEN	CIPPEG - Montpellier 2009	aucune rémunération	01/2009	12/2009
61207	BLOTMAN	Francis	28/06/2009	CF-INT	PROCTER GAMBLE	Work shops annuels : Actonel	aucune rémunération	01/2006	12/2009
61207	BLOTMAN	Francis	28/06/2009	CF-INT	PIERRE FABRE	Traitements fibromyalgie - Zurich	rémunération personnelle	01/2008	12/2008
61207	BLOTMAN	Francis	28/06/2009	CF-INT	PIERRE FABRE	Information - Paris Sénat	rémunération personnelle	01/2006	12/2006
61207	BLOTMAN	Francis	28/06/2009	CF-INT	PIERRE FABRE	Musée de Cluny - Paris	rémunération personnelle	01/2007	12/2007
61207	BLOTMAN	Francis	28/06/2009	CF-INT		Multiples réunions de FMC région		01/2007	12/2007
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	PROCTER et SANOFI	Société française de rhumatologie - Actonel - Paris		01/2008	12/2008
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	SERVIER	Congrès européen rhumatologie - Protelos - Copenhague		01/2009	12/2009
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	AMGEN	Congrès ECTS - Denosumab - Vienne		01/2009	12/2009
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	PFIZER	ACR - San Francisco		01/2008	12/2008
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	IPSEN	Vitamine D - Royaumont		01/2009	12/2009
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	NOVARTIS	ECCEO - Aclasta - Athènes		01/2009	12/2009
61207	BLOTMAN	Francis	28/06/2009	CF-AUD	PROCTER - SANOFI AVENTIS	ASBMR - Actonel - Montréal		01/2008	12/2008
61207	BLOTMAN	Francis	09/09/2004	LD	SNCF	Consultations			
61207	BLOTMAN	Francis	09/09/2004	LD	ANAES	Collège (1999-2005)			
61207	BLOTMAN	Francis	09/09/2004	IP-EC	LABORATOIRE GENEVRIER	Essai Chondrosulf			
61207	BLOTMAN	Francis	09/09/2004	IP-EC	LABORATOIRE SERVIER	Essai Roneleti Stromtium			
61207	BLOTMAN	Francis	09/09/2004	IP-EC	LABORATOIRE MSD	Essai Actonel vs Fosamax			
61207	BLOTMAN	Francis	09/09/2004	IP-EC		Essai Celebrex			
61207	BLOTMAN	Francis	09/09/2004	IP-CF	LABORATOIRE AVENTIS	EPU : groupes experts			
61207	BLOTMAN	Francis	09/09/2004	IP-CF	LABORATOIRE LILLY	EPU : Evista			
61207	BLOTMAN	Francis	09/09/2004	IP-CF	LABORATOIRE MSD				
61207	BLOTMAN	Francis	09/09/2004	IP-CF	LABORATOIRE PIERRE FABRE	Congrès			
61207	BLOTMAN	Francis	09/09/2004	IP-AUT	LABORATOIRE MAYOLY SPINDER	Participation Paris Task Forces, sponsorisation			
61207	BLOTMAN	Francis	09/09/2004	IP-AUT	LABORATOIRE PIERRE FABRE	Groupe de travail			
60723	BOISSEL	Jean-Pierre	28/08/2006	IP-AC	SANOFI-AVENTIS	mise à jour des données actuelles de la science sur l'efficacité clinique des anti-agrégants	Rémunération institution	01/2006	12/2006
60723	BOISSEL	Jean-Pierre	28/08/2006	EC-CO	SANOFI-AVENTIS	modèle d'effet du clopidogrel	conseiller méthodologique	01/2006	12/2006
60723	BOISSEL	Jean-Pierre	28/08/2006	EC-INV	SERVIER	exploration des conditions de transposabilité (pas de produit spécifique)	directeur du projet		
60723	BOISSEL	Jean-Pierre	28/08/2006	EC-INV	SERVIER	modélisation mode d'action Ivabradine	directeur du projet	01/2006	12/2008
60723	BOISSEL	Jean-Pierre	25/01/2004	(Autre)	INNATE PHARMA	Enfant			
60723	BOISSEL	Jean-Pierre	25/01/2004	IP-RE	MERCK LIPHA				
60723	BOISSEL	Jean-Pierre	25/01/2004	IP-AC	SERVIER		Aucune rémunération		
60723	BOISSEL	Jean-Pierre	25/01/2004	IP-CF	WYETH				
60723	BOISSEL	Jean-Pierre	25/01/2004	IP-CF	AVENTIS				
60723	BOISSEL	Jean-Pierre	25/01/2004	IF	RCTS	Actionnaire	>=5000 € ou >=5% du capital		
60723	BOISSEL	Jean-Pierre	29/05/2002	IF	SANOFI SYNTHELABO	Actions (10)			
60723	BOISSEL	Jean-Pierre	29/05/2002	IP-EC	LILLY	Ruth			
60723	BOISSEL	Jean-Pierre	29/05/2002	IP-EC	PHARMACIA	Ephesus			
60723	BOISSEL	Jean-Pierre	29/05/2002	IP-EC	AVENTIS	Diabmycar			
60723	BOISSEL	Jean-Pierre	29/05/2002	IP-AC	SERVIER	Développement			
60723	BOISSEL	Jean-Pierre	29/05/2002	IP-CF	WYETH	Formation EC			
60723	BOISSEL	Jean-Pierre	29/05/2002	IP-CF	AVENTIS	Formation EC et RC			
60723	BOISSEL	Jean-Pierre	29/05/2002	VB		Les cas ci-dessus			
63153	BOISSIER	Marie-Christophe	24/03/2005	IP-AC	NEOVACS	membre du Comité de pilotage. Produit anti TMC			
63153	BOISSIER	Marie-Christophe	24/03/2005	EC-CO	ABBOTT	Humira	co-investigateur		
63153	BOISSIER	Marie-Christophe	24/03/2005	EC-CO	ROCHE	MRA	co-investigateur		
63153	BOISSIER	Marie-Christophe	24/03/2005	CF-AUD	WYETH	congrès de l'ACR (American College of Rheumatology) - 2000/2005			12/2000
63153	BOISSIER	Marie-Christophe	24/03/2005	CF-AUD	MERCK	congrès annuel EULAR - 2000/2005			
63153	BOISSIER	Marie-Christophe	24/03/2005	CF-AUD	SERVIER	congrès SFR (Société Française de Rhumatologie) - 200/2005			
63153	BOISSIER	Marie-Christophe	24/03/2005	VB	AMGEN, WYETH, MERCK, ABBOTT	Associations à but non lucratif : Aurore et Recherche; Naturaliael Biologia; Claude Bernard. Il s'agit de dons (entre 2001 et 2005)			
63153	BOISSIER	Marie-Christophe	24/03/2005	VB	EXPANCIENCES	Aurore et Recherche, association à but non lucratif			
63153	BOISSIER	Marie-Christophe	24/03/2005	PAR	Revue du Rhumatisme	Rédacteur en bref dans la Revue du Rhumatisme (organe officiel de la Société Française de Rhumatologie). La revue du Rhumatisme a des contrats de prestations			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63153	BOISSIER	Marie-Christophe	24/03/2005	EC-CO	AMGEN	Kineret	co-investigateur		
63153	BOISSIER	Marie-Christophe	24/03/2005	CF-AUD	AMGEN	Congrès ASBM - 2000/2005			
63153	BOISSIER	Marie-Christophe	24/03/2005	CF-AUD	LILLY				
63153	BOISSIER	Marie-Christophe	24/03/2005	(Autre)		Rédacteur en chef de la revue Rhumatisme (organe officiel de la Société Française de Rhumatologie)	La revue Rhumatisme a des contrats de prestataires		
63153	BOISSIER	Marie-Christophe	06/02/2004	IP-AC	NEOVACS	Steering Comitee			
63153	BOISSIER	Marie-Christophe	06/02/2004	VB	WYETH	Aurore et Recherche (Association L. 1901 ou syndicat professionnel)			
63153	BOISSIER	Marie-Christophe	06/02/2004	VB	ABBOTT	Aurore et Recherche - Association Claude Bernard, Naturalia et Biologia (Association L. 1901 ou syndicat professionnel)			
63153	BOISSIER	Marie-Christophe	06/02/2004	VB	AMKEN	Association Claude Bernard, Naturalia et Biologia (Association L. 1901 ou syndicat professionnel)			
63153	BOISSIER	Marie-Christophe	06/02/2004	VB	PHARMASCIENCES	Aurore et Recherche (Association L. 1901 ou syndicat professionnel)			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-EC	PIERRE FABRE	Essai clinique phase III	Essais cliniques 1999-2000		
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-EC	HOECHST MARION ROUSSEL	Essai clinique phase I			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-EC	SERVIER (IRIS)	Essai clinique phase III			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-EC	NOVARTIS	Essai clinique phase II			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-EC	BIORGA	Essai clinique phase III			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-RE	PIERRE FABRE				
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-CF	PIERRE FABRE	Formation continue : pas de rémunération personnelle mais prestation de type repas ou défraiement par des voyages, etc.			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-CF	LEO	Formation continue : Idem			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-CF	SANOFI	Formation continue : Idem			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-AUT	ROCHE POSAY	Fondation, participation à un jury (prix scientifique)			
60747	BONERANDI	Jean-Jacques	31/03/2000	IP-AUT	COLOPLAST	Fondation, participation à un jury (prix scientifique)			
60747	BONERANDI	Jean-Jacques	31/03/2000	VB	LIPHA SANTE	Essai clinique - Association			
60747	BONERANDI	Jean-Jacques	31/03/2000	VB	ASTRA MEDICA	Essai clinique - Association			
60747	BONERANDI	Jean-Jacques	31/03/2000	VB	GENETRONICS	Essai clinique - Association			
60221	BONEU	Bernard	04/07/2005	IP-AC	ASTRA ZENECA	Advisory board (Exanta)			
60221	BONEU	Bernard	04/07/2005	IP-AC	SERVIER	Comitee de safety d'un essai d'un antiagrégant			
60221	BONEU	Bernard	04/07/2005	IP-CF	LEO, SANOFI, AVENTIS, ASTRA ZENECA	Pharmacologie des antithrombotiques			
60221	BONEU	Bernard	14/03/2005	IP-EC	ARIXTRA	Phase I, investigateur			
60221	BONEU	Bernard	14/03/2005	IP-EC	PLAVIX	Phase II, investigateur			
60221	BONEU	Bernard	14/03/2005	IP-EC	SANOFI	investigateur			
60221	BONEU	Bernard	14/03/2005	IP-AC	LEO	Innohep, octobre 2004			
60221	BONEU	Bernard	25/08/2003	IP-EC	LEO	Pharmacocinétique Tirizoparine - 1999			
60221	BONEU	Bernard	25/08/2003	IP-EC	SERVIER	Pharmacocinétique S18886 - 2001			
60221	BONEU	Bernard	25/08/2003	IP-EC	SERVIER	Membre comité DS MB - Etude pilote phase III S18886 - 2003			
60221	BONEU	Bernard	25/08/2003	IP-AC	ASTRA ZENECA	Membre Advisory Board			
60221	BONEU	Bernard	25/08/2003	IP-CF	SANOFI SYNTHELABO	Conférences, informations sur Arixtra			
60221	BONEU	Bernard	25/08/2003	IP-AUT	LEO	Invitation Birmingham (2003) - Congrès Société internationale thrombose hématologie			
60221	BONEU	Bernard	25/08/2003	IP-AUT	ASTRA ZENECA	Invitation congrès American society hematology - Philadelphie, déc. 2002			
60221	BONEU	Bernard	25/08/2003	IP-AUT	ASTRA ZENECA	Invitation congrès ASH, San Diego, déc. 2003			
60221	BONEU	Bernard	10/07/2000	IP-EC	LEO	Pharmacocinétique Immotep			
60221	BONEU	Bernard	10/07/2000	IP-EC	SANOFI	Pharmacocinétique Fraxodi			
60221	BONEU	Bernard	10/07/2000	IP-AC	SANOFI	Conseil jusqu'en 1999			
60221	BONEU	Bernard	10/07/2000	IP-CF	SANOFI, LEO, AVENTIS, PHARMACIA UPJOHN	Nombreux enseignements post-universitaires sur héparines			
60221	BONEU	Bernard	19/01/2000	IP-EC	HSPM, SANOFI, LEO	Etudes pharmacocinétiques			
60221	BONEU	Bernard	19/01/2000	IP-AC	SANOFI	Conseil			
60221	BONEU	Bernard	19/01/2000	IP-CF	SANOFI, LEO, RHONE POULENC	Participation à EPU			
10058	BONGRAND	Marie-Claude	24/09/2010	CF-INT	LABORATOIRES SCHERING-PLOUGH	Journées Pharmaceutiques □□"Plan de Gestion des Risques des Médicaments"□□Bordeaux 24 et 25 juin 2	Aucune rémunération	06/2010	06/2010
10058	BONGRAND	Marie-Claude	24/09/2010	IP-AUT	LABORATOIRES GSK	ICAAC□□Boston USA □□12-15 septembre 2010	Prise en charge déplacement et hébergement		
10058	BONGRAND	Marie-Claude	24/09/2010	CF-AUD	LABORATOIRES JANSSENN-CILAG	Présentation de l'étude CGS (Cohorte Générale Shizophrénie)□□PARIS	Hébergement pris en charge mais pas de frais de déplacement	09/2010	09/2010
10058	BONGRAND	Marie-Claude	24/09/2010	IP-AC	LABORATOIRES LILLY	membre du comité scientifique pour les journées destinées aux Pharmaciens Hospitaliers□□PARIS	Aucune rémunération	07/2010	01/2011
10058	BONGRAND	Marie-Claude	11/02/2010	CF-AUD	NOVARTIS	"Le pharmacien hospitalier et la prise en charge du sujet agé"□□PARIS		12/2009	12/2009
10058	BONGRAND	Marie-Claude	11/02/2010	CF-AUD	SANOFI AVENTIS	24ème Journées Pharmaceutiques □□"Vieillissement, génomique : deux enjeux majeurs de société"□□PAR		11/2009	11/2009
10058	BONGRAND	Marie-Claude	11/02/2010	CF-AUD	NOVARTIS	ESMO 34ème Congres European Society for Medical Oncology□□BERLIN		09/2009	09/2009
10058	BONGRAND	Marie-Claude	11/02/2010	CF-AUD	JANSSEN-CILAG	6ème Journée des Pharmaciens Hospitaliers□□PARIS		10/2009	10/2009
10058	BONGRAND	Marie-Claude	11/02/2010	CF-AUD	NOVARTIS	Journées de Pharmacie Hospitalières□□PARIS		09/2009	09/2009
10058	BONGRAND	Marie-Claude	26/02/2009	CF-AUD	PFIZER	49ème ICAAC WASHINGTON □□USA		10/2008	10/2008
10058	BONGRAND	Marie-Claude	26/02/2009	CF-AUD	SANOFI AVENTIS	XXIII journées pharmaceutiques annuelles - Paris		11/2008	11/2008
10058	BONGRAND	Marie-Claude	26/02/2009	CF-INT	ROCHE	Membre du jury pour la bourse SFPC-ROCHE pour les pharmaciens hospitaliers (Société française de pharr	aucune rémunération		
10058	BONGRAND	Marie-Claude	26/02/2009	IP-AC	SCHERING PLOUGH	Groupe experts pharmaciens hospitaliers	Aucune rémunération	01/2009	12/2009
10058	BONGRAND	Marie-Claude	26/02/2009	CF-INT	ACTELION	Membre du jury pour la bourse SFPC-ACTELION pour les pharmaciens hospitaliers□□(Société française de	aucune rémunération		
10058	BONGRAND	Marie-Claude	26/02/2009	CF-INT	MSD	Membre du jury pour la bourse MSD-HOPIPHARM pour les pharmaciens hospitaliers	aucune rémunération		
10058	BONGRAND	Marie-Claude	26/02/2009	IP-AC	JANSSEN CILAG	Membre du board "pharmaciens hospitaliers"	aucune rémunération		
10058	BONGRAND	Marie-Claude	26/02/2009	IP-AC	SANOFI AVENTIS	Membre du comité de rédaction de "Dialog Hopital" : lettre d'information destinée aux pharmaciens des hôpi	rémunération institution	01/2009	12/2009
10058	BONGRAND	Marie-Claude	12/02/2008	IP-AC	SANOFI AVENTIS	membre du comité de rédaction de "Dialog Hopital" : lettre d'information destinée aux pharmaciens des hopi	Aucune rémunération		
10058	BONGRAND	Marie-Claude	12/02/2008	CF-AUD	SANOFI AVENTIS	Istanbul (Turquie) 36ème congrès ESCP (European Society of Clinical Pharmacy)		10/2007	10/2007
10058	BONGRAND	Marie-Claude	12/02/2008	CF-AUD	ASTRAZENECA	Marseille : journées pharmaciens hospitaliers □□Pharmacie clinique en oncologie□□Ateliers professionnels		01/2008	01/2008
10058	BONGRAND	Marie-Claude	12/02/2008	CF-AUD	CELGENE	PARIS : 1er atelier hématologie		10/2007	10/2007
10058	BONGRAND	Marie-Claude	12/02/2008	CF-AUD	GILEAD	Paris : journée antifungiques		03/2007	03/2007
10058	BONGRAND	Marie-Claude	12/02/2008	CF-AUD	JANSSEN CILAG	ICAAC 2007 CHICAGO USA		09/2007	09/2007
10058	BONGRAND	Marie-Claude	12/02/2008	CF-INT	MSD	Marseille : exposé aux nouveaux délégués réseau VIH : role du pharmacien, comedims, corevi, dispensatio	Aucune rémunération	11/2007	11/2007
10058	BONGRAND	Marie-Claude	12/02/2008	CF-INT	MEDIATION SANTE / SCHERING PLOUGH	Aix en provence□□"Contral de Bon Usage et sécurité pour le patient"	Aucune rémunération	01/2008	01/2008
10058	BONGRAND	Marie-Claude	12/02/2008	CF-INT	LFB	PARIS : 4èmes RCP :Rencontres Clinique Pharmaciens. Thème : EPP, communication pharmacien-patient,	Aucune rémunération	12/2007	12/2007
10058	BONGRAND	Marie-Claude	12/02/2008	CF-INT	AMGEN	Marseille□□"Actualités en biothérapie" □□Prise en charge des innovations en biothérapie	Aucune rémunération	10/2007	10/2007
10058	BONGRAND	Marie-Claude	23/01/2007	CF-AUD	CELGENE	Premières journées d'études sur le myélome - Paris		11/2006	11/2006
10058	BONGRAND	Marie-Claude	23/01/2007	CF-AUD	SANOFI AVENTIS	21ème journées pharmaceutiques - Paris	Thème : comportements à risques et société : vers une science des crises	11/2006	11/2006
10058	BONGRAND	Marie-Claude	23/01/2007	CF-AUD	ACTELION	4ème journées HTAP - Paris		11/2006	12/2006
10058	BONGRAND	Marie-Claude	23/01/2007	CF-AUD	PFIZER	1ères journées PREMIUM des pharmaciens hospitaliers - Paris		05/2006	05/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10058	BONGRAND	Marie-Claude	23/01/2007	CF-AUD	JANSSEN CILAG	Visite du centre de recherche Beerse - Belgique		06/2006	06/2006
10058	BONGRAND	Marie-Claude	23/01/2007	CF-AUD	MSD (MERCK SHARP & DOHME-CHIBRET	Congrès ICAAC - San Francisco USA		09/2006	09/2006
10058	BONGRAND	Marie-Claude	16/02/2006	CF-AUD	BMS	Paris / Syndrome métabolique et VIH		01/2006	01/2006
10058	BONGRAND	Marie-Claude	16/02/2006	CF-AUD	GILEAD	41ème congrès de l'ASHP (American Society of Health-system Pharmacists) à Las Vegas -USA		12/2005	12/2005
10058	BONGRAND	Marie-Claude	16/02/2006	CF-AUD	ROCHE	Marseille / Le marketing à l'hopital, comment valoriser l'offre de service au sein de l'établissement, l'innovati		06/2005	06/2005
10058	BONGRAND	Marie-Claude	16/02/2006	CF-AUD	CHUGAI	Stockholm / Congrès ESCP European Society of Clinical Pharmacy / Integrating Research, Education and C		05/2005	05/2005
10058	BONGRAND	Marie-Claude	16/02/2006	CF-AUD	SANOFI AVENTIS	Paris / XXèmes Journées Pharmaceutiques : La nouvelle Gouvernance Hospitalière		11/2005	11/2005
10058	BONGRAND	Marie-Claude	16/02/2006	CF-INT	AMGEN	Marseille/Biomédicaments , enjeux, perspectives et nouveau role du pharmacien/Sortie de la réserve hospit	Aucune rémunération	10/2005	10/2005
10058	BONGRAND	Marie-Claude	13/04/2005	CF-AUD	AMGEN, ASTRAZENECA, AVENTIS, BAYER, BMS, LILLY, GILEAD, GSK, JANSSEN CILAG, LFB, LUNDBECK, MSD, NOVARTIS, PFIZER, PIERRE FABRE, ROCHE, SANOFI, SERVIER, SCHERING PLOUGH, SOLVAY				
10058	BONGRAND	Marie-Claude	17/04/2003	VB	SOCIETE FRANCAISE PHARMACIE CLINIQUE (SFPC)	Trésorier adjoint			
10058	BONGRAND	Marie-Claude	17/04/2003	VB	ORGANISATION REGIONALE DES PHARMACIES HOSPITALIERES DE L'EST MEDITERRANEEN (ORPHEM)	Trésorier			
10058	BONGRAND	Marie-Claude	25/09/2000	Néant					
63164	BONNET	Damien	07/06/2010	LD-AR	ABBOTT	Conseil scientifique/suivi de cohorte/palivizumab	Rémunération institution	06/2005	05/2010
63164	BONNET	Damien	07/06/2010	EC-INV	ACTELION	Essai thérapeutique/pharmacocinétique pédiatrique/bosentan	Coordonateur national	05/2005	06/2010
63164	BONNET	Damien	07/06/2010	EC-INV	SERVIER	Essai thérapeutique/Procoralan	Coordonateur national	09/2010	
63164	BONNET	Damien	07/06/2010	EC-CO	GSK	Essai thérapeutique/Ambrisentan	Co-investigateur/steering committee member	09/2010	
63164	BONNET	Damien	07/06/2010	CF-INT	ACTELION	JF HTAP/ Hypertension pulmonaire des cardiopathies congénitales/bosentan	Rémunération personnelle	12/2009	06/2010
62805	BONNET	Fabrice	20/07/2009	EC-INV	SANOFI AVENTIS	Etude clinique (AVE 0010)	coordonnateur	09/2008	07/2009
62805	BONNET	Fabrice	20/07/2009	RE-AUT	HAS	Expertise pour commission de transparence	rémunération personnelle	07/2008	12/2009
62805	BONNET	Fabrice	20/07/2009	CF-INT	MSD	Réunions Januvia/ Inegy - Rennes	rémunération personnelle	09/2008	07/2009
62805	BONNET	Fabrice	20/07/2009	CF-INT	TAKEDA	Réunions Candesartan - Rennes	rémunération personnelle	07/2009	07/2009
62805	BONNET	Fabrice	20/07/2009	CF-INT	PIERRE FABRE	Réunion Xelevia - St Malo	rémunération personnelle	06/2009	06/2009
62805	BONNET	Fabrice	20/07/2009	CF-AUD	SERVIER	Congrès ALFEFIAM		03/2008	03/2008
62805	BONNET	Fabrice	20/07/2009	CF-AUD	SERVIER	Congrès EASD		09/2008	09/2008
62805	BONNET	Fabrice	20/07/2009	VB	NOVARTIS	Don association	RAC	06/2009	06/2009
62805	BONNET	Fabrice	26/11/2008	EC-INV	SANOFI AVENTIS	Coordonnateur étude clinique (AVE 0010) anti-diabétique injectable	coordonnateur	09/2008	09/2010
62805	BONNET	Fabrice	26/11/2008	RE-AUT	HAS	Expertise pour commission transparence (Rimonabant)	rémunération personnelle	07/2008	08/2008
62805	BONNET	Fabrice	26/11/2008	CF-INT	MSD	Réunion Januvia - Rennes	rémunération personnelle	03/2008	09/2008
62805	BONNET	Fabrice	26/11/2008	CF-INT	MSD	Réunion Inegy - Rennes	rémunération personnelle	03/2008	09/2008
62805	BONNET	Fabrice	26/11/2008	CF-AUD	SERVIER	Congrès ALFEDIAM		03/2008	03/2008
62805	BONNET	Fabrice	26/11/2008	CF-AUD	SERVIER	Congrès EASD		09/2008	09/2008
62805	BONNET	Fabrice	26/11/2008	VB	SERVIER	Don à l'association	NSFA	09/2007	09/2007
63164	BONNET	Damien	27/08/2008	LD-AR	ABBOTT	Conseil scientifique, suivi de cohorte - Palivizumab	rémunération institution	06/2005	
63164	BONNET	Damien	27/08/2008	EC-INV	ACTELION	Essai thérapeutique pharmacocinétique pédiatrique - Bosentan	coordonnateur national	05/2005	
63164	BONNET	Damien	27/08/2008	EC-CO	SANOFI-SYNTHELABO	Essai thérapeutique pharmacocinétique - clopidogrel	investigateur	05/2004	05/2006
63164	BONNET	Damien	27/08/2008	EC-CO	SANOFI-SYNTHELABO	Essai thérapeutique - Clopidogrel	Investigateur - steering committee member	03/2007	12/2008
63164	BONNET	Damien	27/08/2008	RE-DE	HAS	Commission transparence : PEDEA (Orphan- europe)	aucune rémunération	01/2005	
63164	BONNET	Damien	27/08/2008	RE-DE	AFSSAPS	European Paediatric worksharing project : COZAAR (Losartan)	rémunération personnelle	01/2007	
63164	BONNET	Damien	27/08/2008	IP-AC	HAS	Groupe d'évaluation centres de référence maladies rares	aucune rémunération	01/2005	
63164	BONNET	Damien	27/08/2008	CF-INT	ACTELION	Journées françaises d'HTAP - Paris - HTAP chez l'enfan - Bosentan	rémunération personnelle	06/2005	
63164	BONNET	Damien	18/07/2007	LD-AR	ABBOTT	Conseil scientifique / suivi de cohorte / Palivizumab	rémunération versée à une institution	06/2005	
63164	BONNET	Damien	18/07/2007	EC-INV	ACTELION	Essai thérapeutique / pharmacocinétique pédiatrique / Bosentan	coordonnateur national	05/2005	
63164	BONNET	Damien	18/07/2007	EC-CO	SANOFI SYNTHELABO	Essai thérapeutique / pharmacocinétique / Clopidogrel	investigateur	05/2004	05/2006
63164	BONNET	Damien	18/07/2007	EC-CO	SANOFI SYNTHELABO	Essai thérapeutique / Clopidogrel	investigateur - steering committee member	03/2007	12/2008
63164	BONNET	Damien	18/07/2007	RE-DE	HAS	Commission de transparence : PEDEA (Orphan - Europe)	aucune rémunération	01/2005	
63164	BONNET	Damien	18/07/2007	RE-DE	AFSSAPS	European Paediatric Worksharing Project : COZAAR (Losartan)	rémunération personnelle	01/2007	
63164	BONNET	Damien	18/07/2007	IP-AC	HAS	Groupe d'évaluation centres de référence maladies rares	aucune rémunération	01/2005	
63164	BONNET	Damien	18/07/2007	CF-INT	ACTELION	Journées Françaises d'HTAP/ Paris/ HTAP chez l'enfant / Bosentan	rémunération personnelle	01/2005	12/2005
63164	BONNET	Damien	18/07/2007	CF-INT	ACTELION	Journées Françaises d'HTAP/ Paris/ HTAP chez l'enfant / Bosentan	rémunération personnelle	01/2006	12/2006
63164	BONNET	Damien	18/07/2007	CF-INT	ACTELION	Journées Françaises d'HTAP/ Paris/ HTAP chez l'enfant / Bosentan	rémunération personnelle	01/2007	12/2007
63164	BONNET	Damien	28/05/2007	EC-INV	ACTELION	Essai thérapeutique / BOSENTAN (en cours)	Investigateur coordonnateur	01/2005	
63164	BONNET	Damien	28/05/2007	EC-CO	SANOFI AVENTIS	Essai thérapeutique Clopidogrel	Co-investigateur	01/2004	12/2006
63164	BONNET	Damien	28/05/2007	RE-AUT	ORPHAN EUROPE / HAS	Commission transparence / PEDEA	Rémunération personnelle	01/2006	12/2006
63164	BONNET	Damien	28/05/2007	CF-INT	ACTELION	Bâle - HTAP / HTAP des cardiopathies cogénitales / Bosentan	Rémunération personnelle	03/2007	03/2007
62805	BONNET	Fabrice	08/02/2006	EC-INV	GSK	Etude clinique / Rosiglitazone	investigateur associé	11/2004	05/2006
62805	BONNET	Fabrice	08/02/2006	EC-INV	NOVARTIS	Etude clinique / Valsartan	investigateur	05/2006	09/2007
62805	BONNET	Fabrice	08/02/2006	CF-INT	LILLY	Communication aux 15ème journées LILLY sur la néphropathie diabétique - Paris	Rémunération personnelle	01/2009	
62805	BONNET	Fabrice	08/02/2006	CF-INT	PFIZER	Intervention sur le risque cardiovasculaire - Marseille - colloqe pour des médecins	rémunération personnelle	10/2005	
62805	BONNET	Fabrice	08/02/2006	CF-INT	MSD	Intervention sur l'épidémiologie des dyslipidémies - Cannes	rémunération personnelle	11/2005	
62805	BONNET	Fabrice	08/02/2006	CF-AUD	PFIZER	Congrès EASD - Athènes		09/2005	
62805	BONNET	Fabrice	08/02/2006	CF-AUD	NOVO NORDISK	Congrès Société Française d'Endocrinologie		10/2005	
63164	BONNET	Damien	29/12/2005	LD-AR	ABBOTT	Conseil scientifique/suivi de cohorte/palivizumab	Institution	06/2005	06/2005
63164	BONNET	Damien	29/12/2005	EC-INV	ACTELION	Essai thérapeutique/pharmacocinétique pédiatrique/bosentan	Coordonateur national	05/2005	05/2005
63164	BONNET	Damien	29/12/2005	EC-INV	SANOFI-SYNTHELABO	Essai thérapeutique/pharmacocinétique/clopidogrel	Investigateur	05/2004	05/2006
63164	BONNET	Damien	29/12/2005	IP-RE	HAS	Commission transparence : PEDEA (Orphan-europe)		01/2005	12/2005
63164	BONNET	Damien	29/12/2005	IP-AC	HAS	Groupe d'évaluation centres de référence maladies rares		01/2005	12/2005
63164	BONNET	Damien	29/12/2005	CF-INT	ACTELION	Journées françaises d'HTAP/Paris/HTAP chez l'enfant/Bosentan 2005	Rémunération personnelle	01/2005	12/2005
62805	BONNET	Fabrice	21/06/2004	IP-CF	PFIZER	Enseignement à des généralistes			
62805	BONNET	Fabrice	21/06/2004	IP-CF	ASTRA-ZENECA	Enseignement à des généralistes			
62805	BONNET	Fabrice	21/06/2004	IP-CF	BMS	Rédaction de cas cliniques			
62805	BONNET	Fabrice	09/02/2004	IP-CF	MSD - PFIZER - BMS	Conférence formation, enseignement post universitaire, prise en charge, patient diabétique			
62805	BONNET	Fabrice	11/07/2003	IP-CF	Ecole d'infirmières de Lyon	Cours d'Endocrinologie			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62805	BONNET	Fabrice	25/06/2003	IP-CF	Ecole d'infirmières de Lyon	Cours d'Endocrinologie			
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	LILLY	Caelyx □□Evaluation du Pipeline□□SERM dans la prévention du cancer du sein	Rémunération personnelle	01/2007	
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	ABRAXIS	International Board	Rémunération personnelle	01/2008	
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	AMGEN	International Board	Rémunération personnelle	01/2009	
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	WYETH / PFIZER	International Scientific Board	Rémunération personnelle	01/2009	
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	ASTRA ZENECA	Groupe experts France	Rémunération personnelle	01/2009	
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	ROCHE	International Board	Rémunération personnelle	01/2010	
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	ROCHE	Post Asco		01/2007	12/2009
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	ASTRA ZENECA	Post San Antonio		01/2007	
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	NOVARTIS	Post San Antonio		01/2008	
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	PFIZER	Post San Antonio		01/2009	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	GLAXOSMITHKLINE	ASCO		01/2007	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	AVENTIS	SABCS		01/2007	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ASTRA ZENECA	AACR		01/2008	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ROCHE	NCI/ EORTC/ AACR Nouvelles Drogues		01/2008	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	BMS	ASCO		01/2008	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	GSK	SABCS		01/2008	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ROCHE	ASCO		01/2009	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ASTRA ZENECA	AACR		01/2009	
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ROCHE	SABCS		01/2009	
10059	BONNETERRE	Jacques	01/04/2010	PAR	GENZYME	Directeur médical oncologie global Boston USA	Conjoint	07/2005	12/2007
10059	BONNETERRE	Jacques	01/04/2010	PAR	GLAXOSMITHKLINE	Global clinical développement leader MDC oncology Philadelphia USA	CONJOINT	01/2008	04/2008
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	LILLY	CAELYX	rémunération personnelle	01/2007	01/2007
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	LILLY	Evaluation du Pipeline	rémunération personnelle	01/2007	12/2007
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	LILLY	SERM dans la prévention du cancer du sein	rémunération personnelle	01/2007	12/2007
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	ABRAXIS	International Board	rémunération personnelle	01/2008	12/2008
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	AMGEN	International Board	rémunération personnelle	01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	WYETH / PFIZER	International Scientific Board	rémunération personnelle	01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	ASTRA ZENECA	Groupe experts France	rémunération personnelle	01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	IP-AC	ROCHE	International Board	rémunération personnelle	01/2010	
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	ROCHE	POST ASCO		01/2007	12/2009
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	ASTRA ZENECA	POST SAN ANTONIO		01/2007	12/2007
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	NOVARTIS	POST SAN ANTONIO		01/2008	12/2008
10059	BONNETERRE	Jacques	01/04/2010	CF-INT	PFIZER	POST SAN ANTONIO		01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	GLAXOSMITHKLINE	ASCO		01/2007	12/2007
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	AVENTIS	SABCS		01/2007	12/2007
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ASTRA ZENECA	AACR		01/2008	12/2008
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ROCHE	NCI/EORTC/AACR Nouvelles Drogues		01/2008	12/2008
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	BMS	ASCO		01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	GSK	SABCS		01/2008	12/2008
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ROCHE	ASCO		01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ASTRA ZENECA	AACR		01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	CF-AUD	ROCHE	SABCS		01/2009	12/2009
10059	BONNETERRE	Jacques	01/04/2010	PAR	GENZYME	DIRECTEUR MEDICAL□□ONCOLOGIE GLOBAL□□BOSTON USA	Conjoint	07/2005	12/2007
10059	BONNETERRE	Jacques	01/04/2010	PAR	GLAXOSMITHKLINE	GLOBAL CLINICAL□□DEVELOPPMENT LEADER MDC□□ONCOLOGY□□PHILADELPHIA USA	Conjoint	01/2008	04/2008
10059	BONNETERRE	Jacques	22/03/2010	IP-AC	LILLY	Caelyx / évaluation du pipeline / SERM dans la prévention du cancer du sein	Rémunération personnelle	01/2007	
10059	BONNETERRE	Jacques	22/03/2010	IP-AC	ABRAXIS	International Board	Rémunération personnelle	01/2008	
10059	BONNETERRE	Jacques	22/03/2010	IP-AC	AMGEN	International Board	Rémunération personnelle	01/2009	
10059	BONNETERRE	Jacques	22/03/2010	IP-AC	WYETH / PFIZER	International Scientific Board	Rémunération personnelle	01/2009	
10059	BONNETERRE	Jacques	22/03/2010	IP-AC	ASTRA ZENECA	Groupe experts France		01/2009	
10059	BONNETERRE	Jacques	22/03/2010	IP-AC	ROCHE	International Board	Rémunération personnelle	01/2010	
10059	BONNETERRE	Jacques	22/03/2010	CF-INT	ROCHE	Post Asco		01/2007	12/2009
10059	BONNETERRE	Jacques	22/03/2010	CF-INT	ASTRA ZENECA	Post San Antonio		01/2007	
10059	BONNETERRE	Jacques	22/03/2010	CF-INT	NOVARTIS	Post San Antonio		01/2008	
10059	BONNETERRE	Jacques	22/03/2010	CF-INT	PFIZER	Post San Antonio		01/2009	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	GLAXOSMITHKLINE	ASCO		01/2007	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	AVENTIS	SABCS		01/2007	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	ASTRA ZENECA	AACR		01/2008	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	ROCHE	NCI/EORTC/AACR Nouvelles Drogues		01/2008	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	BMS	ASCO		01/2008	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	GSK	SABCS		01/2008	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	ROCHE	ASCO		01/2009	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	ASTRA ZENECA	AACR		01/2009	
10059	BONNETERRE	Jacques	22/03/2010	CF-AUD	ROCHE	SABCS		01/2009	
10059	BONNETERRE	Jacques	22/03/2010	PAR	GENZYME	Directeur médical oncologie global Boston USA	Conjoint	07/2005	12/2007
10059	BONNETERRE	Jacques	22/03/2010	PAR	GLAXOSMITHKLINE	Global clinical développement leader MDC Oncology Philadelphia USA	Conjoint	01/2008	04/2008
10059	BONNETERRE	Jacques	22/03/2010	EC-INV		Voir liste jointe			
10059	BONNETERRE	Jacques	22/03/2010	EC-CO		Voir liste jointe			
10059	BONNETERRE	Jacques	17/02/2009	RE-DE	LILLY	GEMZAR	rémunération personnelle	01/2003	
10059	BONNETERRE	Jacques	17/02/2009	RE-DE	ASTRAZENECA	FASLODEX	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	NOVARTIS	Letrozole : inhibiteur de sulfatase	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	NOVARTIS	RAD001	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	NOVARTIS	Leadsummit pipeline	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	PFIZER		rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	MSD		rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	SCHERING AG		rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	SCHERING PLOUGH	"Mock négociation SUTENT"	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	EISAI	Présidence symposium EMEND (Eurocancer)	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	LILLY	Biophosphonates	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	LILLY	Caelyx	rémunération personnelle	01/2007	12/2007
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	LILLY	Evaluation de Pipeline	rémunération personnelle	01/2007	
10059	BONNETERRE	Jacques	17/02/2009	IP-AC	LILLY	SERM dans la prévention du cander du sein	rémunération personnelle	01/2007	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ASTRAZENECA	Cancer du sein : la parole aux acteurs	rémunération personnelle	01/2005	12/2006
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ASTRAZENECA	Journées d'oncologie et sénologie du Nord-Est	rémunération personnelle	01/2005	12/2006
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ASTRAZENECA	Traitement anti-hormonal (Eurocancer)	rémunération personnelle	01/2005	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ABRAXIS	International Board	rémunération personnelle	01/2008	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	NOVARTIS	SABCS		01/2006	12/2006
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ROCHE	ASCO		01/2006	12/2006
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	SCHERING AG	EBCC		01/2006	12/2006
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	GSK	ASCO		01/2007	12/2007
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	AVENTIS	SABCS		01/2007	12/2007
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ROCHE	AACR		01/2008	12/2008
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ROCHE	NCI, EORTC, AACR : Nouvelles drogues		01/2008	12/2008
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	BMS	ASCO		01/2008	12/2008
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	GSK	SABCS		01/2008	12/2008
0059	BONNETERRE	Jacques	17/02/2009	PAR	GENZYME	Directeur médical (oncologie globale) - Boston	conjoint	07/2005	12/2007
0059	BONNETERRE	Jacques	17/02/2009	PAR	GSK	Global clinical : development leader MDC Oncology - Philadelphie	conjoint	01/2008	04/2008
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	GSK	VEG 108838	coordonnateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	FNCLCC	Phase I GEP 01-0506	investigateur principal		
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	SCHERING - BAYER	Phase II - ZK PRA 309821	investigateur principal		
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	MEDIGENE	Phase II MEDIGENE CT 4002			
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	Institut National du Cancer	Phase III - PHARE			
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	CENTRE OSCAR LAMBRET	Phase IV - SPAM (Etude de physiopathologie)	investigateur principal		
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	CENTRE OSCAR LAMBRET	Phase IV - GENEOM (Eude génétique)	investigateur principal		
0059	BONNETERRE	Jacques	17/02/2009	EC-INV	CAC OSCAR LAMBERT (Lille)	Etude prospective - MENINCA - syndrome méningé ou méningite K	investigateur principal		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	CAC VAL D'AURELLE (Clermont Ferrand)	Phase II - OP 06	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	CAC RENE GAUDUCHEAU (Nantes)	Phase II - GATA	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	ROCHE	BEVERLY 2	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	PFIZER	Phase III - A6181107	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	PFIZER	6181114	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	ROCHE	BEATRICE	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	ROCHE	AVEREL - Etude AVADO	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	EC-CO	CAC OSCAR LAMBRET (Lille)	TSARINE 0602	co-investigateur		
0059	BONNETERRE	Jacques	17/02/2009	RE-AUT	CAC LEON BERARD (Lyon)	GAS2PLUS			
0059	BONNETERRE	Jacques	17/02/2009	RE-AUT	CAC BERGONIE (Bordeaux)	CINNAMONE			
0059	BONNETERRE	Jacques	17/02/2009	RE-AUT	CAC BERGONIE (Bordeaux)	ONCADAGE			
0059	BONNETERRE	Jacques	17/02/2009	RE-AUT	CAC OSCAR LAMBRET (Lille)	MINEMOSYNE			
0059	BONNETERRE	Jacques	17/02/2009	RE-AUT	FNCLCC	LIBER (génétique)			
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	NOVARTIS	LETROZOL E, inhibiteur de sulfatase.	rémunération personnelle	01/2005	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	NOVARTIS	RAD001	rémunération personnelle	01/2005	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	NOVARTIS	LEADSUMMIT PIPELINE	rémunération personnelle	01/2006	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	PFIZER		rémunération personnelle	01/2006	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	MSD		rémunération personnelle	01/2005	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	SCHERING AG		rémunération personnelle	01/2005	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	SCHERING PLOUGH	"MOCK négotiation sutent"	rémunération personnelle	01/2006	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ESAI	Présidence symposium Emend (Euro cancer)		01/2006	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	LILLY	BISPHOSPHONATES	rémunération personnelle	01/2006	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	LILLY	CAELYX : évaluation du Pipline - SERM dans la prévention du cancer du sein	rémunération personnelle	01/2007	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ASTRA ZENECA	Cancer du sein : la parole aux acteurs	rémunération personnelle	01/2005	12/2006
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ASTRA ZENECA	Journées d'oncologie et senologie du Nord-est	rémunération personnelle	01/2005	12/2006
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ASTRA ZENECA	Traitement anti-hormonal (Euro cancer)	rémunération personnelle	01/2005	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	ABRAXIS	International Board	rémunération personnelle	01/2008	
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	AMGEN	International Board	rémunération personnelle	01/2009	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	NOVARTIS	SABCS		01/2006	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ROCHE	ASCO		01/2006	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	SCHERING AG	EBCC		01/2006	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	GLAXOSMITHKLINE	ASCO		01/2007	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	AVENTIS	SABCS		01/2007	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ASTRA ZENECA	AACR		01/2008	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ROCHE	NCI, EORTC, AACR : nouvelles drogues		01/2008	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	BMS	ASCO		01/2008	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	GSK	SABCS		01/2008	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ROCHE	ASCO		01/2009	
0059	BONNETERRE	Jacques	17/02/2009	CF-AUD	ASTRA ZENECA	AACR		01/2009	
0059	BONNETERRE	Jacques	17/02/2009	PAR	GENZYME	Directeur médical : oncologie global (Boston, USA)	conjoint	07/2005	12/2007
0059	BONNETERRE	Jacques	17/02/2009	PAR	GLAXOSMITHKLINE	Global clinical : development leader MCC - Oncology (Philadelphia, USA)	conjoint	01/2008	04/2008
0059	BONNETERRE	Jacques	17/02/2009	IP-AC	AMGEN	International Board	rémunération personnelle	01/2009	
0059	BONNETERRE	Jacques	26/02/2008	LD-AR	ROCHE	Groupe experts cancer du sein	rémunération personnelle	01/2005	04/2008
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	FNCLCC	Phase I : GEP 01-0506			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	GLAXOSMITHKLINE	Phase II : VEG 20007			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	SCHERING	Phase II : ZK PRA 309821			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	GLAXOSMITHKLINE	Phase III : EGF 105485			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	GLAXOSMITHKLINE	Phase III : VEG 108838			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	INCA	Phase III : PHARE			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	EORTC	Phase III : SOFT			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	CENTRE OSCAR LAMBRET	Phase IV : SPAM (étude de physiopathologie)			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	CENTRE OSCAR LAMBRET	Phase IV : GENEOM			
0059	BONNETERRE	Jacques	26/02/2008	EC-INV	CAC NICE	Etude prospective : PHRC 2005			
0059	BONNETERRE	Jacques	26/02/2008	EC-CO	GLAXOSMITHKLINE	Phase III : EGF 30008			
0059	BONNETERRE	Jacques	26/02/2008	EC-CO	FEDERATION NATIONALE DES CENTRES DE LUTTE CONTRE LE CANCER	Phase III : IBIS II			
0059	BONNETERRE	Jacques	26/02/2008	EC-CO	ROCHE	Phase III : CO- BO 17708 AVADO CO- BO 20231 AVERELCO- BO 17929CCO- BO 20289 20050136			
0059	BONNETERRE	Jacques	26/02/2008	EC-CO	AMGEN				
0059	BONNETERRE	Jacques	26/02/2008	EC-CO	PFIZER	A6181107 - A6181114			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10059	BONNETERRE	Jacques	26/02/2008	EC-CO	MEDIGENE	MEDIGENE CT 4002			
10059	BONNETERRE	Jacques	26/02/2008	EC-CO	CENTRE OSCAR LAMBRET	Phase III : TSARINE 0502□□Phase IV : CHIMTEP 0402			
10059	BONNETERRE	Jacques	26/02/2008	EC-CO	NOVARTIS	CFEM345D2406			
10059	BONNETERRE	Jacques	26/02/2008	RE-DE	LILLY	GEMZAR	rémunération personnelle	01/2003	
10059	BONNETERRE	Jacques	26/02/2008	RE-DE	ASTRAZENECA	FASLODEX	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	NOVARTIS	Letrozole ; inhibiteur de sulfatase	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	NOVARTIS	RAD001	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	NOVARTIS	LEADSUMMIT PIPELINE	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	PFIZER	"Mock negotiation SUTENT"	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	MSD	Présidence Symposium EMEND (eurocancer)	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	SCHERING AG	BISPHOSPHONATES	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	SCHERING PLOUGH	CAELYX	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	ESAI	Evaluation du pipeline	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	26/02/2008	IP-AC	LILLY	SERM dans la prévention du cancer du sein	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	26/02/2008	CF-INT	ASTRAZENECA	Cancer du sein : la parole aux acteurs	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	26/02/2008	CF-INT	ASTRAZENECA	Journées d'oncologie et sénologie du Nord-Est	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	26/02/2008	CF-INT	ASTRAZENECA	Traitement anti-hormonal (eurocancer)	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	26/02/2008	CF-AUD	NOVARTIS	SABCS		01/2006	12/2006
10059	BONNETERRE	Jacques	26/02/2008	CF-AUD	ROCHE	ASCO		01/2006	12/2006
10059	BONNETERRE	Jacques	26/02/2008	CF-AUD	SCHERING AG	EBCC		01/2006	12/2006
10059	BONNETERRE	Jacques	26/02/2008	CF-AUD	GLAXOSMITHKLINE	ASCO		01/2007	12/2007
10059	BONNETERRE	Jacques	26/02/2008	CF-AUD	AVENTIS	SABCS		01/2007	12/2007
10059	BONNETERRE	Jacques	26/02/2008	PAR	GENZYME	Directeur médical oncologie global (Boston - USA)	conjoint	07/2005	12/2007
10059	BONNETERRE	Jacques	26/02/2008	PAR	GLAXOSMITHKLINE	Global clinical developpment leader mdc oncology (Philadelphia - USA)	conjoint	01/2008	
10059	BONNETERRE	Jacques	02/03/2007	LD-AR	ROCHE	groupe experts cancer du sein	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	PIERRE FABRE	Phase I□□L00070 IN 109BO			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	GLAXO SMITHKLINE	Phase II / VEG 20007			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	GLAXO SMITHKLINE	Phase III □□EGF 100151□□EGF 105485			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	CENTRE OSCAR LAMBRET	phase IV □□SPAM			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	PIERRE FABRE	Pase I / L00070 IN 114 Q0			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	AVENTIS	Phase II / XRP 9881BB-2001			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	GLAXO SMITHKLINE	Phase III / EGF 30008			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	ASTRA ZENECA	phase III / 9238 IL 0048			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	ROCHE	Phase III / BO 17708 AVADO			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	CENTRE OSCAR LAMBRET	Phase IV / CHIMTEP -0402			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	NOVARTIS	Phase IV / CFEM345D2406			
10059	BONNETERRE	Jacques	02/03/2007	RE-DE	LILLY	GEMZAR	rémunération personnelle	01/2003	
10059	BONNETERRE	Jacques	02/03/2007	RE-DE	ASTRA ZENECA	FASLODEX	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	NOVARTIS	Letrozole ; inhibiteur de sulfatase	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	NOVARTIS	RAD001	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	NOVARTIS	Leadsummit pipeline	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	PFIZER	3 "Mock negotiation SUTENT"	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	MSD	Présidence Symposium EMEND (Eurocancer)	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	SCHERING AG	Bisphosphonates	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	SCHERING PLOUGH	Caelyx	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	ESAI	Evaluation du Pipeline	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	LILLY	SERM dans la prévention du cancer du sein	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	02/03/2007	CF-INT	ASTRA ZENECA	Cancer du sein : la parole aux acteurs	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	02/03/2007	CF-INT	ASTRA ZENECA	Journées d'oncologie et sénologie du Nord-est	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	02/03/2007	CF-AUD	NOVARTIS	Traitement anti-hormonal (Eurocancer)		01/2006	
10059	BONNETERRE	Jacques	02/03/2007	CF-AUD	ROCHE	SABCS		01/2006	
10059	BONNETERRE	Jacques	02/03/2007	CF-AUD	SCHERING AG	ASCO		01/2006	
10059	BONNETERRE	Jacques	02/03/2007	CF-AUD	LILLY	EBCC		01/2005	
10059	BONNETERRE	Jacques	02/03/2007	CF-AUD	MSD	SABCS		01/2005	
10059	BONNETERRE	Jacques	02/03/2007	PAR	GENZYME	ASCO	conjoint	07/2005	
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	Fédération Nationale des Centres de Lutte Contre le Cancer	Directeur médical oncologie global - Boston USA Phase III : IBIS II			
10059	BONNETERRE	Jacques	02/03/2007	EC-CO	ROCHE	Phase III : BO 20231 AVEREL			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	GLAXO SMITHKLINE	Phase III : EGF 105485			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	INCA Institut National du Cancer	Phase III : PHARE			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	AMGEN	Phase III : 20050136			
10059	BONNETERRE	Jacques	02/03/2007	IP-AC	LILLY	SERM dans la prévention du cancer du sein	rémunération personnelle	01/2007	
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	INCA (INSTITUT NATIONAL DU CANCER)	phase III PHARE			
10059	BONNETERRE	Jacques	02/03/2007	EC-INV	AMGEN	Phase III 20050136		01/2006	
10059	BONNETERRE	Jacques	01/03/2007	CF-AUD	NOVARTIS	SABCS			
10059	BONNETERRE	Jacques	01/03/2007	EC-CO	ROCHE	Phase IV - BO 20231 AVEREL	co-investigateur		
10059	BONNETERRE	Jacques	01/03/2007	EC-CO	ROCHE	Phase IV - BO 17708 AVADO	investigateur Principal		
10059	BONNETERRE	Jacques	01/03/2007	EC-INV	CENTRE OSCAR LAMBRET	Phase IV - SPAM	Investigateur Principal		
10059	BONNETERRE	Jacques	01/03/2007	EC-CO	CENTRE OSCAR LAMBRET	Phase IV - SPAM	investigateur principal		
10059	BONNETERRE	Jacques	01/03/2007	EC-INV	AMGEN	Phase III - 20050136	Investigateur principal		
10059	BONNETERRE	Jacques	01/03/2007	EC-INV	INCA	Phase III - PHARE	investigateur principal		
10059	BONNETERRE	Jacques	01/03/2007	EC-INV	GLAXO SMITHKILNE	Phase III - EGF 105485	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	06/07/2006	LD-AR	ROCHE	Groupe experts cancer du sein	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	06/07/2006	LD-AR	PFIZER	Membre du " speaker bureau "	rémunération personnelle	01/2003	
10059	BONNETERRE	Jacques	06/07/2006	RE-DE	LILLY	GEMSAR	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	06/07/2006	RE-DE	ASTRA ZENECA	FASLODEX	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	NOVARTIS	Letrozole : inhibiteur de sulfatase	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	NOVARTIS	RAD001	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	NOVARTIS	Leadsummit pipeline	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	PFIZER	" Mock negotiation SUTENT "	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	MSD	Présidence Symposium EMEND (Eurocancer)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	ASTRA ZENECA	Cancer du sein : la parole aux acteurs	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	ASTRA ZENEGA	Journées d'oncologie et sénologie du Nord-Est	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	06/07/2006	IP-AC	ASTRA ZENEGA	Traitement anti-hormonal (Eurocancer)	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	06/07/2006	CF-AUD	ROCHE	ASCO		01/2006	01/2006
10059	BONNETERRE	Jacques	06/07/2006	CF-AUD	SCHERING PLOUGH	AACR		01/2006	01/2006
10059	BONNETERRE	Jacques	06/07/2006	CF-AUD	SCHERING AG	EBCC		01/2006	01/2006
10059	BONNETERRE	Jacques	06/07/2006	CF-AUD	LILLY	SABCS		01/2005	01/2005
10059	BONNETERRE	Jacques	06/07/2006	CF-AUD	MSD	ASCO		01/2005	01/2005
10059	BONNETERRE	Jacques	06/07/2006	CF-AUD	SCHERING AG	SABCS		01/2003	01/2003
10059	BONNETERRE	Jacques	06/07/2006	PAR	GENZYME	Directeur médical oncologie global - Boston USA	conjoint	07/2005	
10059	BONNETERRE	Jacques	30/06/2006	LD-AR	ROCHE	groupe experts cancer du sein	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	30/06/2006	LD-AR	PFIZER	Membre du "speaker bureau"	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	30/06/2006	RE-DE	LILLY	GEMSAR	rémunération personnelle	01/2003	
10059	BONNETERRE	Jacques	30/06/2006	RE-DE	ASTRA ZENECA	Faslodex	rémunération personnelle	01/2004	
10059	BONNETERRE	Jacques	30/06/2006	EC-INV	PIERRE FABRE	Phase I - L00070 IN 109 BO	investigateur principal		
10059	BONNETERRE	Jacques	30/06/2006	EC-INV	GLAXO SMITHKLINE	Phase II - EGF 102580	investigateur principal		
10059	BONNETERRE	Jacques	30/06/2006	EC-INV	GLAXO SMITHKLINE	Phase III - EGF 100151	investigateur principal		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	PIERRE FABRE	Phase I - L 00070 IN 114 QO	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	AVENTIS	phase II - XRP 988 1 B-2001	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	AMGEN	Phase II - 20040113	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	GLAXO SMITHKLINE	Phase III- EGD 30008	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	ASTRA ZENECA	9238 IL 0048	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	FéDéRATION NATIONALE DES CENTRES DE LUTTE CONTRE LE CANCER	PACS 05	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	FéDéRATION NATIONALE DES CENTRES DE LUTTE CONTRE LE CANCER	IBIS II	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	CENTRE OSCAR LAMBRET	Phase IV - CHIMTEP - 0402	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	EC-CO	NOVARTIS	CFEM 345D2406	co-investigateur		
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	NOVARTIS	Letrozole - inhibiteur de sulfatase	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	NOVARTIS	RAD 001	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	NOVARTIS	Leadsummit pipeline	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	PFIZER	"Mock negociation SUTENT"	rémunération personnelle	01/2006	
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	MSD	Présidence symposium EMEND (Eurocancer)	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	ASTRA ZENECA	Cancer du sein : la parole aux acteurs	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	ASTRA ZENECA	Journées d'oncologie et sénologie du Nord-Est	rémunération personnelle	01/2005	12/2006
10059	BONNETERRE	Jacques	30/06/2006	IP-AC	ASTRA ZENECA	Traitement anti-hormonal (Eurocancer)	rémunération personnelle	01/2005	
10059	BONNETERRE	Jacques	30/06/2006	CF-AUD	ROCHE	ASCO		01/2006	12/2006
10059	BONNETERRE	Jacques	30/06/2006	CF-AUD	SCHERING PLOUGH	AACR		01/2006	12/2006
10059	BONNETERRE	Jacques	30/06/2006	CF-AUD	SCHERING AG	EBCC		01/2006	12/2006
10059	BONNETERRE	Jacques	30/06/2006	CF-AUD	LILLY	SABCS		01/2005	12/2005
10059	BONNETERRE	Jacques	30/06/2006	CF-AUD	MSD	ASCO		01/2005	12/2005
10059	BONNETERRE	Jacques	30/06/2006	CF-AUD	SCHERING AG	SABCS		01/2003	12/2003
10059	BONNETERRE	Jacques	30/06/2006	PAR	GENZYME	Directeur médical oncologie globale - Boston (USA)	conjoint	07/2005	
55628	BONNETERRE	Marie-Edith	15/12/2004	IF	AVENTIS SANOFI	Actions (avec litre d'ancien salarié)			
55628	BONNETERRE	Marie-Edith	15/12/2004	PAR	L'OREAL	1 fils			
55628	BONNETERRE	Marie-Edith	15/12/2004	(Autre)	BEAUFOUR IPSEN	Investigateur étude clinique			
55628	BONNETERRE	Marie-Edith	15/12/2004	(Autre)	PFIZER	Investigateur étude clinique			
10059	BONNETERRE	Jacques	04/11/2004	IP-AC	LILLY - ASTRA ZENECA				
10059	BONNETERRE	Jacques	04/11/2004	IP-CF	AVENTIS - ASTRA ZENECA - NOVARTIS - PFIZER	Présidence de symposiums, conférences			
10059	BONNETERRE	Jacques	04/11/2004	IP-EC	INSTITUT DE RECHERCHE PIERRE FABRE	A dose finding and pharmacokinetic study of I.V. vinflunine in combination with capacitabine in metastatic breast cancer			
10059	BONNETERRE	Jacques	04/11/2004	IP-EC	NOVARTIS	Etude randomisée, en ouvert, multicentrique, évaluant l'efficacité de l'acide zolédronique dans la prévention de la perte osseuse liée au traitement anticancéreux chez des patie			
10059	BONNETERRE	Jacques	04/11/2004	IP-EC	ASTRA ZENECA	A randomized, double blind, multicenter study to compare the efficacy and tolerability of fulvestrant (FASLODEX) vs exemestane (AROMASIN) in postmenopausal women with h			
10059	BONNETERRE	Jacques	04/11/2004	IP-EC	FNCLCC	Etude phase III randomisée évaluant la durée d'une chimiothérapie de type FEC 100 : 6 cycles versus 4 cycles dans le cancer du sein sans envahissement ganglionnaire, essai			
55628	BONNETERRE	Marie-Edith	22/03/2004	IP-EC	IPSEN - BEAUFOUR	Membre advisory board et co-investigation et clinique			
55628	BONNETERRE	Marie-Edith	22/03/2004	IP-AC	IPSEN - BEAUFOUR	Membre advisory board et co-investigation et clinique			
55628	BONNETERRE	Marie-Edith	22/03/2004	VB	NOVARTIS - ILEX - IPSEN - BEAUFOUR - AVENTIS - PHARMACYCLICS	Etude clinique, activite de co-investigateur			
10059	BONNETERRE	Jacques	05/09/2003	IP-EC	BCIRG	Etudes cliniques : BCIRG 006 et BCIRG 007 (en cours) - Rémunération du Centre Oscar Lambret			
10059	BONNETERRE	Jacques	05/09/2003	IP-EC	FNCLCC	Etudes cliniques PACS 05, PAC GERICO 01 - Rémunération du Centre Oscar Lambret			
10059	BONNETERRE	Jacques	05/09/2003	IP-EC	INSTITUT DE RECHERCHE PIERRE FABRE	Etude clinique PM0259 CA 101- Rémunération du Centre Oscar Lambret			
10059	BONNETERRE	Jacques	05/09/2003	IP-EC	CENTRE GEORGES FRANCOIS BACLESSE	Etude clinique TAX-HER-S01- Rémunération du Centre Oscar Lambret			
10059	BONNETERRE	Jacques	05/09/2003	IP-EC	AVENTIS	Etude clinique XPR98B.PR204- Rémunération du Centre Oscar Lambret			
10059	BONNETERRE	Jacques	05/09/2003	IP-RE	LILLY	Dossier d'AMM Gemzar-cancer du sein - 2003			
10059	BONNETERRE	Jacques	05/09/2003	IP-AC	NOVARTIS	Hormonothérapie			
10059	BONNETERRE	Jacques	05/09/2003	IP-AC	LILLY	Jury de prix			
10059	BONNETERRE	Jacques	05/09/2003	IP-CF	ASTRA ZENECA, AVENTIS, ROCHE, PFIZER				
55628	BONNETERRE	Marie-Edith	14/01/2003	IF	AVENTIS France	Actions en bourse			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-EC	AVENTIS	Etude clinique (Investigateur)			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-EC	EORTC	Etude clinique (Investigateur)			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-EC	ILEX ONCOLOGIE	Etude clinique (Investigateur)			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-RE	PHARMA MAR	ET 743 : participation à des réunions d'experts en développement de nouveaux médicaments en oncologie - "Advisory Boards"			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-RE	IPSEN BEAUFOUR	BN 80915 : participation à des réunions d'experts en développement de nouveaux médicaments en oncologie - "Advisory Boards"			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-RE	NOVARTIS	FEMARA : participation à des réunions d'experts en développement de nouveaux médicaments en oncologie - "Advisory Boards"			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-RE	SCHERING-PLOUGH AG	CAELYX : participation à des réunions d'experts en développement de nouveaux médicaments en oncologie - "Advisory Boards"			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-AC	CIRG	Mission de consultant 1 mois et membre du conseil scientifique (oct. 2002)			
55628	BONNETERRE	Marie-Edith	14/01/2003	IP-CF	NOVARTIS	Formation interne			
10059	BONNETERRE	Jacques	15/10/2002	IP-EC	BCIRG	Coordonnateur et investigateur - BCIRG 005 (2002)			
10059	BONNETERRE	Jacques	15/10/2002	IP-EC	BCIRG	Coordonnateur et investigateur - BCIRG 006 (2002)			
10059	BONNETERRE	Jacques	15/10/2002	IP-EC	BCIRG	Coordonnateur et investigateur - BCIRG 007 (2002)			
10059	BONNETERRE	Jacques	15/10/2002	IP-EC	ILEX	Coordonnateur et investigateur - NM 101 (2002)			
10059	BONNETERRE	Jacques	15/10/2002	IP-EC	Institut de Recherche PIERRE FABRE	Coordonnateur et investigateur - PM0259 CA 101 (2002)			
10059	BONNETERRE	Jacques	15/10/2002	IP-EC	AVENTIS	Coordonnateur et investigateur - RP64174A-X-120 (2002)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
0059	BONNETERRE	Jacques	15/10/2002	IP-EC	AVENTIS	Coordonnateur et investigateur - XPR98B,PR204 (2002)			
0059	BONNETERRE	Jacques	15/10/2002	IP-AC	JANSSEN	Erythropoïétine			
0059	BONNETERRE	Jacques	15/10/2002	IP-AC	ROCHE	Herceptine			
0059	BONNETERRE	Jacques	15/10/2002	IP-AC	NOVARTIS	Hormonothérapie			
0059	BONNETERRE	Jacques	15/10/2002	IP-CF	AVENTIS	Symposium de recherche clinique			
0059	BONNETERRE	Jacques	15/10/2002	IP-CF	AVENTIS, ASTRA ZENECA, NOVARTIS, PHARMACIA & UPJOHN	Présidence de symposiums, conférences			
0059	BONNETERRE	Jacques	02/10/2001	IP-AC	JANSSEN	Erythropoétine			
0059	BONNETERRE	Jacques	02/10/2001	IP-AC	ROCHE	Herceptine			
0059	BONNETERRE	Jacques	02/10/2001	IP-AC	NOVARTIS	Hormonothérapie			
0059	BONNETERRE	Jacques	02/10/2001	IP-CF	AVENTIS	Symposium de recherche clinique			
0059	BONNETERRE	Jacques	02/10/2001	IP-CF	AVENTIS, ASTRA ZENECA, NOVARTIS, PHARMACIA UPJOHN	Présidence de symposium			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	ASTRA ZENECA	0473 IL/0011			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	BCIRG	BCIRG 005			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	BCIRG	BCIRG 006			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	IPSEN BIOTECH	E55.52990.003			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	EORTC	EORTC 16989B			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	EORTC	EORTC 16992			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	ILEX	NM 101			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	PIERRE FABRE	PM0259 CA 101			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	AVENTIS	RP64174A-X-120			
0059	BONNETERRE	Jacques	02/10/2001	IP-EC	AVENTIS	XPR98B, PR204			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	EORTC	EORTC 16992			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	FNCLCC	PACS02			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	ILEX (TM) PRODUCTS INC	NM 101			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	IPSEN BIOTECH	E55 52990 001			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	JANSSEN	PRI/EPO-INT76			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	NDDO	EORTC 16989B			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	NOVARTIS	BIG 01.98			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	PIERRE FABRE	PMO259CA101			
0059	BONNETERRE	Jacques	29/12/2000	IP-EC	PIERRE FABRE	9PM25997IN101			
0059	BONNETERRE	Jacques	29/12/2000	IP-AC	JANSSEN	Erythropoétine			
0059	BONNETERRE	Jacques	29/12/2000	IP-AC	ROCHE	Herceptine			
0059	BONNETERRE	Jacques	29/12/2000	IP-CF	AVENTIS	Symposium Méthodologie Etude Clinique			
0059	BONNETERRE	Jacques	29/12/2000	IP-CF	AVENTIS	Présidence de symposiums			
0059	BONNETERRE	Jacques	29/12/2000	IP-CF	ASTRA ZENECA	Présidence de symposiums			
0059	BONNETERRE	Jacques	29/12/2000	IP-CF	NOVARTIS	Présidence de symposiums			
0059	BONNETERRE	Jacques	29/12/2000	IP-CF	PHARMACIA & UPJOHN	Présidence de symposiums			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	AVENTIS	Etude TAXOBEL 226			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	BRISTOL MYERS SQUIBB	Etude CA 146-027			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	CAC NANCY	Etude GIREC S01			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	EORTC	Etude EORTC 16992			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	FNCLCC	Etudes PACS01, PACS02			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	IPSEN BIOTECH	E55 52990 001			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	JANSSEN	Etude PRI/EPO-INT76			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	NDDO	Etude EORTC 16989B, 16989M, BN005/ND029801			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	NOVARTIS	Etude BIG 01.98			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	PHARMACIA	Etude 378 ONC 0030146			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	PIERRE FABRE	Etude 9PM259.97IN101			
0059	BONNETERRE	Jacques	09/10/2000	IP-EC	ZENECA	Etude 9331 IL/ 0018			
0059	BONNETERRE	Jacques	09/10/2000	IP-AC	JANSSEN	Erythropoétine			
0059	BONNETERRE	Jacques	09/10/2000	IP-AC	ROCHE	Herceptin			
0059	BONNETERRE	Jacques	09/10/2000	IP-CF	AVENTIS	Symposium méthodologie étude clinique (présidence)			
0059	BONNETERRE	Jacques	09/10/2000	IP-CF	ASTRA ZENECA	Présidence de symposiums			
0059	BONNETERRE	Jacques	09/10/2000	IP-CF	NOVARTIS	Présidence de symposiums			
0059	BONNETERRE	Jacques	09/10/2000	IP-CF	PHARMACIA UPJOHN	Présidence de symposiums			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	BRISTOL-MYERS SQUIBB	Etude CA 14-027-04			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	FNCLCC	Etudes BIG 1-98 ; PACS 01 ; PACS 02			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	GLAXO WELLCOME	Etude FUMB 2004			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	IPSEN BIOTECH	Etude E55-52990-001			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	NDDO	Etude 16962 M ; BN 005/ND 029801			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	PHARMACIA & UPJOHN	Etude 378 ONC 0030 0146			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	INSTITUT PIERRE FABRE	Etude 9PN 259 97 IN 101			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	RPR-BELLON	Etude TAXOBEL 226			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	SCHERING PLOUGH	Etude 197.042			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	SERVIER	Etude CL3-10036-298-FRA/004			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	CENTRE ALEXIS VAUTRIN (Nancy)	Etude GIREC S01			
0059	BONNETERRE	Jacques	14/04/2000	IP-EC	ZENECA	Etudes 1033 IL/0027 ; 9238 IL/0025 ; 9331 IL/0018 ; 118630/2802/ZEBRA			
0059	BONNETERRE	Jacques	14/04/2000	IP-AC	SCHERING PLOUGH	Conseil sur un projet de prévention du cancer du sein			
0059	BONNETERRE	Jacques	14/04/2000	IP-AC	JANSSEN	Conseil sur un projet d'étude avec Erythropoétine			
0059	BONNETERRE	Jacques	14/04/2000	IP-AC	PHARMACIA UPJOHN	Groupe de travail anti-aromatase			
0059	BONNETERRE	Jacques	14/04/2000	IP-CF	ASTRA ZENECA	Conférences			
0059	BONNETERRE	Jacques	14/04/2000	IP-CF	AVENTIS	Conférences et formations			
0059	BONNETERRE	Jacques	14/04/2000	IP-CF	PHARMACIA UPJOHN	Conférences			
5628	BONNETERRE	Marie-Edith	31/01/2000	IF	RHONE POULENC RORER (AVENTIS)	actions (au titre d'ancien salarié)			
5628	BONNETERRE	Marie-Edith	31/01/2000	IP-CF	SERVIER	orateur aux VIII entretiens le 28/1/99 : ethique et protocoles de recherche en cancerologie			
5628	BONNETERRE	Marie-Edith	31/01/2000	VB	RHONE POULENC (AVENTIS)	centre OSCAR LAMBRET (étude clinique)			
5628	BONNETERRE	Marie-Edith	31/01/2000	VB	KNOLL A.G	CENTRE OSCAR LAMBRET (étude clinique)			
0059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Bellon				
0059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Chugai Rhône Poulenc				
0059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Pharmacia				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Zeneca				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	FNLCC				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Bristol				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Sandoz				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Asta Médica				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Takéda				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	EORTC				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Janssen				
10059	BONNETERRE	Jacques	01/01/1998	IP-AUT	Arcagy				
64004	BONNEVIE	Lionel	20/03/2007	CF-AUD	SERVIER	Journées européennes SFC - Paris		01/2006	01/2006
64004	BONNEVIE	Lionel	20/03/2007	CF-AUD	ASTRAZENECA	MSDA - Marrakech		05/2006	05/2006
64004	BONNEVIE	Lionel	20/03/2007	CF-AUD	MERCK-LIPHA	Heart Failure - Helsinki		06/2006	06/2006
64004	BONNEVIE	Lionel	20/03/2007	CF-AUD	ASTRAZENECA	European society of cardiology : congrès annuel (Barcelone)		09/2006	09/2006
64004	BONNEVIE	Lionel	09/02/2006	EC-INV	SALVAY PHARMA	Tédisamil / Diltiazem	Investigateur	01/1995	12/1998
64004	BONNEVIE	Lionel	09/02/2006	EC-INV	PFIZER	Amlor / R-test évolution dans l'Angor stable (angine de poitrine)	investigateur	01/1999	12/1999
64004	BONNEVIE	Lionel	09/02/2006	EC-INV	TAKEDA	Candesartan et IMT	investigateur	01/1999	
64004	BONNEVIE	Lionel	09/02/2006	EC-INV	NOVARTIS	Suivi échographique IMS	investigateur	01/2004	12/2004
64004	BONNEVIE	Lionel	09/02/2006	EC-INV	SANOFI	USIC 2000	investigateur	01/2000	12/2000
64004	BONNEVIE	Lionel	09/02/2006	IP-AC	VITATRON	enquête d'évaluation de différents dispositifs implantables (stimulateur)	aucune rémunération	03/2005	03/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-INT	SERVIER	Sucy en Brie / HTA, ces cliniques / étude ASCOT (Périndopril / Amlodipine)	aucune rémunération	06/2005	
64004	BONNEVIE	Lionel	09/02/2006	CF-INT	NOVARTIS	Insuffisance cardiaque, étude Val-heft / Valsartan /Tours	aucune rémunération	05/2002	
64004	BONNEVIE	Lionel	09/02/2006	CF-INT	SANOFI AVENTIS	Formation délégués médicaux	aucune rémunération	09/2005	
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	MSD	Journées nationales SFC - Lyon		06/2005	06/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	ASTRAZENECA	Recommandations : Rosuvastatine - Candesartan / Cannes		04/2005	04/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	ASTRAZENECA	ESC - Stockohlm		09/2005	09/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	NOVARTIS	7ème congrès cardio-interventionelle - Paris		09/2005	09/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	SERVIER	Journées de l'HTA - Paris		12/2005	12/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	BMS	Prise en charge des SC aigus - Budapest		09/2005	09/2005
64004	BONNEVIE	Lionel	09/02/2006	CF-AUD	ABBOTT	Journées européennes SFC - Paris		01/2006	01/2006
60477	BONNIN	Philippe	07/01/2010	EC-INV	BMS	Etude ADOPT	écho doppler	01/2008	
60477	BONNIN	Philippe	07/01/2010	EC-INV	SANOFI	Etude MAGELLAN		01/2009	
60477	BONNIN	Philippe	26/09/2008	EC-CO	BAYER	Protocole Magellan - réalisation echo doppler		09/2008	
60477	BONNIN	Philippe	26/09/2008	EC-CO	BMS	Protocole ADOP CV 185-036 - Apixaban - réalisation d'écho doppler		09/2007	
60477	BONNIN	Philippe	26/09/2008	CF-INT	SANOFI	Echo doppler chez le petit animal - St Brévin - Association des angéologues du grand ouest	aucune rémunération	06/2008	06/2008
60477	BONNIN	Philippe	26/09/2008	CF-INT		Brachial vascular flow- reactivity first joint meeting on atherosclerosis and risk factors - Séville	aucune rémunération	03/2008	03/2008
60477	BONNIN	Philippe	26/12/2007	RE-DE	BMS	Etude ADOPT - Apixaban- prévention de la MTEV	Rémunération institution	11/2007	
60477	BONNIN	Philippe	03/10/2006	RE-DE	AVENTIS	Etude Exclaim - Réalisation d'échodoppler	rémunération versée à une institution		
60477	BONNIN	Philippe	03/10/2006	RE-DE	SANOFI SYNTHELABO	étude Van Gogh - Idraparinux - réalisation d'échodoppler	rémunération versée à une institution		
60477	BONNIN	Philippe	03/10/2006	CF-INT	BMS	Atelier d'échodoppler vasculaire périphérique - Paris	rémunération personnelle	05/2005	05/2005
60477	BONNIN	Philippe	03/10/2006	CF-INT	BMS	Atelier d'échodoppler vasculaire périphérique - Paris	rémunération personnelle	07/2005	07/2005
60477	BONNIN	Philippe	03/10/2006	CF-INT	BMS	Atelier d'échodoppler vasculaire périphérique - Paris	rémunération personnelle	10/2005	10/2005
60477	BONNIN	Philippe	03/10/2006	CF-INT	BMS	Atelier d'échodoppler vasculaire périphérique - Paris	rémunération personnelle	11/2005	11/2005
60477	BONNIN	Philippe	03/10/2006	CF-AUD	ABBOTT	Congrès de la société française de cardiologie (XVIième journées européennes) Paris		01/2007	01/2007
60477	BONNIN	Philippe	03/10/2006	CF-AUD	ABBOTT	Congrès de la société française de cardiologie (XVIième journées européennes) Paris		01/2006	12/2006
60477	BONNIN	Philippe	04/11/2005	EC-CO	AVENTIS	Echodoppler	réalisation des échodoppler veineux d'évaluation (en cours)		
60477	BONNIN	Philippe	04/11/2005	EC-CO	SANOFI SYNTHELABO	Echodoppler/ Idraparinux	réalisation des échodoppler veineux d'évaluation (en cours)		
60477	BONNIN	Philippe	04/11/2005	EC-CO	BAYER	Echodoppler / inhibiteur anti X a oral	réalisation des échodoppler veineux d'évaluation (en cours)	07/2005	07/2005
60477	BONNIN	Philippe	04/11/2005	RE-AUT	AFSSAPS	Rapports pour la commission appareil et méthodes	aucune rémunération		
60477	BONNIN	Philippe	04/11/2005	CF-INT	BMS	cours d'échodoppler / Hôtel Sofitel Arc de Triomphe	rémunération personnelle	05/2005	05/2005
60477	BONNIN	Philippe	04/11/2005	CF-INT	BMS	cours d'échodoppler / Hôtel Sofitel Arc de Triomphe	rémunération personnelle	07/2005	07/2005
60477	BONNIN	Philippe	04/11/2005	CF-INT	BMS	cours d'échodoppler / Hôtel Sofitel Arc de Triomphe	rémunération personnelle	10/2005	10/2005
60477	BONNIN	Philippe	20/07/2005	IP-CF	BMS	examens Echo Doppler des vaisseaux			
60477	BONNIN	Philippe	20/07/2005	IP-CF	BIOPHARMA	article pour "Propos de Cardiologie"			
60477	BONNIN	Philippe	20/07/2005	VB	AVENTIS	étude Exclaim	rémunération versée pour partie au service de Médecine A de Laribosière - explorations fonctionnelles		
60477	BONNIN	Philippe	20/07/2005	VB	SANOFI-SYNTHELABO	étude Van Gogh	rémunération versée pour partie au service de Médecine A de Laribosière - explorations fonctionnelles		
60477	BONNIN	Philippe	20/07/2005	VB	BAYER-PHARMA	étude Einstein	rémunération versée pour partie au service de Médecine A de Laribosière - explorations fonctionnelles		
60477	BONNIN	Philippe	24/03/2004	IP-EC	AVENTIS	Etude Exclaim - HBPM chez le sujet agé (oprévention TVP)			
60477	BONNIN	Philippe	24/03/2004	IP-EC	SANOFI-SYNTHELABO	Etude Van Gogh - Idraparinux (traitement de la TVP)			
60477	BONNIN	Philippe	24/03/2004	IP-CF	Staff de service	Explorations fonctionnelles vasculaires			
60477	BONNIN	Philippe	24/03/2004	IP-CF	Congrès médicaux	Physiopathologie des circulations			
60477	BONNIN	Philippe	22/02/2000	IP-EC	INRA	Circulations et hormones			
60477	BONNIN	Philippe	22/02/2000	IP-EC	CNES	Circulation et hypogravité			
60477	BONNIN	Philippe	23/11/1999	IP-EC	HOESCHT MARION ROUSSEL	Oestrogènes de substitution et vasoprévention			
60477	BONNIN	Philippe	23/11/1999	IP-EC	SERVIER	Protocole adère-préforex			
60477	BONNIN	Philippe	23/11/1999	VB	CNES	Contrat avec l'INSERM : réf: 793/98/CNES/7156/00 - protocole vasoréativité / microgravité			

d	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
1328	BORDET	Régis	02/06/2009	LD-AR	GENFIT	Conseiller scientifique	rémunération institution	01/2003	
1328	BORDET	Régis	02/06/2009	EC-INV	SERVIER	Evaluation d'agents neuroprotecteurs	expérimentateur principal	01/2001	12/2005
1328	BORDET	Régis	02/06/2009	EC-INV	ASTRA ZENECA	Evaluation d'agents neuroprotecteurs	expérimentateur principal	01/2005	12/2007
1328	BORDET	Régis	02/06/2009	EC-CO	GENFIT / PFIZER	Etudes des effets neuroprotecteurs de l'atorvastatine	expérimentateur non principal	01/2006	12/2007
1328	BORDET	Régis	02/06/2009	RE-AUT	LUNDBECK	Rapport pour la Commission de la transparence sur la rasagiline	rémunération institution	01/2008	
1328	BORDET	Régis	02/06/2009	CF-INT	JANSSEN CILAG, LUNDBECK, PFIZER, EISAI, SANOFI AVENTIS, BOEHRINGER INGELHEIM		rémunération personnelle		
1328	BORDET	Régis	02/06/2009	CF-AUD	SERVIER	ECNP 2007 - Vienne		09/2007	09/2007
4307	BOTTLAENDER	Michel	06/10/2006	EC-CO	GSK	phase I : sb705498	co-investigateur	11/2006	06/2007
4307	BOTTLAENDER	Michel	06/10/2006	EC-CO	SANOFI-AVENTIS	phase I ave8112	co-investigateur	03/2007	12/2007
4307	BOTTLAENDER	Michel	06/10/2006	EC-CO	SERVIER	développement de nouveaux radiotraceurs pour l'imagerie médicale	expérimentateur		
4307	BOTTLAENDER	Michel	06/10/2006	EC-CO	SANOFI-AVENTIS	évaluation préclinique de ave8112 développement de nouveaux radiotraceurs	expérimentateur		
4307	BOTTLAENDER	Michel	06/10/2006	EC-CO	GSK	évaluation préclinique de vr1 xxx développement de nouveaux radiotraceurs	expérimentateur		
4307	BOTTLAENDER	Michel	06/10/2006	CF-INT	PIERRE FABRE	journées scientifiques du carla, à castres / "la cinétique cérébrale de la nicotine observée par tomographie p	rémunération personnelle	12/2005	
4307	BOTTLAENDER	Michel	06/10/2006	(Autre)	CPP ILE DE France VII	membre suppléant		01/2001	
2622	BOUCCARA	Didier	02/12/2010	LD-AR	GROUPE AMPLIFON	Participation à un groupe assurant régulièrement (2 à 3 fois par an) une formation consacrée aux vertiges et	rémunération personnelle	01/2006	
2622	BOUCCARA	Didier	02/12/2010	EC-CO	AP-HP	PHRC : Evaluation des implants de l'oreille moyenne dans la stratégie thérapeutique de la réhabilitation aud	Co-investigateur : réalisation des évaluations cliniques.	01/2007	12/2009
2622	BOUCCARA	Didier	02/12/2010	EC-CO	AP-HP	Etude multicentrique randomisée Acetyl leucine à différentes posologies versus placebo, au cours de la név	Co-investigateur : réalisation des évaluations cliniques.	01/2008	01/2009
2622	BOUCCARA	Didier	02/12/2010	IP-AC	LABORATOIRES SERVIER	Rédaction d'un article concernant les résultats de l'étude France Cochlée.	aucune rémunération	01/2007	10/2007
2622	BOUCCARA	Didier	02/12/2010	IP-AC	LABORATOIRE UCB PHARMA	Rédaction d'un rapport ponctuel	aucune rémunération	01/2005	03/2005
2622	BOUCCARA	Didier	02/12/2010	CF-AUD	LABORATOIRES SERVIER	San Diego (USA) : 10th International Conference on cochlear implants and other implantable auditory technologies.		04/2008	04/2008
2622	BOUCCARA	Didier	02/12/2010	CF-AUD	LABORATOIRE ENTENDRE	Paris : Enseignement Post-universitaire du Collège National d'Audioprothèse.		12/2008	12/2008
2622	BOUCCARA	Didier	02/12/2010	CF-AUD	NEURELEC	Stockholm (Suède) : 11th International Conference on cochlear implants and other implantable auditory technologies.		06/2010	07/2010
2622	BOUCCARA	Didier	25/10/2010	LD-AR	GROUPE AMPLIFON	Participation à un groupe assurant régulièrement (2 à 3 fois par an) une formation consacrée aux vertiges et	rémunération personnelle	01/2006	
2622	BOUCCARA	Didier	25/10/2010	EC-CO	PHRC : Evaluation des implants de l'oreille moyenne dans la stratégie thérapeutique de la réhabilitation auditive	Etude randomisée multicentrique. AP-HP	Co-investigateur : réalisation des évaluations cliniques	01/2007	12/2009
2622	BOUCCARA	Didier	25/10/2010	EC-CO		Etude multicentrique randomisée Acetyl leucine à différentes posologies versus placebo, au cours de la név	Co-investigateur : réalisation des évaluations cliniques.	01/2008	01/2009
2622	BOUCCARA	Didier	25/10/2010	IP-AC	LABORATOIRES SERVIER	Rédaction d'un article concernant les résultats de l'étude France Cochlée	aucune rémunération	01/2007	10/2007
2622	BOUCCARA	Didier	25/10/2010	IP-AC	LABORATOIRE UCB PHARMA	Rédaction d'un rapport ponctuel	aucune rémunération	01/2005	03/2005
2622	BOUCCARA	Didier	25/10/2010	CF-AUD	LABORATOIRES SERVIER	San Diego (USA) : 10th International Conference on cochlear implants and other implantable auditory technologies.		04/2008	04/2008
2622	BOUCCARA	Didier	25/10/2010	CF-AUD	LABORATOIRE ENTENDRE	Paris : Enseignement Post-Universitaire au Collège National d'Audioprothèse.		12/2008	12/2008
2622	BOUCCARA	Didier	25/10/2010	CF-AUD	SOCIETE NEURELEC	Stockholm (Suède) : 11th International Conference on cochlear implants and other implantable auditory technologies.		06/2010	07/2010
2622	BOUCCARA	Didier	16/01/2009	LD-AR	GROUPE AMPLIFON	Participation à un groupe assurant régulièrement (2 à 3 fois par an) une formation consacrée aux vertiges e	rémunération personnelle	01/2006	
2622	BOUCCARA	Didier	16/01/2009	EC-CO	PHRC	Evaluation des implants de l'oreille moyenne dans la stratégie thérapeutique de la réhabilitation auditive - étu	Co-investigateur : réalisation des évaluations cliniques	01/2007	12/2009
2622	BOUCCARA	Didier	16/01/2009	EC-CO		Acetyl leucine - étude multicentrique randomisée Acetyl leucine à différentes posologies versus placebo, au	Co-investigateur : réalisation des évaluations cliniques	01/2008	01/2009
2622	BOUCCARA	Didier	16/01/2009	IP-AC	SERVIER	Rédaction d'un article concernant les résultats de l'étude France Cochlée	aucune rémunération	01/2007	10/2007
2622	BOUCCARA	Didier	16/01/2009	IP-AC	UCB PHARMA	Rédaction d'un rapport ponctuel	aucune rémunération	01/2005	03/2005
2622	BOUCCARA	Didier	16/01/2009	CF-AUD	SERVIER	10 th International Conference on cochlear implants and other implantable auditory technologies - San Diego		04/2008	04/2008
2622	BOUCCARA	Didier	16/01/2009	CF-AUD	ENTENDRE	Enseignement Post-Universitaire du Collège National d'Audioprothèse - Paris		12/2008	12/2008
2622	BOUCCARA	Didier	20/01/2008	CF-INT	GROUPE AMPLIFON	participation à un groupe assurant régulièrement (2 à 3 fois /an) une formation sur les vertiges	Rémunération personnelle	01/2006	01/2009
2622	BOUCCARA	Didier	20/01/2008	IP-AC	SERVIER	Rédaction d'un article concernant les résultats de l'étude France Cochlée	Aucune rémunération	01/2007	10/2007
2622	BOUCCARA	Didier	20/01/2008	EC-CO	AP-HP	PHRC: Evaluation des implants de l'oreille moyenne dans la stratégie thérapeutique de la réhabilitation audi	Co investigateur	01/2007	01/2009
2622	BOUCCARA	Didier	20/01/2008	EC-CO	PIERRE FABRE	Etude multicentrique randomisée Acetyl leucine à différentes posologies versus placebo, au cours de la név	Co investigateur	01/2008	
2622	BOUCCARA	Didier	23/01/2007	LD-AR	SERVIER	participation d'un groupe d'expert dans le cadre d'une étude clinique	rémunération personnelle	01/2004	12/2004
2622	BOUCCARA	Didier	23/01/2007	LD-AR	GROUPE AMPLIFON	participation à un groupe assurant régulièrement (2 à 3 fois /an) une formation sur les vertiges	rémunération personnelle	01/2006	
2622	BOUCCARA	Didier	23/01/2007	EC-INV	COLLIN ORL France	Etude clinique implant cochléaire bilatéral	pas de rémunération personnelle	01/2003	12/2005
2622	BOUCCARA	Didier	23/01/2007	EC-INV	COLLIN ORL	Etude clinique d'un marqueur biologique de l'autoimmunité de l'oreille	coordonnateur pas de rémunération personnelle	01/2004	12/2005
2622	BOUCCARA	Didier	23/01/2007	EC-INV	MEDTRONIC XOMED	Etude clinique utilisant le procédé MENIETT ®	pas de rémunération personnelle	01/2004	12/2005
2622	BOUCCARA	Didier	23/01/2007	EC-CO	COCHLEAR France	Etude clinique implant Cochlear électroacoustique	co-investigateur pas de rémunération personnelle	01/2003	12/2005
2622	BOUCCARA	Didier	23/01/2007	RE-DE	BOUCHARA RECORDATI	Conception de documents destinés à la formation interne	aucune rémunération	01/2003	12/2004
2622	BOUCCARA	Didier	23/01/2007	IP-AC	UCB PHARMA	Rapport ponctuel	aucune rémunération	01/2005	03/2005
2622	BOUCCARA	Didier	23/01/2007	CF-INT	GROUPE AMPLIFON	Participation à un groupe assurant régulièrement (2 à 3 fois/an) une formation sur les vertiges	rémunération personnelle	01/2006	
2622	BOUCCARA	Didier	23/01/2007	CF-AUD	BOUCHARA RECORDATI	Symposium international maladie de Ménière 2005 - Los Angeles		03/2005	03/2005
2622	BOUCCARA	Didier	23/01/2007	CF-AUD	UCB PHARMA	Symposium International Tinnitus 2005 - Pau (France)		09/2005	09/2005
2622	BOUCCARA	Didier	13/06/2006	LD-AR	AMPLIFON (CCA GROUPE)	Réunions de formation consacrées au matériel de vidéonystagmographie□□explorations fonctionnelles ORL	rémunération personnelle	06/2005	
2622	BOUCCARA	Didier	13/06/2006	LD-AR	GRAND AUDITION	conseil et animation de réunions de formation	rémunération personnelle	06/2005	
2622	BOUCCARA	Didier	13/06/2006	EC-CO	COLLIN ORL	etude PO : étude d'un test diagnostic portant sur l'auto-immunité oreille interne	co-investigateur	01/2004	12/2006
2622	BOUCCARA	Didier	13/06/2006	EC-CO	MEDTRONIC XOMED	Evaluation de l' apport thérapeutique du MENIETT ® au cours de la maladie de Ménière	co-investigateur	01/2003	12/2005
2622	BOUCCARA	Didier	13/06/2006	RE-AUT	UCB	Utilisation du Xyzall au cours de la rhinite allergique (pas de rémunération directe -financement congrès)	aucune rémunération	01/2005	12/2005
2622	BOUCCARA	Didier	13/06/2006	RE-AUT	SERVIER	Participation à un groupe de travail évaluant les résultats audiométriques au cours d'une étude clinique Trim	rémunération personnelle	01/2004	12/2004
2622	BOUCCARA	Didier	13/06/2006	IP-AC	BOUCHARA	Elaboration d'un support pour formation interne□□pas de rémunération directe financement congrès	aucune rémunération	01/2003	12/2004
2622	BOUCCARA	Didier	13/06/2006	CF-INT	ASTRA ZENECA	Participation à un symposium consacré à la rhinite allergique lors du Rhinoforum à Poitiers	rémunération personnelle	01/2003	12/2003
2622	BOUCCARA	Didier	13/06/2006	CF-AUD	COCHLEAR France	Symposium consacré aux résultats de l'implantation cochléaire avec l'implant électroacoustique - Toulouse -	France	12/2005	12/2005
2622	BOUCCARA	Didier	05/12/2005	LD-AR	PFIZER	Participation à un groupe de travail sur la Pivalone Neomycine - 1999-2002	Rémunération personnelle	01/1999	12/2002
2622	BOUCCARA	Didier	05/12/2005	LD-AR	SERVIER	Participation à un groupe d'expert dans le cadre d'une étude clinique	Rémunération personnelle	01/2004	12/2004
2622	BOUCCARA	Didier	05/12/2005	EC-INV	COLLIN ORL France	Etude clinique implant Cochleaire bilatéral	Pas de rémunération personnelle	01/2003	12/2005
2622	BOUCCARA	Didier	05/12/2005	EC-INV	COLLIN ORL France	Etude clinique d'un marqueur biologique de l'autoimmunité de l'oreille	Coordonnateur-Pas de rémunération personnelle	01/2004	12/2005
2622	BOUCCARA	Didier	05/12/2005	EC-CO	COCHLEOR France	Etude clinique implant cochleaire Electro acoustique	Co-investigateur-Pas de rémunération personnelle	01/2003	12/2005
2622	BOUCCARA	Didier	05/12/2005	IP-RE	BOUCHARA RECORDATI	Conception de documents destinés à la formation interne	Aucun rémunération	01/2003	12/2004

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62622	BOUCCARA	Didier	05/12/2005	IP-AC	UCB PHARMA	Rapport ponctuel	Aucune	01/2005	03/2005
62622	BOUCCARA	Didier	05/12/2005	IP-CF	GLAXO	Journée de formation ORL PARIS	Rémunération personnelle	03/2001	03/2001
62622	BOUCCARA	Didier	05/12/2005	IP-CF	EUTHERAPIE	Plusieurs réunions de FMC		01/2002	12/2003
62622	BOUCCARA	Didier	05/12/2005	CF-AUD	BOUCHARA RECORDATI	Symposium international maladie de Ménière / Los Angeles		03/2005	03/2005
62622	BOUCCARA	Didier	05/12/2005	CF-AUD	UCB PHARMA	Symposium International Acouphènes (Tinnitus 2005) Pau France		09/2005	09/2005
62622	BOUCCARA	Didier	12/04/2005	CF-INT	ASTRA ZENECA	RHINOFORUM 2003		01/2003	12/2003
62622	BOUCCARA	Didier	12/04/2005	IP-AC	SERVIER	participation à un groupe de travail sur Vastarel. Etude cochlée : analyse des données audiométriques			
62622	BOUCCARA	Didier	12/04/2005	CF-AUD	BOUCHARA	Symposium Maladie de Ménière . Pas d'intervention. Rédaction d'un résumé du congrès.		01/2005	12/2005
62622	BOUCCARA	Didier	04/01/2003	IP-AC	PFIZER	Participation à un groupe de travail sur la Pivalone Neomycine - arrêt d'activité en 2002			
62622	BOUCCARA	Didier	04/01/2003	IP-CF	EUTHERAPIE	Réunions de FMC sans rémunération directe			
62622	BOUCCARA	Didier	04/01/2003	IP-CF	GLAXO (SARL)	En 2001, participation à une journée			
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	JANSSEN	Rencontre scientifique sur les antipsychotiques à action prolongée (Montpellier)	rémunération personnelle	06/2009	06/2009
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	BIOCODEX	Symposium sur anxiété aux différents stades de la vie (aspects biologiques)	rémunération personnelle	06/2009	06/2009
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	SERVIER	Congrès de la WPA . Florence : symposium agomélatine (Valdoxan)	Rémunération personnelle	04/2009	04/2009
60293	BOULENGER	Jean-Philippe	08/08/2009	IP-AC	LUNDBECK DANEMARK	Board scientifique escitalopram	rémunération personnelle	05/2009	05/2009
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	SANOFI-AVENTIS TUNISIE	Symposium : Innovations thérapeutiques dans la dépression (Athènes)	rémunération personnelle	11/2008	11/2008
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	LILLY	Congrès CIPPEG : état dépressif du sujet âgé (Montpellier)	rémunération personnelle	12/2008	12/2008
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	SANOFI-AVENTIS TUNISIE	Symposium sur troubles anxieux et leur traitement (Tozeur)	rémunération personnelle	03/2009	03/2009
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	LILLY	Congrès CIPPEG (Montpellier)	rémunération personnelle	12/2008	12/2008
60293	BOULENGER	Jean-Philippe	08/08/2009	CF-INT	SANOFI-AVENTIS	Symposium innovation thérapeutique . Athènes	Rémunération personnelle	11/2008	11/2008
60293	BOULENGER	Jean-Philippe	08/08/2009	EC-CO	BIOCODEX	Caractérisation psychophysiologique des troubles de l'adaptation . Pas de produit impliqué dans cette étude	membre du comité scientifique	01/2009	
60293	BOULENGER	Jean-Philippe	08/08/2009	EC-CO	SIGMA-TAU	Etude Lysanxia vs Xanax dans le sevrage des traitements benzodiazépiniques	membre du comité scientifique	01/2009	
60293	BOULENGER	Jean-Philippe	08/08/2009	EC-INV	LUNDBECK	LUAA21004 : étude de prévention de rechute dans trouble anxieux généralisé	coordonnateur national	06/2008	
60293	BOULENGER	Jean-Philippe	08/08/2009	EC-CO	SANOFI-AVENTIS	Programme-pilote d'accès au médicament en santé mentale dans les pays en développement	membre du comité scientifique	01/2008	
60293	BOULENGER	Jean-Philippe	20/09/2008	CF-INT	SANOFI-AVENTIS	FMC sur dépression pour les psychiatres d'Afrique du Nord□□Conférence sur l'escitalopram	Rémunération personnelle	10/2008	11/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	CF-INT	EUTHERAPIE	FMC sur dépression et troubles du rythme veille-sommeil	Rémunération personnelle	09/2008	09/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	CF-INT	BIOCODEX	FMC sur le diagnostic des troubles anxieux en médecine générale	Rémunération personnelle	06/2008	06/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	CF-INT	PIERRE FABRE	FMC sur la fibromyalgie□□Conférence sur la prise en charge psychiatrique	Aucune rémunération	05/2008	05/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	CF-INT	BIOCODEX	Symposium sur les troubles de l'adaptation□□Conférence sur les aspects neuro - biologiques de la vulnérat	Rémunération personnelle	03/2008	03/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	CF-INT	LUNDBECK	Congrès de l'Encéphale : Conférence sur les antidépresseurs ISRS	Rémunération personnelle	01/2008	01/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	IP-AC	ASTRA-ZENECA	Conseils scientifiques pour le développement du produit AZD 3480	Rémunération personnelle	03/2008	03/2008
60293	BOULENGER	Jean-Philippe	20/09/2008	EC-CO	SANOFI-AVENTIS	Programme-pilote d'accès au médicament en santé mentale dans les pays en développement	membre du comité scientifique	01/2008	
60293	BOULENGER	Jean-Philippe	20/09/2008	EC-INV	LUNDBECK	LUAA21004 : étude de prévention de rechute dans trouble anxieux généralisé	coordonnateur national	06/2008	
60293	BOULENGER	Jean-Philippe	20/09/2008	IP-AUT	PIERRE FABRE	CD-Rom sur l'évaluation clinique en psychiatrie	Coordonateur et rédacteur	10/2007	01/2008
60293	BOULENGER	Jean-Philippe	13/08/2007	CF-INT	LUNDBECK	Conférence sur la comorbidité anxiété-dépression au congrès régional de l'ECNP - Sofia	Rémunération personnelle	04/2007	04/2007
60293	BOULENGER	Jean-Philippe	13/08/2007	EC-CO	LYNAPHARM	Etude des symptomes de sevrage : Prazépam vs Alprazolam	membre du comité scientifique	02/2007	
60293	BOULENGER	Jean-Philippe	13/08/2007	CF-INT	LILLY	Conférence à l'occasion d'un atelier sur la dépression - Moscou	Rémunération personnelle	01/2007	01/2007
60293	BOULENGER	Jean-Philippe	13/08/2007	CF-INT	BIOCODEX	FMC sur les troubles de l'adaptation - Perpignan	Rémunération personnelle	02/2007	02/2007
60293	BOULENGER	Jean-Philippe	13/08/2007	CF-INT	SERVIER	Conférences sur la dépression à l'occasion des 1ères journées franco-chinoises de psychiatrie	Aucune rémunération	09/2007	09/2007
60293	BOULENGER	Jean-Philippe	13/08/2007	IP-AC	LUNDBECK	Participation à un board d'experts-consultants	Rémunération personnelle	09/2007	09/2007
60293	BOULENGER	Jean-Philippe	13/08/2007	EC-INV	LUNDBECK	LU AA21004 : étude de prévention de rechute dans les états dépressifs majeurs	coordinateur international	06/2005	
60293	BOULENGER	Jean-Philippe	29/11/2006	CF-INT	SERVIER-EUTHERAPIE	Pékin : Présentation agomélatine au 1ères rencontres franco-chinoises de neurologie	Rémunération personnelle	11/2006	11/2006
60293	BOULENGER	Jean-Philippe	29/11/2006	CF-INT	VEDIM-PHARMA	Montpellier : FMC anxiété□□Discussion cas cliniques	Rémunération personnelle	11/2006	11/2006
60293	BOULENGER	Jean-Philippe	29/11/2006	CF-INT	LUNDBECK	Arles : FMC antidépresseurs : Résultats essais escitalopram	Rémunération personnelle	10/2006	10/2006
60293	BOULENGER	Jean-Philippe	29/11/2006	IP-AC	ASTRA-ZENECA	Conseil quétiapine	Rémunération personnelle	11/2006	11/2006
60293	BOULENGER	Jean-Philippe	15/08/2006	CF-AUD	LUNDBECK CANADA	Congrès APA Toronto		05/2006	05/2006
60293	BOULENGER	Jean-Philippe	15/08/2006	CF-INT	BIOCODEX	Conférence sur dépression du sujet agé / moclobémide	Rémunération personnelle	06/2006	06/2006
60293	BOULENGER	Jean-Philippe	15/08/2006	CF-INT	ARDIX	Conférence sur la biologie de la dépression à Avignon	Rémunération personnelle	05/2006	05/2006
60293	BOULENGER	Jean-Philippe	15/08/2006	CF-INT	ARDIX		Aucune rémunération	01/2005	12/2005
60293	BOULENGER	Jean-Philippe	15/08/2006	IP-AC	PFIZER	Groupe de travail prégabaline	Rémunération personnelle	01/2006	12/2006
60293	BOULENGER	Jean-Philippe	15/08/2006	EC-INV	ASTRA-ZENECA	Quétiapine : essai clinique - anxiété généralisée	investigateur principal France	05/2006	07/2007
60293	BOULENGER	Jean-Philippe	04/03/2006	IP-AC	GSK	Hypnotiques nouveaux	Rémunération personnelle	10/2005	12/2005
60293	BOULENGER	Jean-Philippe	04/03/2006	EC-INV	LUNDBECK	Escitalopram : essai clinique - dépression	investigateur principal (en cours)	12/2003	07/2006
60293	BOULENGER	Jean-Philippe	04/03/2006	EC-CO	GSK	Paroxétine : suivi des prescriptions dans anxiété généralisée	collaborateur (en cours)	10/2003	12/2005
60293	BOULENGER	Jean-Philippe	04/03/2006	IP-AC	LUNDBECK	Conseil Escitalopram	rémunération personnelle	01/2002	12/2006
60293	BOULENGER	Jean-Philippe	04/03/2006	IP-AC	WYETH	Groupe de travail Gabapentine	rémunération personnelle	01/2005	01/2006
60293	BOULENGER	Jean-Philippe	04/03/2006	IP-AC	SERVIER	Groupe de travail Agomelatine	rémunération personnelle	01/2006	12/2006
60293	BOULENGER	Jean-Philippe	04/03/2006	IP-AC	GSK	Conseil - Hypnotiques		09/2005	12/2005
60293	BOULENGER	Jean-Philippe	04/03/2006	CF-INT	ARDIX, BIOCODEX, VEDIM PHARMA, LUNDBECK	Conférences sur l'anxiété, dépression et leur traitement	rémunération personnelle - une intervention pour chaque laboratoire (je n'ai noté ni les dates ni les lieux)	01/2005	12/2005
60293	BOULENGER	Jean-Philippe	04/03/2006	CF-AUD	WYETH	Congrès APA / Atlanta (USA)		05/2005	12/2005
60293	BOULENGER	Jean-Philippe	04/03/2006	CF-AUD	GSK	Congrès ECNP / Amsterdam		10/2005	12/2005
60293	BOULENGER	Jean-Philippe	19/07/2004	EC-INV	LUNDBECK	Escitalopram et TOC, escitalopram et dépression	rémunération personnelle	01/2003	
60293	BOULENGER	Jean-Philippe	19/07/2004	EC-CO	JANSSEN	Ripéridone et schizophrénie	rémunération versée à une association	01/2003	12/2004
60293	BOULENGER	Jean-Philippe	19/07/2004	IP-AC	WYETH	Venlafaxine et phobie sociale	rémunération personnelle	01/2004	08/2005
60293	BOULENGER	Jean-Philippe	19/07/2004	EC-CO	GSK - WYETH	Paroxetine et phobie sociale	rémunération personnelle (Le laboratoire est seulement WYETH ; l'élude est sur paroxetine et anxiete generalisee)	10/2003	
60293	BOULENGER	Jean-Philippe	19/07/2004	IP-AC	SANOFI SYNTHELABO	Clorazepate : positionnement	Rémunération personnelle	01/2004	12/2004
60293	BOULENGER	Jean-Philippe	19/07/2004	IP-AC	VEDIM PHARMA	Hydroxyzine : positionnement	Rémunération personnelle	01/2004	08/2005
60293	BOULENGER	Jean-Philippe	19/07/2004	IP-AC	ASTRA ZENECA	Quetiapine : positionnement	Rémunération personnelle	07/2003	12/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
0293	BOULENGER	Jean-Philippe	19/07/2004	IP-AC	LUNDBECK	Escitalopram : positionnement	Rémunération personnelle	01/2001	
0293	BOULENGER	Jean-Philippe	19/07/2004	IP-CF	GSK	FMC : troubles anxieux			
0293	BOULENGER	Jean-Philippe	19/07/2004	IP-CF	ARDIX - LUNDBECK	FMC : dépression			
0293	BOULENGER	Jean-Philippe	19/07/2004	IP-AUT	GSK	Invitation congrès ECNP			
0293	BOULENGER	Jean-Philippe	19/07/2004	IP-AUT	WYETH	Invitation congrès APA			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-EC	LUNDBECK	Escitalopram - Coordination étude TOC (2003)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-EC	LUNDBECK	Escitalopram - Coordination étude TAG (2001)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-EC	LUNDBECK	Esccitalopram - Coordination étude phobie sociale (2000)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-RE	PFIZER	Sertraline et troubles paniques (2000)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	ASTRA ZENECA	Développement sertindole (2003)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	BRISTOL MYERS SQUIBB	Développement aripiprazole (2003)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	CHIESI	Etude paroxitine (2002)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	LUNDBECK	Développement excitalopram (2001, 2002, 2003)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	PARKE DAVIS	Développement pagoclone (2000)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	ROCHE NICHOLAS	Etudes Euphytose (2001)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	SANOFI SYNTHELABO	Etudes Clorazepate (2002)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	SMITHKLINE BEECHAM/GLAXO SMITHKLINE	Positionnement paroxetine (2001, 2002)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	UCD PHARMA	Etudes hydroxyzine (2000, 2002)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-AC	WYETH LEDERLE	Positionnement venlafaxine (2000, 2002)			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	ARDIX	1999, 2000, 2001			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	BIOCODEX	1999			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	JANSSEN	1999, 2000, 2002			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	LILLY	1999, 2000, 2001, 2002			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	LUNDBECK	1999, 2003			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	PIERRE FABRE	2000			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	PFIZER	2001			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	SANOFI	2002			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	SMITHKLINE BEECHAM/GLAXO SMITHKLINE	1999, 2000, 2001, 2002			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	VEDIM PHARMA	1999, 2000			
0293	BOULENGER	Jean-Philippe	16/09/2003	IP-CF	WYETH LEDERLE	1999, 2000, 2001, 2002			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-EC	LUNDBECK	Coordination d'un essai national sur Seropram® et phobie sociale			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-RE	PFIZER	Rapport sur sertraline et panique			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-CF	PFIZER	Stress, troubles de l'adaptation			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-CF	LILLY	Troubles anxieux			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-CF	SMITHKLINE BEECHAM	Troubles dépressifs			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-CF	WYETH LEDERLE	Traitements pharmacologiques			
0293	BOULENGER	Jean-Philippe	09/07/2000	IP-CF	UCB PHARMA	Thérapies comportementales			
0067	BREART	Gérard	01/01/1999	IP-EC	Air Liquide Santé				
0067	BREART	Gérard	01/01/1999	IP-AC	Laboratoire Iprad				
0067	BREART	Gérard	01/01/1999	IP-AC	Laboratoire Servier				
0067	BREART	Gérard	01/01/1999	IP-AC	Laboratoire Fournier				
0067	BREART	Gérard	01/01/1999	VB	Contrat avec l'Inserm et les laboratoires Serono pour subvention d'une étude.		Inserm		
0067	BREART	Gérard	01/01/1998	IP-AUT	Air Liquide Santé				
0067	BREART	Gérard	01/01/1998	IP-AUT	Innothéra				
0067	BREART	Gérard	01/01/1998	IP-AUT	Lilly				
0067	BREART	Gérard	01/01/1998	IP-AUT	Fournier				
0067	BREART	Gérard	01/01/1998	VB	Sérono		Avec l'INSERM		
0067	BREART	Gérard	01/01/1998	VB	Lilly		Avec l'INSERM		
0067	BREART	Gérard	01/01/1998	VB	Fournier		Avec l'INSERM		
0067	BREART	Gérard	01/01/1998	VB	MSD Chibret		Avec l'INSERM		
0698	BRICAIRE	Claire	09/06/2000	IP-RE	SERVIER	Experte du Groupe de travail sur la ménopause			
0698	BRICAIRE	Claire	09/06/2000	IP-CF		Enseignement post-universitaire - Enseignement endocrinologie - reproduction (diplôme universitaire)			
3017	BRION	Jean-Daniel	08/02/2009	EC-INV	LABORATOIRES SERVIER	Recherche pharmacochimique de molécules à potentialité thérapeutique	Contrat de recherche : Université Paris-Sud - CNRS - SERVIER Responsable de la synthèse chimique des molécules	10/2000	09/2009
0920	BROCH-OLIERIC	Chantal	28/01/2000	IP-EC	SERVIER (Orléans)	Stage de 6 mois dans le cadre du DESS de Pharmacocinétique et métabolisme des médicaments : mise au point d'un modèle d'étude de l'absorption intestinale			
0069	BRONNER	Claude	10/03/2010	(Autre)	FORMATEUR FMC	Organisateur, animateur et expert de formations		05/1985	
0069	BRONNER	Claude	10/03/2010	(Autre)	PRéSIDENT DE SYNDICAT DE MéDECINS	Défense des médecins		11/2005	
0069	BRONNER	Claude	31/03/2009	CF-INT	MYLAN	Soirée TSO	Rémunération personnelle	02/2009	02/2009
0069	BRONNER	Claude	31/03/2009	CF-INT	SCHERING PLOUGH	Soirées de formation sur Entretiens motivationnels et Addictions(Quelques soirées)	Rémunération personnelle	04/2009	
0069	BRONNER	Claude	31/03/2009	IP-AC	SCHERING PLOUGH	Participation à l'élaboration d'un CD Rom destiné aux professionnels et patients sur le traitement des hépatit	Rémunération personnelle	12/2008	
0069	BRONNER	Claude	31/03/2009	IP-AC	MYLAN	Comité de lecture d'une revue financée par le laboratoire	Rémunération personnelle	02/2009	
0069	BRONNER	Claude	16/12/2008	IP-AC	MYLAN	Journée de réflexion	Rémunération personnelle	11/2008	11/2008
0069	BRONNER	Claude	07/02/2008	EC-CO	SCHERING PLOUGH	Ecriture d'un article sur les enquêtes réalisées par TNS Healthcare (enquêtes APPROPOS)	Co rédacteur	12/2007	11/2008
0069	BRONNER	Claude	11/12/2007	CF-INT	SCHERING PLOUGH	Participation à l'organisation d(un module de formation "Entretiens motivationnels"	Rémunération personnelle	09/2007	
0069	BRONNER	Claude	11/12/2007	CF-INT	SCHERING PLOUGH	Participation à la conception d'un module de formation (actualités TSO), formation de formateurs, animation	Rémunération personnelle	04/2007	
0069	BRONNER	Claude	29/10/2006	CF-AUD	SCHERING PLOUGH	Congrès Europad (Bratislava)		10/2006	10/2006
0069	BRONNER	Claude	09/05/2006	CF-INT	SCHERING PLOUGH	Colloque Pragma (Paris, suite Agora)	Rémunération personnelle	03/2006	03/2006
0069	BRONNER	Claude	09/05/2006	CF-INT	SCHERING PLOUGH	Soirée Agora à Ostwald (67) sur le mésusage	Rémunération personnelle	02/2006	02/2006
0069	BRONNER	Claude	03/01/2006	VB	SCHERING PLOUGH	Congrès Maternité et Addiction à Dolleren	Réseau Ville Hopital Strasbourg	09/2005	10/2005
0069	BRONNER	Claude	03/01/2006	IP-AUT	SCHERING PLOUGH	Journée Bilan Subutex à Paris		11/2005	11/2005
0069	BRONNER	Claude	03/01/2006	CF-INT	SCHERING PLOUGH	journées de formation aux entretiens motivationnels pour des groupes de soignants (5 en 2005)	Rémunération personnelle	10/2004	06/2006
0069	BRONNER	Claude	22/05/2005	IP-AUT	SCHERING PLOUGH	Financement d'un congrès annuel		01/2000	12/2005
0069	BRONNER	Claude	22/05/2005	VB	SCHERING PLOUGH	Réseau Valle Hopital avec financement d'actions ponctuelles		01/2005	12/2005
0069	BRONNER	Claude	29/07/1999	IP-CF	SCHERING PLOUGH	Soirées toxicomanie (1 à 3 par an)			
0069	BRONNER	Claude	01/01/1999	IP-EC	SCHERING PLOUGH	Spesud			
0069	BRONNER	Claude	01/01/1999	IP-EC	BIG PRO 2				
0069	BRONNER	Claude	01/01/1999	IP-EC	FORM PHARMA (Médiator)				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10069	BRONNER	Claude	01/01/1999	IP-CF	SCHERING PLOUGH	Expert dans des formations en toxicomanie (2 à 3 fois par an)			
10069	BRONNER	Claude	01/01/1998	IP-AUT	Schering				
10069	BRONNER	Claude	01/01/1998	IP-AUT	Servier				
60379	BROUARD	Agnès	01/07/2000	IP-AUT	LABORATOIRE SERVIER	(conference hippocrate) formation préparation prolcat			
60379	BROUARD	Agnès	01/07/2000	(Autre)	SANOFI SYNTHELABO	conjoint			
60254	BRUCKERT	Eric	15/10/2007	EC-INV	PFIZER	Etude Torcetrapid et épaisseur intima média	rémunération versée sur association loi 1901 : nouvelle Société Française d'Athérosclérose		12/2007
60254	BRUCKERT	Eric	15/10/2007	EC-INV	TAKEDA	Etude TAK 475 chez les patients homozygotes	rémunération versée sur association loi 1901 : nouvelle Société Française d'Athérosclérose		
60254	BRUCKERT	Eric	15/10/2007	EC-INV	FOURNIER DIJON	Etude fenofibrate et vigilance	rémunération versée sur association loi 1901 : nouvelle Société Française d'Athérosclérose		
60254	BRUCKERT	Eric	15/10/2007	EC-INV	MSD	Etude MK et épaisseur intima média	rémunération versée sur association loi 1901 : nouvelle Société Française d'Athérosclérose		
60254	BRUCKERT	Eric	15/10/2007	EC-INV	GENZYME	Etude colestagel	rémunération versée sur association loi 1901 : nouvelle Société Française d'Athérosclérose		
60254	BRUCKERT	Eric	15/10/2007	CF-INT	Astra Zeneca, MSD, Pfizer, Sanofi-Avantis, Shering-Plough, Merck, Servier.	La quasi-totalité sont des présentations orales lors de symposiums Nationaux ou internationaux	Dans des symposiums, enseignements post universitaires, club de spécialistes (industrie pharmaceutique		
60254	BRUCKERT	Eric	15/10/2007	IP-RE	Pierre Fabre, Astra Zeneca, MSD, Pfizer, Fournier, Sanofi-Avantis, Merck, Servier, MADAUS	Participations ponctuelles à des travaux de recherche, phase II à phase IV sur les médicaments.			
60254	BRUCKERT	Eric	15/10/2007	IP-AC	Astra Zeneca, Pfizer, Sanofi Avantis, Pierre Fabre				
60254	BRUCKERT	Eric	15/10/2007	VB	MSD, Pfizer, Shering-Plough, BMS, MADAUS	Versement à la nSFA pour des travaux de recherche sur les médicaments effectués dans le service d'endocrinologie-métabolisme de la Pitié Salpétrière			
60254	BRUCKERT	Eric	15/10/2007	(Autre)		aucune activité durable ni intérêt financier ni rapport d'expertise sur une durée de 5 ans. Les activités ponctuelles sur une période de 5 ans sont trop nombreuses pour être notée			
60254	BRUCKERT	Eric	25/02/2005	IP-EC	PFIZER	CETP			
60254	BRUCKERT	Eric	25/02/2005	IP-EC	MERCK SHARP	Ezetimibe			
60254	BRUCKERT	Eric	25/02/2005	IP-CF		très nombreuses interventions			
60254	BRUCKERT	Eric	25/02/2005	VB	Société Française d'Athérosclérose	perçoit les sommes d'argent correspondant aux protocoles			
60254	BRUCKERT	Eric	25/02/2005	(Autre)	Société Française d'Athérosclérose	Membre et président			
60254	BRUCKERT	Eric	25/02/2005	(Autre)	FOURNIER	négociation pour un protocole sur le lipanthyl			
60254	BRUCKERT	Eric	25/02/2005	(Autre)	ASTRA ZENECA	Etudes hors produits mais avec des laboratoires pharmaceutiques - éducation thérapeutique			
60254	BRUCKERT	Eric	25/02/2005	(Autre)	SANOFI, PIERRE FABRE (etc)	Plusieures études, enquêtes phase IV			
60254	BRUCKERT	Eric	20/03/2004	IP-EC	TOUS LABORATOIRES		Trop nombbreux pour être détaillés - concerne tous les laboratoires		
60254	BRUCKERT	Eric	20/03/2004	IP-RE	TOUS LABORATOIRES				
60254	BRUCKERT	Eric	20/03/2004	IP-AC	TOUS LABORATOIRES				
60254	BRUCKERT	Eric	20/03/2004	IP-CF	TOUS LABORATOIRES				
60254	BRUCKERT	Eric	20/03/2004	VB		Activité de recherche			
60254	BRUCKERT	Eric	20/03/2004	(Autre)		parent salarié : à ma connaissance non mais ma famille comporte plus de 300 personnes			
60254	BRUCKERT	Eric	03/07/2000	IF	NOVARTIS	1 action			
60254	BRUCKERT	Eric	03/07/2000	IP-EC	L'ensemble des laboratoires	Participation à de nombreux essais cliniques			
60254	BRUCKERT	Eric	03/07/2000	IP-AC	Avec la plupart des laboratoires	Conseils ponctuels			
60254	BRUCKERT	Eric	03/07/2000	IP-CF	Fréquent, ensemble des laboratoires	Prise en charge des hyperlipidémies, diabétiques, etc			
60254	BRUCKERT	Eric	03/07/2000	VB		Protocoles cliniques d'étude des médicaments			
10080	CAPRON	Loïc	01/01/1999	IP-CF	SANOFI WINTHROP	Séminaires intensifs : Thrombose			
10080	CAPRON	Loïc	01/01/1999	VB	Groupe EGICCA/SYNTHELABO				
10080	CAPRON	Loïc	01/01/1998	IP-AUT	Sanofi				
10080	CAPRON	Loïc	01/01/1998	IP-AUT	Bristol Myers Squibb				
10080	CAPRON	Loïc	01/01/1998	IP-AUT	Merck Sharp Dohme				
10080	CAPRON	Loïc	01/01/1998	IP-AUT	Servier				
10080	CAPRON	Loïc	01/01/1998	IP-AUT	Hoechst				
10080	CAPRON	Loïc	01/01/1998	IP-AUT	Synthélabo				
10080	CAPRON	Loïc	01/01/1998	VB	Hoechst		Association Claude Bernard		
10080	CAPRON	Loïc	01/01/1998	VB	Bayer		Association Claude Bernard		
10080	CAPRON	Loïc	01/01/1998	VB	Synthélabo		Association Claude Bernard		
10081	CARLIER	Patrick	30/01/2010	CF-AUD	ASTRA ZENECA	Riga/ rencontres medecine générale		03/2009	03/2009
10081	CARLIER	Patrick	30/01/2010	CF-AUD	EXPENSCIENCE	Lisbonne/Congrès médecine générale		10/2009	10/2009
10081	CARLIER	Patrick	30/01/2010	CF-INT	ASTRA ZENECA	3 Réunions de FMC avec la SFMG dans l'année 2009	Rémunération personnelle	06/2009	12/2009
10081	CARLIER	Patrick	23/09/2008	IP-AC	IPRAD	Extension d'AMM SECNOL® (groupe de travail)	aucune rémunération	01/2008	
10081	CARLIER	Patrick	20/11/2007	Néant					
10081	CARLIER	Patrick	22/05/2006	IP-AC	SERVIER	Relecture de rapport ivrabradine (avant dépot d'AMM) (données de reproduction)	aucune rémunération	01/2005	03/2005
10081	CARLIER	Patrick	22/05/2006	CF-AUD	BOEHRINGER INGELHEIM	Eurostage - Montréal		04/2006	04/2006
10081	CARLIER	Patrick	27/04/2006	IP-AC	SERVIER	Relecture critique d'un dossier de tératologie expérimentale (XXX) avant demande d'AMM□□(réunion après	Aucune rémunération	02/2005	02/2005
10081	CARLIER	Patrick	27/04/2006	CF-AUD	BOEHRINGER INGELHEIM	Eurostage - Cardiologie / Montréal		04/2006	04/2006
10081	CARLIER	Patrick	15/02/2006	CF-AUD	BOEHRINGER INGELHEIM	Echanges Franco Canadien de médecine		04/2006	04/2006
10081	CARLIER	Patrick	15/02/2006	EC-CO	BMS		Expérimentateur non principal	10/2004	10/2006
60931	CESARO	Pierre	13/09/2004	IP-EC	SERVIER	Coordination d'un essai multicentrique			
60931	CESARO	Pierre	13/09/2004	IP-EC	SANOFI	Essai phase III international + essai phase II			
60931	CESARO	Pierre	13/09/2004	IP-EC	BIOGEN	Essai phase III			
60931	CESARO	Pierre	13/09/2004	IP-EC	SCHWARZ	Essai phase III			

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60931	CESARO	Pierre	13/09/2004	IP-AC	NOVARTIS	2 réunions par an (ENTACAPONE)			
60931	CESARO	Pierre	13/09/2004	IP-AC	SERVIER	2 réunions par an (TRIVASTA)			
60931	CESARO	Pierre	13/09/2004	IP-AC	SCHWARTZ	2 réunions par an (ROTIGOTINE)			
60931	CESARO	Pierre	22/05/2004	IP-EC	SERVIER	Essai - Conseil			
60931	CESARO	Pierre	22/05/2004	IP-EC	NOVARTIS	Essai			
60931	CESARO	Pierre	22/05/2004	IP-AC	NOVARTIS	Conseil (groupe entacopore)			
60931	CESARO	Pierre	22/05/2004	IP-AC	SERVIER	Conseil sur le développement			
60931	CESARO	Pierre	22/05/2004	IP-AC	UCB	A venir			
60931	CESARO	Pierre	22/05/2004	IP-CF	LILLY	1 colloque/an			
60931	CESARO	Pierre	22/05/2004	IP-CF	NOVARTIS	1 colloque/an			
60931	CESARO	Pierre	22/05/2004	IP-CF	SERVIER	2-4 FMC en 2003			
60931	CESARO	Pierre	22/05/2004	VB	SCHERING AG	Contrat BEST- AP-HP			
60931	CESARO	Pierre	25/02/2000	IP-EC	SERVIER	Coordonnateur national d'un essai clinique de Piribedil (1999-2000)			
60931	CESARO	Pierre	25/02/2000	IP-EC	SERVIER	Essai clinique de Sulbutiamine (2000)			
60931	CESARO	Pierre	25/02/2000	IP-EC	NOVARTIS	Essai clinique Entacapone (1998-1999)			
60931	CESARO	Pierre	25/02/2000	IP-EC	SERONO	Essai clinique REBIF (1999-2000)			
60931	CESARO	Pierre	25/02/2000	IP-RE	RHONE POULENC	Expertise sur Riluzole (1997)			
60931	CESARO	Pierre	25/02/2000	IP-AC	PHARMACIA UPJOHN	Conseil Mirapexin			
60931	CESARO	Pierre	25/02/2000	IP-AC	LILLY	Conseil Pergolide			
60931	CESARO	Pierre	25/02/2000	IP-CF	NOVARTIS	Colloque Comtan-Pan (1999)			
60931	CESARO	Pierre	25/02/2000	IP-CF	SERVIER	Colloque International Trivestal			
61888	CHABBERT-BUFFET	Nathalie	21/10/2003	IP-EC	HRA PHARMA	(En discussion) - contraception			
61888	CHABBERT-BUFFET	Nathalie	21/10/2003	IP-CF	IFSI	Cours			
61888	CHABBERT-BUFFET	Nathalie	10/09/2002	IP-EC	NOVO	Etude AITCO			
61888	CHABBERT-BUFFET	Nathalie	10/09/2002	IP-EC	HRA PHARMA				
61888	CHABBERT-BUFFET	Nathalie	10/09/2002	IP-CF	FORA ORION	Formation de visiteurs médicaux			
61888	CHABBERT-BUFFET	Nathalie	10/09/2002	IP-AUT		Références en GO ; membre comités de rédaction			
61888	CHABBERT-BUFFET	Nathalie	04/05/2004	IP-EC	ORGANON	Essais cliniques			
61888	CHABBERT-BUFFET	Nathalie	04/05/2001	IP-EC	NOVO	Essais cliniques			
61888	CHABBERT-BUFFET	Nathalie	04/05/2001	IP-RE	SERVIER	Ménopause (01/01 à 03/01)			
61888	CHABBERT-BUFFET	Nathalie	04/05/2001	IP-AC	ORION PHARMA	Ménopause (05/01 - ?)			
61888	CHABBERT-BUFFET	Nathalie	04/05/2001	IP-CF	ORION PHARMA	Formation (gynécologie - 01/01-?)			
61888	CHABBERT-BUFFET	Nathalie	04/05/2001	IP-EC	THERAMEX				
64397	CHABRIAT	Hugues	27/01/2009	LD-AR	LUNDBECK	Membre du steering committee (étude DIAS 4 : desmoteplase et infarctus cérébral)	rémunération personnelle	06/2008	12/2010
64397	CHABRIAT	Hugues	27/01/2009	LD-AR	SERVIER	Memebre du steering committee pour la sous étude IRM (étude PERFORM, tenutroban et infarctus cérébral)	rémunération personnelle	01/2008	12/2011
64397	CHABRIAT	Hugues	27/01/2009	LD-AR	JOHNSON & JOHNSON	Membre de l'Adjudication Committee	rémunération personnelle	01/2008	12/2011
64397	CHABRIAT	Hugues	27/01/2009	EC-INV	LUNDBECK	Desmoteplase	Investigateur principal et coordonnateur en France	11/2008	12/2010
64397	CHABRIAT	Hugues	27/01/2009	EC-INV	DELEGATION RECHERCHE CLINIQUE PHRC CADASIL	Suivi d'une cohorte de patients	investigateur principal	01/2006	12/2011
64397	CHABRIAT	Hugues	27/01/2009	EC-CO	DELEGATION RECHERCHE CLINIQUE PHRC	Identification des gènes impliqués dans les leucoencéphalopathies vasculaires - cohorte et analyse clinique	co-investigateur	01/2007	12/2011
64397	CHABRIAT	Hugues	27/01/2009	CF-AUD	LUNDBECK	Réunion VASCOG - Singapour		01/2009	01/2009
64397	CHABRIAT	Hugues	20/11/2007	EC-CO	SERVIER	Etude Perform / Steering committee MRI	Membre SC	01/2007	
64397	CHABRIAT	Hugues	15/06/2006	EC-CO	PAION	Essai DIAS 2 / desmoteplase	Co-investigateur	01/2005	12/2006
64397	CHABRIAT	Hugues	15/06/2006	EC-CO	NOVO-NORDISK	Essai FAST / Novoseven	Co-investigateur	06/2005	
64397	CHABRIAT	Hugues	15/06/2006	EC-CO	EISAI	Donepezil / CADASIL	Co-investigateur	05/2006	06/2006
64397	CHABRIAT	Hugues	15/06/2006	IP-AC	EISAI	Consultation / Donepezil (Ponctuellement)	Rémunération personnelle		
64397	CHABRIAT	Hugues	15/06/2006	CF-INT	EISAI	Conférence VASCOG - Imagerie CADASIL	Aucune rémunération		
64580	CHAMBIN	Odile	10/12/2010	VB	MERCK MEDICATION FAMILIALE	Taxe d'apprentissage	UFR Pharmacie□ Laboratoire de Pharmacie galénique	02/2010	12/2010
64580	CHAMBIN	Odile	10/12/2010	VB	BRISTOL MYERS SQUIBB	Taxe d'apprentissage	UFR Pharmacie□ Laboratoire de Pharmacie galénique	02/2010	12/2010
64580	CHAMBIN	Odile	23/11/2009	VB	LABORATOIRES MERCK, BMS ET PIERRE FABRE	Taxe d'apprentissage pour 2009	UFR Pharmacie□ Laboratoire de Pharmacie Galénique	05/2009	12/2009
64580	CHAMBIN	Odile	23/11/2009	EC-INV	MERCK MEDICATION FAMILIALE	Etude de la comprimabilité d'une formule de comprimés	Expérimentateur	08/2008	05/2009
64580	CHAMBIN	Odile	03/02/2009	VB	SANOFI AVENTIS	Taxe d'apprentissage 2008	UFR Pharmacie□ Laboratoire de Pharmacie Galénique	06/2008	12/2008
64580	CHAMBIN	Odile	03/02/2009	VB	MERCK MEDICATION FAMILIALE	Taxe d'apprentissage 2008	UFR Pharmacie□ Laboratoire de Pharmacie Galénique	06/2008	12/2008
64580	CHAMBIN	Odile	03/02/2009	VB	BRISTOL MYERS SKUIBB	Taxe d'apprentissage 2008	UFR Pharmacie□ Laboratoire de Pharmacie Galénique	06/2008	12/2008
64580	CHAMBIN	Odile	14/01/2008	EC-INV	GATTEFOSSE	Etude sur les propriétés du Gélucire 44/14 (un de leur excipient)	Expérimentateur	01/2006	06/2008
64580	CHAMBIN	Odile	14/01/2008	VB	SANOFI-AVENTIS, MERCK, GLAXO-WELLCOME	Taxe d'apprentissage pour 2007	UFR Pharmacie□ Laboratoire de Pharmacie Galénique	05/2007	10/2007
64580	CHAMBIN	Odile	12/09/2006	EC-INV	GATTEFOSSE	Etude sur les propriétés du Gélucire 44/14 ® (de leur excipient)	expérimentateur	01/2006	09/2007
64580	CHAMBIN	Odile	12/09/2006	VB	SERVIER-MERCK-SANOFI AVENTIS-GLAXO WELLCOME-BRISTOL-MYERS-SQUIBB	Taxe d'apprentissage pour 2006	UFR Pharmacie - Labo de Pharmacie Galénique	05/2006	09/2006
60148	CHAMINADE	Pierre	15/03/2010	VB	TECHNOLOGIES SERVIER	Contrat de Recherche / Thèse CIFRE	Faculté de Pharmacie Paris Sud□ Laboratoire de Chimie Analytique	01/2009	01/2012
60148	CHAMINADE	Pierre	13/02/2009	VB	TECHNOLOGIES SERVIER	Contrat de Recherche / Thèse CIFRE	Faculté de Pharmacie Paris Sud□ Laboratoire de Chimie Analytique	01/2009	01/2012
60148	CHAMINADE	Pierre	29/06/2007	RE-DE	SANOFI AVENTIS	Modification de dossier d'AMM	Rémunération institution	03/2007	03/2007

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60148	CHAMINADE	Pierre	29/06/2007	VB	FLOWGENE	Contrat de recherche Université Paris Sud - Financement d'un doctorant en contrat CIFRE	Faculté de Pharmacie Paris Sud - Laboratoire de Chimie Analytique	01/2007	02/2008
60148	CHAMINADE	Pierre	15/06/2006	RE-DE	SANOFI AVENTIS OTC	Procédure de variation, modification de méthodes de dosage	rémunération versée à une institution	01/2003	12/2006
60148	CHAMINADE	Pierre	15/06/2006	CF-INT	GENZYME	1ères rencontres multidisciplinaires sur la maladie de Fabry - conférence sur les méthodes de dosage - Pari	aucune rémunération	06/2005	06/2005
60148	CHAMINADE	Pierre	15/06/2006	CF-AUD	GENZYME	2èmes rencontres multidisciplinaires sur la maladie de Fabry - conférence sur les éthodes de dosage - Paris	juin 2006	06/2006	06/2006
60148	CHAMINADE	Pierre	15/06/2006	VB	BIOALLIANCE	Contrat de recherche , développement analytique - Université Paris Sud	faculté de pharmacie Paris Sud laboratoire de chimie analytique	06/2005	
60148	CHAMINADE	Pierre	15/06/2006	VB	NOVAGALI	Réalisation de dosages, contrat université Paris Sud n°6752	Faculté de pharmacie Paris Sud - laboratoire de chimie analytique	01/2005	06/2005
60148	CHAMINADE	Pierre	15/06/2006	(Autre)	BUCHI SARL, EUROSEP INSTRUMENTS, FLOWGENE	Instrumentation d'analyse	Mise à disposition de matériel de laboratoire et prototypes (année 2000, 2002, 2005)		
60148	CHAMINADE	Pierre	07/01/2005	IP-RE	SANOFI AVENTIS	Modification méthode d'analyse proche IR			
60148	CHAMINADE	Pierre	07/01/2005	IP-CF	GENZYME	Participation aux journées "Fabry Disease"			
60148	CHAMINADE	Pierre	07/01/2005	(Autre)		Travaux scientifiques en partenariat avec les firmes Eurosep Instruments (délecteur à diffusion de la lumière) et Buchi SARL (spectrométrie dans l'infrarouge proche) donnant lie			
60148	CHAMINADE	Pierre	24/12/2003	IP-CF	EUROSEP INSTRUMENTS	Techniques analytique, délecteur DEDEL			
60148	CHAMINADE	Pierre	24/12/2003	IP-CF	BUCHI SARL	Technique analytique, proche infrarouge			
60148	CHAMINADE	Pierre	24/12/2003	IP-RE	AVENTIS PHARMA	Modification de méthode d'analyse - infra rouge proche			
60148	CHAMINADE	Pierre	24/12/2003	(Autre)	EUROSEP INSTRUMENTS et BUCHI	Travaux scientifique en partenariat (détecteur à diffussion de la lumière) et (spectrométrie dans l'infrarouge proche) donnant lieu à des prêts et mise à disposition d'appareillage			
60148	CHAMINADE	Pierre	19/05/2003	VB	LAVIPHARM S.A.	Université Paris Sud - Faculté de Pharmacie			
60148	CHAMINADE	Pierre	19/05/2003	VB	EUROSEP INSTRUMENTS	Université Paris Sud - Faculté de Pharmacie			
60148	CHAMINADE	Pierre	19/05/2003	VB	BUCHI S.A.	Université Paris Sud - Faculté de Pharmacie			
10092	CHANU	Bernard	31/03/2010	CF-AUD	SANOFI-AVENTIS	JOURNEE D'ACTUALITE DU DIABETE - PARIS	INSCRIPTION□ DEJEUNER	12/2009	12/2009
10092	CHANU	Bernard	31/03/2010	IP-AC	IPSEN	ENTRETIEN "conseil stratégique"	Rémunération personnelle	06/2009	06/2009
10092	CHANU	Bernard	31/03/2010	CF-AUD	SANOFI-AVENTIS	JOURNEE D'ACTUALITE DU DIABETE - PARIS	INSCRIPTION□ DEJEUNER	12/2009	12/2009
10092	CHANU	Bernard	31/03/2010	IP-AC	IPSEN	Entretien conseil stratégique"	Rémunération personnelle	06/2009	06/2009
10092	CHANU	Bernard	22/01/2009	(Autre)	SOLVAY PHARMA - LIPANTHYL	Rédaction et conception d'un carnet de suivi pour les diabétiques de type 2.		06/2008	09/2008
10092	CHANU	Bernard	22/01/2009	(Autre)	SOLVAY PHARMA - LIPANTHYL	Intervention orale à l'European Cardiology Conference for General Practitioners, Budapest - HONGRIE	Epidémiologie des dyslipidémies chez les patients diabétiques de type 2.	06/2007	06/2007
10092	CHANU	Bernard	22/01/2009	(Autre)	NOVARTIS - LESCOL	Rédaction d'un article sur les hypercholestérolémies		03/2006	06/2006
10092	CHANU	Bernard	17/03/2008	CF-AUD	NOVARTIS	MARSEILLE□□ALFEDIAM		03/2007	03/2007
10092	CHANU	Bernard	17/03/2008	CF-INT	SOLVAY PHARMACEUTICALS	EPIDEMIOLOGY OF DUSLIPIDEMIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS	Rémunération personnelle	06/2007	06/2007
10092	CHANU	Bernard	17/03/2008	VB	SERVIER	Prise en charge du salaire d'une attachée de recherche clinique	Nouvelle Société Française d'Athérosclérose	04/2005	03/2006
10092	CHANU	Bernard	17/02/2007	CF-AUD	NOVARTIS	ALFEDIAM - Marseille		03/2007	03/2007
10092	CHANU	Bernard	17/02/2007	VB	SERVIER	Subvention salaire d'une attachée de recherche étrangère	NSFA	10/2005	09/2006
10092	CHANU	Bernard	17/02/2007	CF-AUD	FOURNIER	Congrès annuel de la Société Française d'Endocrinologie - Montpellier		09/2006	09/2006
10092	CHANU	Bernard	17/02/2007	CF-AUD	SANOFI AVENTIS	Journées Européennes de la Société Française de Cardiologie - Paris		01/2007	01/2007
10092	CHANU	Bernard	17/02/2007	CF-AUD	PFIZER	COEUR ET DIABETE- Paris		02/2007	02/2007
10092	CHANU	Bernard	06/02/2007	EC-CO	SCHERING PLOUGH	Investigateur EZETIMIBE	expérimentateur non principal	01/2000	12/2005
10092	CHANU	Bernard	06/02/2007	CF-AUD	FOURNIER (Dijon)	Montpellier - Société Française d'Endocrinologie		10/2006	10/2006
10092	CHANU	Bernard	06/02/2007	CF-AUD	SANOFI-AVENTIS	Journée Européenne de la Société Franccaise de Cardiologie - Paris		01/2007	01/2007
10092	CHANU	Bernard	06/02/2007	VB	SERVIER	Prise en charge du salaire d'une attachée de recherche clinique	Nouvelle Société Française d'Athérosclérose		
10092	CHANU	Bernard	13/03/2006	EC-CO	SCHERING-PLOUGH	Investigation Ezetimibe	co-investigateur	01/1999	12/2005
10092	CHANU	Bernard	13/03/2006	IP-AC	FOURNIER	Groupe de réflexion Lipanthyl	Rémunération personnelle	01/2004	12/2006
10092	CHANU	Bernard	03/09/2000	IP-EC	ASTRA ZENECA	Etude 4522 IL 0027			
10092	CHANU	Bernard	03/09/2000	IP-EC	SCHERING PLOUGH	Etude SCH58235			
10092	CHANU	Bernard	03/09/2000	IP-EC	BMS	Etude CV 123.212			
10092	CHANU	Bernard	03/09/2000	IP-AC	CIEL ET TERRE	Conseils rédactionnels en pathologie cardio-vasculaire			
10092	CHANU	Bernard	03/09/2000	IP-CF	SOLVAY PHARMA	Le traitement hormonal substitutif : congrès de gynécologie de Nice (juin 2000)			
10092	CHANU	Bernard	28/04/2000	IP-EC	BMS	Pravastatine M-R CV 123-212			
10092	CHANU	Bernard	01/01/1999	IP-EC	Laboratoires Bayer Pharma				
10092	CHANU	Bernard	01/01/1999	IP-EC	Laboratoires Novartis				
10092	CHANU	Bernard	01/01/1999	IP-EC	Laboratoires Menarini				
10092	CHANU	Bernard	01/01/1999	IP-AC	Agence Ciel et terre.				
10092	CHANU	Bernard	01/01/1999	IP-AUT	Laboratoires Parke Davis				
10092	CHANU	Bernard	01/01/1998	IP-AUT	Sandoz				
10092	CHANU	Bernard	01/01/1998	IP-AUT	Bayer				
10092	CHANU	Bernard	01/01/1998	IP-AUT	Agence Ciel et Terre				
10092	CHANU	Bernard	01/01/1998	IP-AUT	Pfizer				
10092	CHANU	Bernard	01/01/1998	IP-AUT	Sanofi				
60255	CHANUDET	Xavier	13/04/2010	PAR	BMS	Pharmacien responsable	beau-frère		
60255	CHANUDET	Xavier	30/03/2009	CF-AUD	MENARINI	Munich - 30th European Society of Cardiology	Prise en charge par la laboratoire ; inscription, transport, hébergement, restauration	08/2008	09/2008
60255	CHANUDET	Xavier	30/03/2009	CF-AUD	ABBOTT	Vienne - Abbott Cardio Vascular SUMMIT	Prise en charge par le laboratoire	02/2008	03/2008
60255	CHANUDET	Xavier	30/03/2009	PAR	BMS	Pharmacien responsable	beau-frère		
60255	CHANUDET	Xavier	04/01/2008	CF-AUD	NOVARTIS	Paris JHTA 2006	Inscription prise en charge par le laboratoire	12/2006	12/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60255	CHANUDET	Xavier	04/01/2008	CF-AUD	BAYER	Malte - Symposium international Pritor	Inscription prise en charge par le laboratoire	09/2006	09/2006
60255	CHANUDET	Xavier	04/01/2008	CF-AUD	NOVARTIS	Madrid - ESH 2006	Inscription prise en charge par le laboratoire	06/2006	06/2006
60255	CHANUDET	Xavier	04/01/2008	CF-AUD	ABBOTT	Paris - XVI journées européennes de la SFC	Inscription prise en charge par le laboratoire	01/2006	01/2006
60255	CHANUDET	Xavier	04/01/2008	CF-INT	MSD	EPU : Une nouvelle vision de la puissance anti LDL cholesterol	Rémunération personnelle	05/2006	05/2006
60255	CHANUDET	Xavier	04/01/2008	PAR	BMS	Pharmacien responsable	beau-frère		
60255	CHANUDET	Xavier	04/01/2008	CF-AUD	BAYER	Milan - Université Bayer de cardio-métabolisme	Inscription payée par le laboratoire	09/2007	09/2007
60255	CHANUDET	Xavier	04/01/2008	IP-AUT	NOVARTIS	Milan - ESH 2007	Inscription payée par le laboratoire	06/2007	06/2007
60255	CHANUDET	Xavier	04/01/2008	CF-AUD	ABBOTT	Paris - Coeur et Diabete 2007	Inscription payée par le laboratoire (290 €)	02/2007	02/2007
60255	CHANUDET	Xavier	11/06/2006	CF-INT	BAYER	Place des inhibiteurs calciques dans les stratégies thérapeutiques de prévention chez l'hypertendu - aucune	rémunération personnelle	06/2003	06/2003
60255	CHANUDET	Xavier	11/06/2006	CF-INT	PFIZER	Budapest - De l'artère au risque cardiovasculaire. Au delà des chiffres tensionnels . La baisse nécessaire - /	rémunération personnelle	01/2004	01/2004
60255	CHANUDET	Xavier	11/06/2006	CF-AUD	PFIZER	ESC 2005 - Stockholm		09/2005	09/2005
60255	CHANUDET	Xavier	11/06/2006	CF-AUD	NOVARTIS	ESH 2005 - Milan		06/2005	06/2005
60255	CHANUDET	Xavier	11/06/2006	CF-AUD	SERVIER	JHTA 2005 - Paris		12/2005	12/2005
60255	CHANUDET	Xavier	11/06/2006	CF-AUD	ABBOTT	Journées Européennes de Cardiologie 2006 - Paris		01/2006	01/2006
60255	CHANUDET	Xavier	11/06/2006	CF-AUD	NOVARTIS	ESH 2006 - Madrid		06/2006	06/2006
60255	CHANUDET	Xavier	11/06/2006	CF-INT	MSD	EPU : Paris / Nouvel horizon pour le patient hypertendu de 2003 / Losartan	rémunération personnelle	05/2003	06/2006
60255	CHANUDET	Xavier	11/06/2006	CF-INT	MSD	EPU : La Varenne / Prise en charge du patient à risque cardio-vasculaire / Aucune référence à un produit	rémunération personnelle	02/2004	02/2004
60255	CHANUDET	Xavier	11/06/2006	CF-INT	MSD	EPU : La Varenne / Innovation dans la prise en charge des dyslipidémies - plus d'efficacité grace à la double	rémunération personnelle	05/2005	05/2005
60255	CHANUDET	Xavier	11/06/2006	CF-INT	ASTRA ZENECA	EPU : Neuilly sur Seine / Le concept de risque cardiovasculaire : de la théorie à la pratique / Aucune référen	rémunération personnelle	10/2005	10/2005
60255	CHANUDET	Xavier	11/06/2006	CF-INT	MSD	EPU : La Varenne / Des combos à la polypill / Aucune référence à un produit	rémunération personnelle	05/2006	05/2006
60255	CHANUDET	Xavier	11/06/2006	PAR	BMS	pharmacien responsable	beau-frère		
60255	CHANUDET	Xavier	18/05/2006	IP-CF	SERVIER	En qualité d'auditeur, mai 2000			05/2000
60255	CHANUDET	Xavier	18/05/2006	PAR	BMS	Pharmacien responsable	Beau-frère		
60255	CHANUDET	Xavier	18/05/2006	IP-CF	BAYER	En qualité d'auditeur, juin 2001			06/2001
60255	CHANUDET	Xavier	18/05/2006	IP-CF	BMS	En qualité d'auditeur, septembre 2001			09/2001
60255	CHANUDET	Xavier	18/05/2006	IP-CF	BAYER	En qualité d'auditeur, septembre 2002			09/2002
60255	CHANUDET	Xavier	18/05/2006	IP-CF	PFIZER	En qualité d'auditeur, janvier 2003			01/2003
60255	CHANUDET	Xavier	18/05/2006	IP-CF	SANOFI	En qualité d'auditeur, juin 2003			06/2003
60255	CHANUDET	Xavier	18/05/2006	IP-CF	MSD	En qualité d'auditeur, mai 2003			05/2003
60255	CHANUDET	Xavier	18/05/2006	IP-CF	BAYER	En qualité d'auditeur, juin 2003			06/2003
60255	CHANUDET	Xavier	18/05/2006	IP-CF	AVENTIS	En qualité d'auditeur, octobre 2003			10/2003
60255	CHANUDET	Xavier	18/05/2006	IP-CF	BMS	En qualité d'auditeur, septembre 2004			09/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	ABBOTT	En qualité d'auditeur, décembre 2003			12/2003
60255	CHANUDET	Xavier	18/05/2006	IP-CF	MSD	En qualité d'auditeur, janvier 2004			01/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	PFIZER	En qualité d'auditeur, janvier 2004			01/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	MSD	En qualité d'auditeur, février 2004			02/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	SANOFI	En qualité d'auditeur, mars 2004			03/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	ABBOTT	En qualité d'auditeur, juin 2004			06/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	BAYER	En qualité d'auditeur, septembre 2004			09/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	ASTRA ZENECA	En qualité d'auditeur, octobre 2004			10/2004
60255	CHANUDET	Xavier	18/05/2006	IP-CF	MSD	En qualité d'auditeur, janvier 2005			01/2005
60255	CHANUDET	Xavier	18/05/2006	IP-CF	ABBOTT	En qualité d'auditeur, octobre 2004			10/2004
60255	CHANUDET	Xavier	18/05/2006	IP-AC	MSD	Etude LIFE LOSARTAN (mars 2002)			03/2002
60255	CHANUDET	Xavier	18/05/2006	IP-EC	SERVIER	PRETERAX, investigateur étude pivot			12/2001
60255	CHANUDET	Xavier	18/05/2006	IP-EC	SERVIER	PRETERAX, investigateur principal			12/2001
60255	CHANUDET	Xavier	27/02/2005	IP-AC	MSD	Etude LIFE LOSARTAN (mars 2002)			
60255	CHANUDET	Xavier	27/02/2005	IP-EC	SERVIER	PRETERAX, investigateur étude pivot			
60255	CHANUDET	Xavier	27/02/2005	IP-EC	SERVIER	PRETERAX, investigateur principal			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	ABBOTT	En qualité d'auditeur, octobre 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	MSD	En qualité d'auditeur, janvier 2005			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	ASTRA ZENECA	En qualité d'auditeur, octobre 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	BAYER	En qualité d'auditeur, septembre 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	ABBOTT	En qualité d'auditeur, juin 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	SANOFI	En qualité d'auditeur, mars 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	MSD	En qualité d'auditeur, février 2004			
60255	CHANUDET	Xavier	27/02/2005	PAR	BMS	Pharmacien responsable			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	PFIZER	En qualité d'auditeur, janvier 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	MSD	En qualité d'auditeur, janvier 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	ABBOTT	En qualité d'auditeur, décembre 2003			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	BMS	En qualité d'auditeur, septembre 2004			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	AVENTIS	En qualité d'auditeur, octobre 2003			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	BAYER	En qualité d'auditeur, juin 2003			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	MSD	En qualité d'auditeur, mai 2003			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	SANOFI	En qualité d'auditeur, juin 2003			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	PFIZER	En qualité d'auditeur, janvier 2003			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	BAYER	En qualité d'auditeur, septembre 2002			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	BMS	En qualité d'auditeur, septembre 2001			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	BAYER	En qualité d'auditeur, juin 2001			
60255	CHANUDET	Xavier	27/02/2005	IP-CF	SERVIER	En qualité d'auditeur, mai 2000			
60255	CHANUDET	Xavier	17/09/2003	IP-EC	SERVIER	Coordonateur essai Prelerax, 1997-2000			
60255	CHANUDET	Xavier	17/09/2003	IP-CF	BAYER	Conférence Inhibiteurs calciques			
60255	CHANUDET	Xavier	17/09/2003	IP-CF	MERCK SHARP & DOHME	Conférence Etude LIFE			
60255	CHANUDET	Xavier	17/09/2003	PAR	BRISTOL MYERS SQUIBB	Beau-frère			
60255	CHANUDET	Xavier	13/04/2003	IP-AC	MSD	Analyse étude LIFE			
60255	CHANUDET	Xavier	13/04/2003	IP-CF	MSD	Etude LIFE			
60255	CHANUDET	Xavier	13/04/2003	IP-CF	BAYER	Conférence sur inhibiteurs calciques			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60255	CHANUDET	Xavier	13/04/2003	PAR	BRISTOL MYERS SQUIBB	Beau-frère			
60255	CHANUDET	Xavier	30/06/2000	IP-EC	SERVIER	Coordination étude Preterax/losartan			
60255	CHANUDET	Xavier	30/06/2000	IP-EC	TAKEDA	Investigateur étude MITEC			
60255	CHANUDET	Xavier	30/06/2000	IP-CF	SERVIER	Présentation résultats Tretarax/Losartan			
60255	CHANUDET	Xavier	30/06/2000	PAR	BMS/UPSA	Beau-frère (Pharmacien responsable)			
63758	CHAPURLAT	Roland	10/10/2007	CF-INT	SANOFI	réunion de FMC	Rémunération personnelle	10/2007	
63758	CHAPURLAT	Roland	10/10/2007	CF-AUD	MSD	ECTS - Copenhage		05/2007	05/2007
63758	CHAPURLAT	Roland	10/10/2007	CF-AUD	ROCHE	ECCEO - Porto		09/2007	09/2007
63758	CHAPURLAT	Roland	10/10/2007	CF-AUD	LILLY	ASBMR - Honolulu		09/2007	09/2007
63758	CHAPURLAT	Roland	10/10/2007	CF-INT	LILLY	plusieurs réunions annuelles de FMC	Rémunération personnelle	02/2007	
63758	CHAPURLAT	Roland	10/10/2007	CF-INT	ROCHE	plusieurs réunions annuelles de FMC	Rémunération personnelle	02/2007	
63758	CHAPURLAT	Roland	10/10/2007	CF-INT	MSD	plusieurs réunions annuelles de FMC	Rémunération personnelle	02/2007	
63758	CHAPURLAT	Roland	10/10/2007	EC-CO	ROCHE	biopsies osseuses / Ibandronate	co-investigateur	10/2007	
63758	CHAPURLAT	Roland	10/10/2007	EC-CO	SERVIER	biopsies osseuses ranélate de strontium	co-investigateur	10/2007	
63758	CHAPURLAT	Roland	10/10/2007	LD-AR	PROCTER AND GAMBLE	groupe d'experts	Aucune rémunération	02/2007	
63758	CHAPURLAT	Roland	10/10/2007	LD-AR	SERVIER	Groupe d'experts	Rémunération personnelle	02/2007	
63758	CHAPURLAT	Roland	10/10/2007	LD-AR	NYCOMED	Groupe d'experts	Rémunération personnelle	02/2007	
63758	CHAPURLAT	Roland	10/10/2007	LD-AR	NOVARTIS	Groupe d'experts	Rémunération personnelle	10/2007	
63758	CHAPURLAT	Roland	02/02/2006	Néant					
10094	CHASSANY	Olivier	20/03/2009	IP-AC	SERVIER	Conseil sur les critères de qualité de vie pour une étude clinique dans la coronaropathie (SIGNIFY)	Rémunération institution	01/2009	
10094	CHASSANY	Olivier	11/11/2008	IP-AC	BMS	Conseil dans l'analyse des données de l'étude observationnelle Aramis	Rémunération institution	12/2007	03/2008
10094	CHASSANY	Olivier	11/11/2008	IP-AC	ASTRAZENECA	Conseil sur les données patient-reported outcomes d'une molécule en développement dans le RGO	Rémunération personnelle	11/2007	
10094	CHASSANY	Olivier	11/11/2008	IP-AC	SANOFI-PASTEUR	comité scientifique étude observationnelle Arizona	Rémunération institution	09/2008	09/2008
10094	CHASSANY	Olivier	11/11/2008	IP-AC	BMS-GILEAD	comité scientifique d'une étude observationnelle - Atripla	Rémunération institution	03/2008	03/2008
10094	CHASSANY	Olivier	11/11/2008	IP-AC	PFIZER	comité scientifique de validation d'un auto-questionnaire de perception de la dyspnée dans la BPCO	Rémunération personnelle	02/2008	04/2009
10094	CHASSANY	Olivier	11/11/2008	CF-INT	GSK	membre du jury du prix d'épidémiologie	Aucune rémunération	05/2008	05/2008
10094	CHASSANY	Olivier	11/11/2008	IP-AC	CEPHALON	Comité scientifique pour Spasfon	Rémunération institution	09/2008	09/2008
10094	CHASSANY	Olivier	11/11/2008	RE-DE	IPSEN	plan d'analyse statistique des données patient-reported outcomes du dossier toremifene	Rémunération institution	01/2008	04/2008
10094	CHASSANY	Olivier	11/11/2008	CF-AUD	BMS	AIDS 2008 XVII international Conference		08/2008	08/2008
10094	CHASSANY	Olivier	11/11/2008	IP-AC	THERABEL	Membre comité de validation d'un auto-questionnaire dans la rhinite allergique	Rémunération institution	11/2007	
10094	CHASSANY	Olivier	11/11/2008	RE-AUT	ALLERBIO	Conseil sur le dossier de transparence de Grazax	Rémunération institution	10/2007	11/2007
10094	CHASSANY	Olivier	11/11/2008	EC-CO	SANOFI-AVENTIS	activité de conseil dans une étude clinique avec NEW FIILL	comité scientifique	11/2006	
10094	CHASSANY	Olivier	11/11/2008	IP-AC	SANOFI-AVENTIS (Ex THERAPLIX)	Membre comité "antalgie" sur des actions de FMC et d'études cliniques	Rémunération personnelle	01/2006	
10094	CHASSANY	Olivier	11/11/2008	IP-AC	SANOFI-AVENTIS	membre comité "zona" sur des actions de FMC (rédaction d'un livre en cours)	Rémunération personnelle	01/2006	
10094	CHASSANY	Olivier	11/11/2008	IP-AUT	PRIMED	membre comité de FMC pour la société PRIMED qui organise des actions de FMC		02/2006	
10094	CHASSANY	Olivier	11/11/2008	IP-AC	DANONE	activité de conseil sur les études cliniques (troubles digestifs dans le domaine des probioliques)	Rémunération institution	01/2006	
10094	CHASSANY	Olivier	11/11/2008	EC-CO	GRIMBERG	activité de conseil dans une étude clinique avec CARBOSYMAG	comité scientifique	02/2007	
10094	CHASSANY	Olivier	11/11/2008	EC-CO	DANONE	activité de conseil sur plusieurs études cliniques (troubles digestifs) dans le domaine des probioliques	comité scientifique	01/2006	
10094	CHASSANY	Olivier	23/10/2007	IP-AC	CEPHALON	activité de conseil sur la rédaction d'un livre blanc sur les antispasmodiques dans les TFI	Rémunération institution	01/2007	03/2007
10094	CHASSANY	Olivier	23/10/2007	CF-INT	CEPHALON	intervention à un symposium aux entretiens de Bichat sur les résultats d'une étude clinique avec SPASFON	Rémunération institution	09/2007	09/2007
10094	CHASSANY	Olivier	23/10/2007	EC-CO	GRIMBERG	activité de conseil dans une étude clinique avec CARBOSYMAG	comité scientifique	02/2007	
10094	CHASSANY	Olivier	23/10/2007	CF-INT	GSK	intervention chez GSK sur la mesure de la qualité de vie dans les essais cliniques	Rémunération institution	09/2006	09/2006
10094	CHASSANY	Olivier	23/10/2007	CF-INT	BMS	plusieurs interventions lors d'une action de FMC sur les essais de non-infériorité	Rémunération institution	05/2007	11/2007
10094	CHASSANY	Olivier	23/10/2007	IP-AC	GSK	activité de conseil sur des recommandations sur les essais internationaux	Rémunération institution	11/2006	03/2007
10094	CHASSANY	Olivier	23/10/2007	CF-INT	BMS	intervention sur la mesure de la qualité de vie en pratique clinique	Rémunération institution	01/2007	01/2007
10094	CHASSANY	Olivier	23/10/2007	CF-INT	ALEXION	intervention à un symposium au congrès européen d'hématologie sur la mesure de la qualité de vie	Rémunération institution	06/2007	06/2007
10094	CHASSANY	Olivier	23/10/2007	CF-INT	Dil	intervention à la réunion annuelle "laboratoires et CROs 2007" : recommandations lors d'une soumission à u	Aucune rémunération	09/2007	09/2007
10094	CHASSANY	Olivier	23/10/2007	CF-INT	ROCHE	intervention sur les soins courants à la journée annuelle de la recherche clinique	Rémunération personnelle	12/2007	12/2007
10094	CHASSANY	Olivier	23/10/2007	CF-INT	ROCHE	intervention sur les DSMB à la journée annuelle de la recherche clinique	Rémunération personnelle	12/2006	12/2006
10094	CHASSANY	Olivier	23/10/2007	IP-AC	SANOFI-AVENTIS	activité de conseil sur l'enquête nationale de l'hémoglobine glycosylée en 2005 : écriture du manuscrit	Aucune rémunération	01/2007	12/2007
10094	CHASSANY	Olivier	23/10/2007	IP-AC	SANOFI-AVENTIS	activité de conseil sur le dossier LANTUS	Rémunération institution	01/2007	01/2007
10094	CHASSANY	Olivier	23/10/2007	IP-AC	ALTANA	activité de conseil dans le développement d'un questionnaire de qualité de vie spécifique du RGO	Rémunération personnelle/institution	01/2007	12/2007
10094	CHASSANY	Olivier	23/10/2007	IP-AUT	PRIMED	membre comité de FMC pour la société PRIMED qui organise des actions de FMC		02/2006	
10094	CHASSANY	Olivier	23/10/2007	IP-AC	SANOFI-AVENTIS	membre comité "zona" sur des actions de FMC (rédaction en cours d'un livre)	Rémunération personnelle	01/2006	
10094	CHASSANY	Olivier	23/10/2007	EC-CO	SANOFI-AVENTIS	activité de conseil dans une étude clinique avec NEWFIILL	comité scientifique	11/2006	
10094	CHASSANY	Olivier	23/10/2007	EC-CO	DANONE	activité de conseil sur plusieurs études cliniques (troubles digestifs) dans le domaine des probioliques	comité scientifique	01/2006	
10094	CHASSANY	Olivier	23/10/2007	IP-AC	DANONE	activité de conseil sur les études cliniques (troubles digestifs dans le domaine des probiotiques)	Rémunération institution	01/2006	
10094	CHASSANY	Olivier	23/10/2007	IP-AC	SANOFI-AVENTIS (EX THERAPLIX)	Membre comité "antalgie" sur des actions de FMC et d'études cliniques	Rémunération personnelle	01/2006	
10094	CHASSANY	Olivier	19/06/2006	CF-AUD	ASCO	American Society of Clinical Oncology : 2 sessions d'enseignement sur patient-reported outcomes en 2004 (		01/2004	12/2006
10094	CHASSANY	Olivier	19/06/2006	CF-AUD	MAPI	organisation avec la société MAPI d'un workshop sur patient-reported outcomes		01/2004	12/2004
10094	CHASSANY	Olivier	19/06/2006	CF-AUD	ISPOR, ISOQOL	plusieurs interventions aux congrès annuels de ces sociétés savantes		01/2004	12/2006
10094	CHASSANY	Olivier	19/06/2006	CF-AUD	DIA	plusieurs interventions aux DIA euromeeting annuels		01/2004	12/2006
10094	CHASSANY	Olivier	19/06/2006	CF-INT	ISPEN	conférence de presse en phlébologie, intervention sur qualité de vie	Rémunération institution	01/2006	12/2006
10094	CHASSANY	Olivier	19/06/2006	CF-INT	BAXTER	congres société de nutrition (Bordeaux), intervention sur qualité de vie	Rémunération institution	01/2005	12/2005
10094	CHASSANY	Olivier	19/06/2006	CF-INT	NAXIS	congrès pharmaco-épidémiologie□□co-organisateur (2005), intervenant (2005)	Rémunération personnelle/institution	01/2004	12/2005
10094	CHASSANY	Olivier	19/06/2006	IP-AC	DANONE	développement questionnaire patient nutrition	Rémunération institution	01/2005	12/2007
10094	CHASSANY	Olivier	19/06/2006	IP-AC	MAPI	acitivités ponctuelles de conseil, de formation	Rémunération personnelle/institution	01/2004	12/2006
10094	CHASSANY	Olivier	19/06/2006	IP-AC	ALTANA	developpement questionnaire patient dans le RGO	Rémunération institution	01/2004	12/2007
10094	CHASSANY	Olivier	19/06/2006	RE-DE	BOERHINGER	dossier transparence SIFROL	Rémunération institution	01/2006	12/2006
10094	CHASSANY	Olivier	19/06/2006	RE-DE	BOERHINGER	dossier transparence APTIVUS	Rémunération institution	01/2005	12/2005
10094	CHASSANY	Olivier	19/06/2006	RE-DE	BOEHRINGER	dossier transparence SPIRIVA	Rémunération institution	01/2005	12/2005
10094	CHASSANY	Olivier	19/06/2006	RE-DE	LOB CONSEIL	rapport expertise automédication : cétirizine + pseudoéphédrine	Rémunération personnelle	01/2005	12/2005
10094	CHASSANY	Olivier	19/06/2006	RE-DE	LOB CONSEIL	rapport expertise automédication : ibuprofène	Rémunération personnelle	01/2004	12/2004
10094	CHASSANY	Olivier	19/06/2006	EC-CO	AVENTIS	enquete nationale de la perception de l'HbA1AC (diabète)	comité scientifique	01/2005	12/2006
10094	CHASSANY	Olivier	19/06/2006	EC-CO	CEPHALON	étude clinique spasfon, gastroentérite	comité scientifique	01/2006	12/2007
10094	CHASSANY	Olivier	19/06/2006	EC-CO	SERVIER	étude clinique AVC, new drug	expert qualité de vie	01/2005	12/2009
10094	CHASSANY	Olivier	19/06/2006	EC-CO	SERVIER	étude clinique insuffisance cardiaque, new drug	expert qualité de vie	01/2005	12/2009
10094	CHASSANY	Olivier	19/06/2006	EC-CO	TEVA PHARMA	étude observationnelle qualité de vie dans la SEP	comité scientifique	01/2005	12/2007
10094	CHASSANY	Olivier	19/06/2006	EC-CO	GSK	étude observationnelle Trizivir	comité scientifique	01/2001	12/2004

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
0094 CHASSANY	Olivier	19/06/2006	EC-INV	BOERHINGER	étude observationnelle QUALVI, Viramune	Coordonnateur	01/2003	12/2006
0094 CHASSANY	Olivier	19/06/2006	EC-INV	CEPHALON	étude clinique Spasfon, TFI	coordonnateur	01/2005	12/2006
0094 CHASSANY	Olivier	15/06/2006	EC-INV	BOEHRINGER	étude observationnelle Viramune	coordonnateur	01/2003	12/2006
0094 CHASSANY	Olivier	15/06/2006	EC-INV	ALFIS, INNOTHERA	étude observationnelle Qualité de vie	coordonnateur	01/2003	12/2006
0094 CHASSANY	Olivier	15/06/2006	EC-INV	THERAPLIX	étude évaluation programme FMC arthrose	coordonnateur	01/2001	12/2006
0094 CHASSANY	Olivier	15/06/2006	EC-INV	CEPHALON	étude clinique TFI / SPASFON	coordonnateur	01/2005	12/2006
0094 CHASSANY	Olivier	15/06/2006	EC-CO	GSK	étude observationnelle - TRIZIVIR	comité scientifique	01/2001	12/2004
0094 CHASSANY	Olivier	15/06/2006	EC-CO	TEVA PHARMA	étude observationnelle Qualité de vie SEP	comité scientifique	01/2005	12/2007
0094 CHASSANY	Olivier	15/06/2006	EC-CO	SERVIER	étude clinique heart failure / expert qualité de vie		05/2005	
0094 CHASSANY	Olivier	15/06/2006	EC-CO	SERVIER	étude clinique stroke / expert qualité de vie		01/2006	
0094 CHASSANY	Olivier	15/06/2006	EC-CO	CEPHALON	étude clinique Spasfon / diarrhée	comité scientifique	01/2006	12/2007
0094 CHASSANY	Olivier	15/06/2006	EC-CO	AVENTIS	enquête nationale diabète (HBA1c)	comité scientifique	01/2005	12/2006
0094 CHASSANY	Olivier	15/06/2006	RE-DE	LOB CONSEIL	rapport expertise auto-med Ibuprofène	rémunération personnelle	01/2004	01/2004
0094 CHASSANY	Olivier	15/06/2006	RE-DE	LOB CONSEIL	rapport expertise auto-med Flunibuprofène + PSE	rémunération personnelle	01/2005	01/2005
0094 CHASSANY	Olivier	15/06/2006	RE-DE	BOEHRINGER	dossier transparence SPIRIVA	rémunération personnelle	01/2005	01/2005
0094 CHASSANY	Olivier	15/06/2006	RE-DE	BOEHRINGER	dossier transparence APTIVUS	rémunération personnelle	01/2005	01/2005
0094 CHASSANY	Olivier	15/06/2006	RE-DE	BOEHRINGER	dossier transparence SIFROL	rémunération personnelle	01/2006	01/2006
0094 CHASSANY	Olivier	15/06/2006	IP-AC	ALTANA	conseil développement questionnaire RGO	rémunération personnelle /institution	01/2004	
0094 CHASSANY	Olivier	15/06/2006	IP-AC	MAPI	activités ponctuelles de conseil, de formation (ponctuellement)	rémunération personnelle / institution		06/2007
0094 CHASSANY	Olivier	15/06/2006	IP-AC	DANONE	conseil développement questionnaire nutrition	rémunération personnelle / institution	01/2005	
0094 CHASSANY	Olivier	15/06/2006	CF-INT	NAXIS	congrès pharmaco-épidémiologie	co-organisateur - aucune rémunération	01/2004	01/2004
0094 CHASSANY	Olivier	15/06/2006	CF-INT	NAXIS	congrès pharmaco-épidémiologie / qualité de vie		01/2005	01/2005
0094 CHASSANY	Olivier	15/06/2006	CF-INT	BAXTER	congrès nutrition / qualité de vie		01/2005	01/2005
0094 CHASSANY	Olivier	15/06/2006	CF-INT	DRUG INFORMATION ASSOCIATION (DIA)	Euromeeting / qualité de vie	rémunération personnelle / institution	01/2005	01/2005
0094 CHASSANY	Olivier	15/06/2006	CF-INT	MAPI (DIA)	Euromeeting / qualité de vie	rémunération personnelle / institution	01/2006	01/2006
0094 CHASSANY	Olivier	15/06/2006	CF-INT	ISPOR, ISOQOL	différents congrès de ces sociétés savantes		01/2004	12/2006
0094 CHASSANY	Olivier	15/06/2006	CF-INT	IPSEN	Conférence Presse / qualité de vie		01/2006	01/2006
0094 CHASSANY	Olivier	15/06/2006	CF-INT	ASCO	American Society of Clinical Oncology meeting / qualité de vie (2004 et 2006)	Aucune rémunération		
0094 CHASSANY	Olivier	20/07/2004	EC-INV	ALFIS	Etude transversale de la qualité de vie dans 3 pathologies		01/2003	12/2006
0094 CHASSANY	Olivier	20/07/2004	EC-INV	INNOTHERA	Etude transversale de la qualité de vie dans 3 pathologies		01/2003	12/2006
0094 CHASSANY	Olivier	20/07/2004	EC-INV	THERAPLIX	Etude d'évaluation d'un programme de FMC dans l'arthron		01/2001	12/2006
0094 CHASSANY	Olivier	20/07/2004	IP-EC	UCB	Rédaction d'un article			12/2005
0094 CHASSANY	Olivier	20/07/2004	IP-RE	LOB CONSEIL	Rapport d'expertise ibuprofène OTC			
0094 CHASSANY	Olivier	20/07/2004	IP-RE	MAPI	Etudes sur la qualité de vie			
0094 CHASSANY	Olivier	20/07/2004	IP-AC	ALTANA PHARMA	Développement questionnaire RGO	Aucune rémunération		
0094 CHASSANY	Olivier	20/07/2004	IP-AC	BOEHRINGER	Comité scientifique étude observationnelle VIH	Aucune rémunération		
0094 CHASSANY	Olivier	20/07/2004	IP-CF	BMS BOEHRINGER	Symposium, quality of life, HIV			
0094 CHASSANY	Olivier	20/07/2004	IP-CF	3M	Formation, quality of life, cardiology			
0094 CHASSANY	Olivier	20/07/2004	IP-AC	CEPHALON	Rédaction protocole dans la colopathie	Aucune rémunération		
0094 CHASSANY	Olivier	20/07/2004	IP-AC	MEDIX	Développement questionnaire radiodermite	Aucune rémunération		
0094 CHASSANY	Olivier	20/07/2004	IP-AUT	SANOFI				
0094 CHASSANY	Olivier	20/07/2004	IP-AUT	MAPI	Activité de conseil d'expertise de formation avec cette société sur la qualité de vie			
0094 CHASSANY	Olivier	18/12/2000	IP-EC	ROCHE	Etude transipeg/constipation			
0094 CHASSANY	Olivier	18/12/2000	IP-EC	ROCHE	Etude pHmétrique, cross over			
0094 CHASSANY	Olivier	18/12/2000	IP-EC	THERAPLIX	Doliprane 1000			
0094 CHASSANY	Olivier	18/12/2000	IP-AC	NOVARTIS, ASTRA	Qualité de vie Colopathie			
0094 CHASSANY	Olivier	18/12/2000	IP-AC	THERAPLIX	Conseiller scientifique (Doliprane)			
0094 CHASSANY	Olivier	18/12/2000	IP-AC	PFIZER, 3M, ORGANON	Qualité de vie			
0094 CHASSANY	Olivier	18/12/2000	IP-CF	IFIP, MAPI, AMC	Formation			
0094 CHASSANY	Olivier	18/12/2000	VB	Différentes études réalisées à URT à la demande de firmes pharmaceutiques	En tant que trésorier de Unité de Recherches Thérapeutiques (URT)			
0094 CHASSANY	Olivier	29/06/2000	IP-EC	ROCHE	Etude Tramipeg / constipation			
0094 CHASSANY	Olivier	29/06/2000	IP-EC	ROCHE	Etude PH métrique cross over			
0094 CHASSANY	Olivier	29/06/2000	IP-AC	NOVARTIS	Qualité de vie colopathie			
0094 CHASSANY	Olivier	29/06/2000	IP-AC	ASTRA ZENECA	Qualité de vie colopathie			
0094 CHASSANY	Olivier	29/06/2000	IP-AC	THERAPLIX	Conseiller scientifique (Doliprane)			
0094 CHASSANY	Olivier	29/06/2000	IP-CF	IFIP	Formation			
0094 CHASSANY	Olivier	29/06/2000	IP-CF	MAPI	Formation			
0094 CHASSANY	Olivier	29/06/2000	IP-CF	AMC	Formation			
0094 CHASSANY	Olivier	29/06/2000	VB	Différentes études réalisées à l'URT à la demande des firmes	En tant que trésorier de l'URT - Unité de Recherches Thérapeutiques			
0094 CHASSANY	Olivier	24/01/2000	IP-EC	ROCHE	Etude tramipeg vs placebo/constipation			
0094 CHASSANY	Olivier	24/01/2000	IP-EC	ROCHE	Etude pH métrique cross over			
0094 CHASSANY	Olivier	24/01/2000	IP-AC	NEX & COM	Qualité de vie dans le reflux (RGO)			
0094 CHASSANY	Olivier	24/01/2000	IP-AC	PUBLICIS ETOILE	Bonnes pratiques de communications médicales			
0094 CHASSANY	Olivier	24/01/2000	IP-AC	NOVARTIS	Qualité de vie dans la colopathie			
0094 CHASSANY	Olivier	24/01/2000	IP-CF	IFIP	Dossier d'enregistrement clinique			
0094 CHASSANY	Olivier	24/01/2000	IP-CF	IFIP	Analyse critique d'un essai clinique			
0094 CHASSANY	Olivier	24/01/2000	VB	BOOTS HEALTHCARE	Unité de recherche thérapeutique URT			
0094 CHASSANY	Olivier	24/01/2000	VB	NORGINE	Unité de recherches thérapeutiques (URT)			
0094 CHASSANY	Olivier	24/01/2000	VB	SANOFI	Unité de recherches thérapeutiques (URT). Trésorier de l'URTqui réalise des études pour ces firmes actuellement ou récemment			
0094 CHASSANY	Olivier	10/05/1999	(Autre)	Société MAPI (Qualité de vie)	Participation à plusieurs groupes de travail sur l'élaboration de recommandations sur l'évaluation de la qualité de vie dans les essais thérapeutiques			
0094 CHASSANY	Olivier	10/05/1999	IP-EC	JOUVEINAL (PARKE- DAVIS)	Développement d'un questionnaire de qualité de vie			
0094 CHASSANY	Olivier	10/05/1999	IP-EC	LILLY	Réalisation de 2 mémentos sur la méthologie des essais			
0094 CHASSANY	Olivier	10/05/1999	IP-EC	ROCHE	Ecriture d'un article			
0094 CHASSANY	Olivier	10/05/1999	IP-AC	BOOTS HEALTHCARE	Avis sur le développement d'une association antalgique			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10094	CHASSANY	Olivier	10/05/1999	IP-AC	Société IBS	Avis sur un rapport d'expert			
10094	CHASSANY	Olivier	10/05/1999	IP-CF	MERCK	Exposé sur les BPC			
10094	CHASSANY	Olivier	10/05/1999	IP-CF	IFIP	Plusieurs actions de formation			
10094	CHASSANY	Olivier	10/05/1999	IP-CF	PFIZER	Séminaire de méthodologie			
10094	CHASSANY	Olivier	10/05/1999	IP-CF	PARKE- DAVIS	Intervention sur l'effet-centre			
10094	CHASSANY	Olivier	10/05/1999	(Autre)	MAPI	Participation avec la société MAPI (qualité de vie) à plusieurs groupes de travail sur l'établissement de Guideline concernant les données de qualité de vie			
10094	CHASSANY	Olivier	01/01/1999	IP-EC	ASTRA	Bacampicilline, 1996			
10094	CHASSANY	Olivier	01/01/1999	IP-EC	SANOFI	SR 48968, 1997			
10094	CHASSANY	Olivier	01/01/1999	IP-EC	JANSSEN	1995			
10094	CHASSANY	Olivier	01/01/1999	IP-AC	UCB PHARMA	Coordinateur d'une enquête, 1995			
10094	CHASSANY	Olivier	01/01/1999	IP-AC	JOUVEINAL	Développement d'une échelle de Qualité de vie			
10094	CHASSANY	Olivier	01/01/1999	IP-AC	MAPI				
10094	CHASSANY	Olivier	01/01/1999	IP-CF	ASTRA	1997			
10094	CHASSANY	Olivier	01/01/1999	IP-CF	CASSENNE	1995			
10094	CHASSANY	Olivier	01/01/1999	IP-AUT	ASTRA	Congrès de Gastroentéroloqie, Strasbourg, 1997			
10094	CHASSANY	Olivier	01/01/1999	IP-AUT	MAPI Institute	Congrès de Qualité de vie, Vienne, 1997			
10094	CHASSANY	Olivier	01/01/1999	IP-RE	FARMALYOC	1996			
10094	CHASSANY	Olivier	01/01/1999	IP-RE	AEROCID				
10094	CHASSANY	Olivier	01/01/1999	IP-CF	JOUVEINAL				
10094	CHASSANY	Olivier	01/01/1999	IP-CF	PARKE DAVIS	Exposé statistique, avril 1998			
10094	CHASSANY	Olivier	01/01/1999	IP-CF	MSD	Exposé BPC, mai 1998			
10094	CHASSANY	Olivier	01/01/1999	IP-AC	UCB-VEDIM	Etude épidémiologique des troubles fonctionnels intestinaux			
10094	CHASSANY	Olivier	01/01/1998	IP-AUT	Lilly				
64569	CHAVATTE	Philippe	12/09/2006	VB	SERVIER	Bourses de thèse	ICPAL	01/2003	
64569	CHAVATTE	Philippe	12/09/2006	VB	SERVIER	Taxes d'apprentissage	ICPAL	01/2003	
64569	CHAVATTE	Philippe	12/09/2006	VB	SERVIER	subventions	EA 1043	01/2003	
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	MSD	Groupe experts Arthrose□□(en cours)	rémunération personnelle	01/2009	
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	EXPANSCIENCE	Groupe experts Arthrose □□Projet FMC	rémunération personnelle	01/2009	12/2009
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	NEGMA	Groupe experts Arthrose	rémunération personnelle	10/2008	12/2008
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	IDEA	Expertise Pommade AINS	rémunération personnelle	01/2007	12/2007
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	ROTTAPHARM	Steering Comitee□□(en cours)	rémunération personnelle	01/2008	
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	SERVIER	Steering Comitee□□(en cours)	rémunération personnelle	01/2009	
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	NORDIC PHARMA	Conseils sur dossier	rémunération personnelle	01/2009	12/2009
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	GENEVRIERS	Conseils□□(en cours)	aucune rémunération	01/2008	
64121	CHEVALIER	Xavier	22/02/2010	LD-AR	GENEVRIERS	Programme de FMC□□(en cours)	aucune rémunération	01/2010	
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	SERVIER	Etude Polka : Protelos dans la gonarthrose□□(en cours)	Coordonnateur France		
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	GENZYME	Etude Synvisc one	Investigateur principal	01/2005	12/2007
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	SANKYO France	Adant dans la coxarthrose	Investigateur principal	01/2005	12/2007
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	PFIZER	Peurs et croyances dans l'arthrose - groupe d'experts	Investigateur	01/2008	12/2008
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	Preuves et Pratiques	Enquête Généraliste et gonarthrose	Investigateur principal	01/2007	12/2008
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	APHP	DORA□□(en cours)	Coordonnateur et Investigateur principal	01/2008	
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	NEGMA	Essai ART 44□□(en cours)	Coordonnateur et investigateur principal	01/2009	
64121	CHEVALIER	Xavier	22/02/2010	EC-INV	PIERRE FABRE	Enquête patients - mobilité surpoids et douleurs des membres□□(en préparation)	Coordonnateur	01/2010	
64121	CHEVALIER	Xavier	22/02/2010	EC-CO	SFR	Essai synvisc et biomarqueurs	Co-coordonnateur	01/2008	12/2010
64121	CHEVALIER	Xavier	22/02/2010	EC-CO	BioXtract	Essai□□(en cours)	Membre du comité scientifique	01/2009	
64121	CHEVALIER	Xavier	22/02/2010	RE-DE	AFSSAPS	Les chondroitines sulfates	rémunération personnelle	01/2007	12/2008
64121	CHEVALIER	Xavier	22/02/2010	RE-DE	GENZYME	Synvisc : réévaluation rapport efficacité / bénéfice	rémunération personnelle	01/2009	12/2009
64121	CHEVALIER	Xavier	22/02/2010	IP-AC	AFSSAPS	CHONDROITINE SULFATE PIERRE FABRE	rémunération personnelle	01/2008	
64121	CHEVALIER	Xavier	22/02/2010	IP-AC	GENEVRIERS	Futur des anti cytokines□□(en cours)	aucune rémunération	01/2008	
64121	CHEVALIER	Xavier	22/02/2010	IP-AC	BioXtract	Devenir du Curcumin dan l'arthrose□□(en cours)	rémunération personnelle	01/2008	
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	GENZYME	Symposium SFR 2007	Rémunération personnelle	12/2007	12/2007
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	GENZYME	Symposium Lille 2009	rémunération personnelle	05/2009	05/2009
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	GENZYME	Congrès Grec de Rhumatologie 2010	rémunération personnelle	03/2009	03/2009
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	GENZYME	Board Bruxelles 2009	rémunération personnelle	12/2010	12/2010
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	EXPANSCIENCE PROGRAMME PYRAMID	Symposium Budapest 2009	rémunération personnelle	05/2009	05/2009
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	BOARD ABBOTT	Boston 2009	rémunération personnelle	07/2009	07/2009
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	BOARD MSD	Londres Octobre 2009	rémunération personnelle	10/2009	10/2009
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	MSD	Symposium SFR Décembre 2009	rémunération personnelle	12/2009	12/2009
64121	CHEVALIER	Xavier	22/02/2010	CF-INT	OARSI	Futurs des traitements Intra-articulaires	aucune rémunération	12/2008	12/2008
64121	CHEVALIER	Xavier	22/02/2010	CF-AUD	GENZYME	Audit FDA sur Synvisc one - Washington			
64121	CHEVALIER	Xavier	15/01/2009	LD-AR	MSD	Groupe Experts Arthrose	rémunération personnelle	01/2009	
64121	CHEVALIER	Xavier	15/01/2009	LD-AR	EXPANSCIENCE	Groupe experts Arthrose□□Projet FMC	rémunération personnelle	01/2008	12/2008
64121	CHEVALIER	Xavier	15/01/2009	LD-AR	NEGMA	Groupe experts Alhrose	rémunération personnelle	01/2008	12/2008
64121	CHEVALIER	Xavier	15/01/2009	LD-AR	IDEA	Expertise Pommade AINS	rémunération personnelle	01/2007	12/2007
64121	CHEVALIER	Xavier	15/01/2009	LD-AR	ROTTAPHARM	Steering Comité	rémunération personnelle	01/2008	
64121	CHEVALIER	Xavier	15/01/2009	LD-AR	GENEVRIER	Conseils	aucune rémunération	01/2008	
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	SERVIER	Etude Polka : Protelos dans la gonarthrose	coordonnateur France		
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	GENZYME	Etude Synvisc one	Investigateur principal	01/2005	12/2007
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	AMGEN	IL 1 RA dans la gonarthrose	investigateur principal	01/2004	12/2005
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	SANKYO France	Adant dans la coxarthrose	investigateur principal	01/2005	12/2007
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	PFIZER	Peurs et croyances dans l'arthrose groupe d'experts	investigateur	01/2008	
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	PREUVES ET PRATIQUES	Enquête Généraliste et gonarthrose	Investigateur principal	01/2007	12/2008
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	APHP	DORA	Coodonateur et investigateur principal	01/2008	
64121	CHEVALIER	Xavier	15/01/2009	EC-INV	NEGMA	Essai ART 44	Coordonateur et investigateur principal	01/2009	
64121	CHEVALIER	Xavier	15/01/2009	EC-CO	SFR	Essai synvisc et biomarqueurs	Co Coordonnateur	01/2008	
64121	CHEVALIER	Xavier	15/01/2009	RE-DE	AFSSAPS	Les chondroitines sulfates	rémunération personnelle	01/2007	12/2008
64121	CHEVALIER	Xavier	15/01/2009	IP-AC	AFSSAPS (sur demande)	CHONDROITINE SULFATE PIERRE FABRE	aucune rémunération	01/2008	

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
4121 CHEVALIER	Xavier	15/01/2009	IP-AC	GENEVRIER	Futur des anti cytokines	aucune rémunération	01/2008	
4121 CHEVALIER	Xavier	15/01/2009	IP-AC	BIOXTRACT	Devenir du Curcumin dans l'arthrose	rémunération personnelle	01/2008	
4121 CHEVALIER	Xavier	15/01/2009	CF-INT	GENZYME	Symposium SFR 2007	rémunération personnelle	12/2007	12/2007
4121 CHEVALIER	Xavier	15/01/2009	CF-INT	GENZYME	Symposium Lille 2009	rémunération personnelle	05/2009	05/2009
4121 CHEVALIER	Xavier	15/01/2009	CF-INT	EXPANSCIENCE PROGRAMME PYRAMID	Symposium 2009	rémunération personnelle	03/2009	03/2009
4121 CHEVALIER	Xavier	15/01/2009	CF-INT	OARSI	Futurs des traitements intra articulaires	aucune rémunération		
4121 CHEVALIER	Xavier	15/01/2009	CF-AUD	GENZYME	Adil FDA sur Synvisc one - Washington		12/2008	12/2008
4121 CHEVALIER	Xavier	06/02/2008	IP-EC	BMS	Enquêtes épidémiologiques (coordinateur)		01/2003	12/2004
4121 CHEVALIER	Xavier	06/02/2008	IP-EC	AMGEN	Essai clinique Anakinra (coordinateur et investigateur principal)		01/2004	12/2005
4121 CHEVALIER	Xavier	06/02/2008	IP-EC	SANKYO France	Essai clinique Adant (coordinateur et investigateur principal)		01/2005	12/2007
4121 CHEVALIER	Xavier	06/02/2008	IP-EC	GENZYME	Essai clinique Synvise (investigateur principal)		01/2006	12/2007
4121 CHEVALIER	Xavier	06/02/2008	IP-EC	SERVIER	Essai clinique Proicios (investigateur - coordinateur france)		01/2007	
4121 CHEVALIER	Xavier	06/02/2008	IP-EC	PFIZER	Enquêtes épidémiologiques (investigateur)		01/2007	
4121 CHEVALIER	Xavier	06/02/2008	EC-CO	HOPITAUX DE LYON SOUTIEN GNEZYME	Essai clinique marqueurs (co-investigateur)		01/2008	
4121 CHEVALIER	Xavier	06/02/2008	IP-RE	GENEVRIERS	Evaluation sur le chondrosulf		01/2002	12/2002
4121 CHEVALIER	Xavier	06/02/2008	IP-AC	EXPANSCIENCE	Expertiss scientifique, analyse de dossiers, plasclédine		01/2007	
4121 CHEVALIER	Xavier	06/02/2008	IP-AC	GENZYME	Expertise scientifique Synvise		01/2008	
4121 CHEVALIER	Xavier	06/02/2008	IP-CF	SERVIER	Actualités Rhumatologie (Paris) : arthrose		01/2006	12/2006
4121 CHEVALIER	Xavier	06/02/2008	IP-CF	GENEVRIERS	Porto : congrès ECCEO : mécanismes d'action des acides hyaluroniques Synovial		01/2007	12/2007
4121 CHEVALIER	Xavier	06/02/2008	IP-CF	IBSA	Barcelone: cadre EULAR : rôle de chondroitines sulfates, chnodrosulf		01/2007	12/2007
4121 CHEVALIER	Xavier	06/02/2008	IP-CF	IBSA	Istambul : congrès ECCEO : mécanisme d'action des chondroitines, chondrosulf		01/2008	
4121 CHEVALIER	Xavier	06/02/2008	IP-CF	GENZYME	Paris : congrès SFR : symposium sur les acides hyaluroniques, synvic		01/2007	12/2007
4121 CHEVALIER	Xavier	06/02/2008	IP-AUT	COLLABORATION INSEM-GENEVRIERS	Brevet pour réparation tissulaire de cartillage: gel chtosan		01/2004	12/2004
4121 CHEVALIER	Xavier	06/02/2008	VB	ABBOT	Soutien à la recherche (association service de rhumatologie)		01/2005	12/2007
4121 CHEVALIER	Xavier	06/02/2008	VB	SERVIER	Soutien à la recherche (association service de rhumatologie)		01/2007	12/2008
4121 CHEVALIER	Xavier	06/02/2008	VB	WYETH	Soutien à la recherche (association service de rhumatologie)		01/2008	
4121 CHEVALIER	Xavier	23/04/2006	LD-AR	PHARMASCIENCE	A venir	rémunération personnelle	01/2006	
4121 CHEVALIER	Xavier	23/04/2006	EC-INV	GENEVRIERS	Aide du laboratoire sur les protocles de recherche. Aide au laboratoire Inserm U 99	coordonnateur	01/2001	12/2004
4121 CHEVALIER	Xavier	23/04/2006	EC-INV	SANKYO	Essai clinique multicentrique	coordonnateur	01/2005	
4121 CHEVALIER	Xavier	23/04/2006	EC-INV	AMGEN	Essai clinique multicentrique international	coordonnateur	01/2004	12/2005
4121 CHEVALIER	Xavier	23/04/2006	EC-CO	GENZYME	Essai clinique	co-investigateur	01/2006	
4121 CHEVALIER	Xavier	23/04/2006	RE-DE	GENEVRIERS	Chondrosulf	rémunération personnelle	01/2004	
4121 CHEVALIER	Xavier	23/04/2006	RE-AUT	PHRC	Demande anonyme	aucune rémunération	01/2003	12/2003
4121 CHEVALIER	Xavier	23/04/2006	RE-AUT	PHRC	Demande anonyme	aucune rémunération	01/2006	12/2006
4121 CHEVALIER	Xavier	23/04/2006	IP-AC	BMS	Consultant ponctuel- Sur les 3 dernières années 2003-2006	rémunération personnelle	01/2003	12/2006
4121 CHEVALIER	Xavier	23/04/2006	CF-INT	GENEVRIERS	ECCEO congrès international sur l'arthrose et l'ostéoporose	rémunération personnelle	01/2006	12/2006
4121 CHEVALIER	Xavier	23/04/2006	CF-INT	BMS	Prise en charge de l'arthrose : symposium	rémunération personnelle	01/2005	12/2005
4121 CHEVALIER	Xavier	23/04/2006	IP-AUT	EN COLLABORATION AVEC GENEVRIERS ET UNITE INSERM U99	Brevet sur les greffes de cartilage		01/2003	
4121 CHEVALIER	Xavier	23/04/2006	VB	ASSOCIATION RECHERCHE LOI 1901 DU SERVICE DE RHUMATOLOGIE DE L'HOPITAL HENRI MONDOR	Aide ponctuelles pour la recherche clinique toujours inférieur à 15% du budget	Recherche Hôpital Henri Mondor		
4121 CHEVALIER	Xavier	23/04/2006	EC-CO	GENZYME	Essai clinique	co-investigateur	01/2004	12/2004
0100 CHIRON	Catherine	30/08/2010	EC-CO	BIOCODEX	Past-marketting survey / Stiripentol (Diacomit)	co-investigateur	08/2008	
0100 CHIRON	Catherine	30/08/2010	LD-AR	BIOCODEX	Expertise et Conseil / Stiripentol (Diacomit)	Rémunération personnelle	01/2001	07/2009
0100 CHIRON	Catherine	30/08/2010	VB	EISAI	Subvention pour réunion de recherche	ARIEE	06/2010	06/2010
0100 CHIRON	Catherine	30/08/2010	VB	BIOCODEX	Subvention pour réunion de recherche	ARIEE	08/2010	08/2010
0100 CHIRON	Catherine	30/08/2010	CF-AUD	JANSEN-CILAG	Londres / Nouveaux antiépileptiques	Aucune rémunération	06/2010	06/2010
0100 CHIRON	Catherine	30/08/2010	CF-INT	NOVARTIS	Paris Réunion NOvartis / Sclérose tubéreuse de Bourneville	Rémunération personnelle	05/2010	05/2010
0100 CHIRON	Catherine	30/08/2010	CF-INT	EISAI	Montpelier Symposium Eisai SFNP / Rufinamide	Rémunération personnelle	01/2010	01/2010
0100 CHIRON	Catherine	30/08/2010	CF-INT	EISAI	Paris Réunion Eisai / Lennox Gastaut / Rufinamide	Rémunération personnelle	11/2009	11/2009
0100 CHIRON	Catherine	30/08/2010	RE-AUT	BIOCODEX	Rapport EMEA / Diavey / Stiripentol (Diacomit)	Rémunération personnelle	06/2009	06/2009
0100 CHIRON	Catherine	30/08/2010	LD-AR	BIOCODEX	Expertise et Conseil / Stiripentol (Diacomit)	Rémunération personnelle	01/2001	07/2009
0100 CHIRON	Catherine	30/08/2010	IP-AC	LUNDBECK	Consulting IDMC (Clobazam (Urbanyl)	Rémunération personnelle	03/2009	
0100 CHIRON	Catherine	30/08/2010	EC-CO	EISAI	Essai clinique / Zonisamide	co-investigateur	01/2008	
0100 CHIRON	Catherine	30/08/2010	EC-CO	BIAL	Essai clinique / Eslicarbazepine	co-investigateur	01/2008	
0100 CHIRON	Catherine	30/08/2010	LD-AR	BIOCODEX	Expertise et Conseil / Stiripentol (Diacomit)	Rémunération personnelle//institution	01/2001	07/2009
2005 CHIRON	Jean-Paul	28/07/2009	IP-AUT	INNOTHERA	Audit et Conseil		02/2008	02/2008
2005 CHIRON	Jean-Paul	28/07/2009	IP-AUT	DU PONT DE NEMOURS	Travaux scientifiques	Evaluation d'activités antimicrobiennes	04/2007	
2005 CHIRON	Jean-Paul	28/07/2009	IP-AUT	INNOTHERA	Audit & Conseil		02/2008	02/2008
2005 CHIRON	Jean-Paul	28/07/2009	IP-AUT	EAU ECARLATE	Travaux scientifiques	Evaluation d'activités antimicrobiennes	09/2008	
2005 CHIRON	Jean-Paul	28/07/2009	EC-CO	TOP PHARM	travaux scientifiques	expérimentateur pour la microbiologie	06/2006	
2005 CHIRON	Jean-Paul	28/07/2009	LD-AR	ADREMI-TOURS	Consultant Expert / directeur scientifique	Rémunération institution	10/1996	
2005 CHIRON	Jean-Paul	28/07/2009	LD-ODE	ÉTAT NéANT				
2005 CHIRON	Jean-Paul	28/07/2009	IF	ÉTAT NéANT		<5000 € ou <5% du capital		
0100 CHIRON	Catherine	19/07/2009	CF-INT	BIOCODEX	Madrid SENP : Stiripentol (Diacomit)	rémunération personnelle	04/2009	04/2009
0100 CHIRON	Catherine	19/07/2009	CF-INT	BIOCODEX	Bruxelles Diavey : Stiripentol (Diacomit)	rémunération personnelle	03/2009	03/2009
0100 CHIRON	Catherine	19/07/2009	EC-CO	BIAL	Essai clinique : Eslicarbazepine	co-investigateur	01/2008	
0100 CHIRON	Catherine	19/07/2009	EC-CO	EISAI	Essai clinique : Zonisamide	co-investigateur	01/2008	
0100 CHIRON	Catherine	19/07/2009	IP-AC	JOHNSON & JOHNSON	Consulting : Carisbamate	aucune rémunération	01/2009	01/2009
0100 CHIRON	Catherine	19/07/2009	IP-AC	OVATION PHARMACEUTICALS	Consulting IDMC : Clobazam (urbanyl)	rémunération personnelle	01/2007	03/2009
0100 CHIRON	Catherine	19/07/2009	IP-AC	UCB PH - SCHWARTZ	Consulting : Lacosamide	rémunération personnelle	01/2008	10/2008
0100 CHIRON	Catherine	19/07/2009	IP-AC	LUNDBECK	Consulting IDMC / Clobazam (urbanyl)	Aucune rémunération	03/2009	
0100 CHIRON	Catherine	19/07/2009	EC-CO	OVATION PHARMACEUTICALS	Essai clinique : Vigabatrin (Sabril)	co-investigateur	07/2007	12/2008
0100 CHIRON	Catherine	19/07/2009	RE-AUT	HAS	Transparence : Rufinamide (Inovelon)	rémunération personnelle	01/2009	01/2009
0100 CHIRON	Catherine	19/07/2009	LD-AR	BIOCODEX	Expertise et Conseil : Stiripentol (Diacomit)	rémunération personnelle	01/2001	
0100 CHIRON	Catherine	19/07/2009	LD-AR	SANOFI-AVENTIS	Steering Committee	rémunération personnelle	01/2001	09/2006
0100 CHIRON	Catherine	19/07/2009	EC-INV	UCB - PHARMA	Essai clinique : Levetiracetam (Keppra)	investigateur coordonnateur	01/2005	09/2007
0100 CHIRON	Catherine	19/07/2009	EC-INV	SANOFI - AVENTIS	Essai clinique : Micropakine	investigateur principal	01/2006	09/2008

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10100	CHIRON	Catherine	19/07/2009	EC-INV	BIOCODEX	Essai clinique :Diacomit	investigateur principal	01/2008	12/2008
10100	CHIRON	Catherine	19/07/2009	RE-DE	AFSSAPS	AMM nourrisson : Lamotrigine (Lamictal)	rémunération personnelle	06/2007	07/2007
10100	CHIRON	Catherine	19/07/2009	RE-DE	AFSSAPS	Perampanel	rémunération personnelle	07/2008	07/2008
10100	CHIRON	Catherine	19/07/2009	RE-DE	BIOCODEX	Prix Galien	rucune rémunération	07/2008	09/2008
62005	CHIRON	Jean-Paul	23/03/2009	LD-ODE	ADREMI-TOURS	Directeur scientifique (en cours)	Honoraires	01/1996	
62005	CHIRON	Jean-Paul	23/03/2009	IP-RE	TOP PHARM	Efficacité des conservateurs □□, Alfa Amylase sirop□□, Actigencyl dentifrice	Rémunération personnelle	01/2005	04/2008
10100	CHIRON	Catherine	29/09/2008	EC-INV	BIOCODEX	Stiripentol	investigateurprincipal	01/2007	12/2008
10100	CHIRON	Catherine	29/09/2008	EC-INV	NOVARTIS	Oxcarbazépine	investigateur principal	01/2003	12/2005
10100	CHIRON	Catherine	29/09/2008	EC-INV	UCB PHARMA	Levetiracetam	investigateur principal	01/2005	12/2007
10100	CHIRON	Catherine	29/09/2008	EC-INV	SANOFI AVENTIS	Micropakine	investigateur principal	01/2006	12/2008
10100	CHIRON	Catherine	29/09/2008	EC-CO	EISAI	Zonisamide	co-investigateur	01/2008	
10100	CHIRON	Catherine	29/09/2008	EC-CO	BIAL	Eslicarbazépine	co-investigateur	01/2008	
10100	CHIRON	Catherine	29/09/2008	IP-RE	UCB PHARMA	Levetiracetam	rémunération personnelle	01/2003	12/2003
10100	CHIRON	Catherine	29/09/2008	IP-AC	EISAI	Rufinamide	rémunération personnelle	01/2006	12/2006
10100	CHIRON	Catherine	29/09/2008	IP-AC	EISAI	Zonisamide	rémunération personnelle	01/2006	12/2007
10100	CHIRON	Catherine	29/09/2008	IP-AC	UCB PHARMA	Lacosamide	rémunération personnelle	01/2008	
10100	CHIRON	Catherine	29/09/2008	IP-AC	OVATION PHARMACEUTICALS (USA)	Clobazam	rémunération personnelle	01/2007	
10100	CHIRON	Catherine	29/09/2008	CF-INT	BIOCODEX	Allemagne	aucune rémunération	01/2008	12/2008
10100	CHIRON	Catherine	29/09/2008	CF-INT	BIOCODEX	Pays-Bas (Rotterdam)	aucune rémunération	01/2008	12/2008
10100	CHIRON	Catherine	29/09/2008	CF-AUD	PFIZER	AES : Seattle		12/2008	12/2008
10100	CHIRON	Catherine	29/09/2008	VB	SANOFI AVENTIS	Bourse de recherche	Association Naturalia Biologia	01/2006	12/2007
10100	CHIRON	Catherine	29/09/2008	VB	BIOCODEX	Subvention de recherche	Association Naturalia Biologia	01/2006	12/2007
62005	CHIRON	Jean-Paul	20/09/2007	IF	ÉTAT NéANT		<5000 € ou <5% du capital		
10100	CHIRON	Catherine	11/09/2007	LD-AR	BIOCODEX	Expertise - conseil / Diacomit (en cours)	rémunération partagée personnelle/institution	01/2001	
10100	CHIRON	Catherine	11/09/2007	LD-AR	SANOFI AVENTIS	Steering Committee - protocole PV / Sabril	rémunération personnelle	01/2001	12/2006
10100	CHIRON	Catherine	11/09/2007	EC-INV	UCB PHARMA	Essai clinique / Keppra (en cours)	investigateur coordonnateur	01/2005	
10100	CHIRON	Catherine	11/09/2007	EC-INV	SANOFI AVENTIS	Essai clinique / Micropakine	investigateur principal	01/2005	12/2006
10100	CHIRON	Catherine	11/09/2007	EC-INV	NOVARTIS	Essai clinique / Trileptal	investigateur coordonnateur	01/2002	12/2004
10100	CHIRON	Catherine	11/09/2007	RE-DE	UCB PHARMA	AMM enfant / keppra	rémunération personnelle	01/2005	12/2005
10100	CHIRON	Catherine	11/09/2007	RE-DE	BIOCODEX	AMM enfant / Diacomit	rémunération partagée personnelle / institution	01/2005	12/2006
10100	CHIRON	Catherine	11/09/2007	RE-AUT	AFSSAPS	AMM enfant / Rufinamide	rémunération personnelle	01/2005	12/2005
10100	CHIRON	Catherine	11/09/2007	RE-AUT	AFSSAPS	AMM / Lamictal	aucune rémunération	01/2007	12/2007
10100	CHIRON	Catherine	11/09/2007	IP-AC	EISAI	Consultante / Rufinamide / Zonisamide	rémunération personnelle	01/2006	12/2006
10100	CHIRON	Catherine	11/09/2007	IP-AC	SANOFI AVENTIS	Consultante / Sabril / Clobazam	rémunération personnelle	01/2005	12/2006
10100	CHIRON	Catherine	11/09/2007	CF-INT	PFIZER	Groupe de recherche en épileptologie	aucune rémunération	01/2005	12/2005
10100	CHIRON	Catherine	11/09/2007	CF-INT	PFIZER	AES / Stripentol	aucune rémunération	01/2006	12/2006
10100	CHIRON	Catherine	11/09/2007	CF-INT	SANOFI AVENTIS	Réunion EILAT - AEDS / Stripentol	aucune rémunération	01/2004	12/2004
10100	CHIRON	Catherine	11/09/2007	CF-INT	SANOFI AVENTIS	Réunion EILAT- AEDS / Vigabatrin	aucune rémunération	01/2006	12/2006
10100	CHIRON	Catherine	11/09/2007	CF-INT	SANOFI AVENTIS	Congrès ANLLF / Plasticité	rémunération personnelle	01/2006	12/2006
10100	CHIRON	Catherine	11/09/2007	VB	BIOCODEX	Paiement d'un 1/2 temps de secrétariat / ARC (en cours)	Inserm U 663 (Dr C. CHIRON)	01/2005	
10100	CHIRON	Catherine	25/10/2006	LD-AR	BIOCODEX	Expertise/ Stiripentol	rémunération personnelle et institution	01/2001	
10100	CHIRON	Catherine	25/10/2006	EC-INV	SANOFI AVENTIS	Essai clinique / Micropakine	investigateur coordonnateur	01/2005	
10100	CHIRON	Catherine	25/10/2006	EC-INV	NOVARTIS	Essai clinique / Oxcarbazepine	investigateur coordonateur	01/2002	12/2004
10100	CHIRON	Catherine	25/10/2006	EC-INV	SANOFI-AVENTIS	Essai clinique : Vigabatrin	investigateur coordonnateur	01/1999	12/2006
10100	CHIRON	Catherine	25/10/2006	EC-INV	UCB - PHARMA	Essai clinique / Levetiracetam	investigateur coordonnateur	01/2005	
10100	CHIRON	Catherine	25/10/2006	RE-DE	UCB - PHARMA	AMM enfant / Levetiracetam	rémunération personnelle	01/2005	12/2005
10100	CHIRON	Catherine	25/10/2006	RE-DE	BIOCODEX	AMM enfant / Stiripentol	rémunération personnelle / institution	01/2006	
10100	CHIRON	Catherine	25/10/2006	RE-AUT	AFSSAPS	AMM enfant / Rufinamide	rémunération personnelle	01/2006	12/2006
10100	CHIRON	Catherine	25/10/2006	IP-AC	EISAI	Consultance pour essais clinique à venir / Zonisamide	rémunération personnelle	01/2006	
10100	CHIRON	Catherine	25/10/2006	IP-AC	OVATION PHARMACEUTICALS	Consultance pour essais aux US (orphans drugs) / Vigabatrin - Clobazam	rémunération personnelle	01/2005	12/2006
10100	CHIRON	Catherine	25/10/2006	CF-INT	PFIZER	Groupe de Recherche en Epileptologie (GRE) AES Stiripentol	aucune rémunération	01/2005	12/2005
10100	CHIRON	Catherine	25/10/2006	CF-INT	SANOFI AVENTIS	Réunion EILAT AEDS / Stiripentol / Vigabatrin	aucune rémunération	01/2004	12/2004
10100	CHIRON	Catherine	25/10/2006	CF-INT	SANOFI AVENTIS	Congrès ANLLF / Plasticité Cérébrale	rémunération personnelle	01/2006	12/2006
10100	CHIRON	Catherine	25/10/2006	(Autre)	BIOCODEX	Paiement d'un 1/2 temps de Secrétariat / ARC	INSERM U 663 (Dr Chiron)	01/2005	
10100	CHIRON	Catherine	25/10/2006	CF-INT	PFIZER	Groupe de Recherche en Epileptologie (GRE) AES / Stiripentol	aucune rémunération	01/2006	12/2006
10100	CHIRON	Catherine	25/10/2006	CF-INT	SANOFI AVENTIS	Réunion EILAT AEDS / Stiripentol / Vigabatrin	aucune rémunération	01/2006	12/2006
10100	CHIRON	Catherine	20/06/2005	IP-EC	BIOCODEX	Essais enfant avec le Stiripentol			
10100	CHIRON	Catherine	20/06/2005	IP-EC	NOVARTIS	Essais enfant avec l'oxcarbazépine			
10100	CHIRON	Catherine	20/06/2005	IP-EC	UCB-PHARMA	Essais enfant avec le Lévétiracétam			
10100	CHIRON	Catherine	20/06/2005	IP-EC	SANOFI	Essais enfant avec la Micropakine			
10100	CHIRON	Catherine	20/06/2005	IP-EC	AVENTIS	Essais enfant avec le Sabril (pharmacovigilance)			
10100	CHIRON	Catherine	20/06/2005	IP-RE	BIOCODEX	Demande AMM orpheline Stiripentol			
10100	CHIRON	Catherine	20/06/2005	IP-RE	UCB PHARMA	Demande AMM enfant Lévétiracétam			
10100	CHIRON	Catherine	20/06/2005	IP-AC	BIOCODEX	Conseil pour PK Stiripentol			
10100	CHIRON	Catherine	20/06/2005	IP-AC	AVENTIS	Conseil pour PK Sabril enfant			
10100	CHIRON	Catherine	20/06/2005	IP-CF	BIOCODEX	Bon usage du Stiripentol chez l'enfant			
10100	CHIRON	Catherine	20/06/2005	IP-CF	PFIZER	??			
10100	CHIRON	Catherine	20/06/2005	IP-CF	JANSSEN	Epilepsy in childhood			
10100	CHIRON	Catherine	20/06/2005	IP-CF	SANOFI	Imagining in childhood epilepsy ,			
10100	CHIRON	Catherine	20/06/2005	VB	BIOCODEX	Financement d'une secrétaire en CDD à mi-temps pour le suivi des essais de Stiripentol chez l'enfant			
62005	CHIRON	Jean-Paul	21/06/2004	LD-AR	ADREMI (TOURS)	Consultant expert / directeur scientifique	Honoraires	10/1996	
62005	CHIRON	Jean-Paul	21/06/2004	IP-EC	CDM LAVOISSIER ; TOP PHARM ; LISO FORM (BERLIN) ; ECOLAS ; CEETAL	Travaux scientifiques			
62005	CHIRON	Jean-Paul	21/06/2004	IP-RE	INSTITUT DE RECHERCHE SCIENTIFIQUE SERVIER	Rapport d'expertise et essais			
62005	CHIRON	Jean-Paul	21/06/2004	IP-CF	NOE	Formation			

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
2005 CHIRON	Jean-Paul	21/06/2004	IP-CF	PFIZER	Formation			
				DUPON ANTEC ; LANGLOIS ; FABRICATION CHIMIQUE				
2005 CHIRON	Jean-Paul	21/06/2004	IP-AUT	ARDECHOISE	Travaux scientifiques			
0100 CHIRON	Catherine	16/03/2004	IP-EC	NOVARTIS	Coordination d'un essai thérapeutique de PV			
0100 CHIRON	Catherine	16/03/2004	IP-EC	AVENTIS	Coordination d'un essai thérapeutique de PV			
0100 CHIRON	Catherine	16/03/2004	IP-EC	SANOFI-SYNTHELABO	Coordination d'un essai thérapeutique de PV			
0100 CHIRON	Catherine	16/03/2004	IP-CF	BIOCODEX	Colloque			
0100 CHIRON	Catherine	16/03/2004	IP-CF	JANSSEN-CILAG	Formations			
0100 CHIRON	Catherine	16/03/2004	VB	BIOCODEX	Palement d'un ARC in situ			
0100 CHIRON	Catherine	27/09/2001	LD	BIOCODEX	Honoraires pour suivi de protocoles			
0100 CHIRON	Catherine	27/09/2001	IP-EC	JANSSEN-CILAG	Essai clinique Topiranate			
0100 CHIRON	Catherine	27/09/2001	IP-EC	JANSSEN-CILAG	Travail scientifique (cassette vidéo)			
0100 CHIRON	Catherine	27/09/2001	VB	AVENTIS	ARIEE (Service Neuropédiatrie, Hôpital Saint-Vincent de Paul)			
0100 CHIRON	Catherine	15/11/1999	VB	BIOCODEX	2 essais contrôlés et 1 essai de niveau long terme : Versements à l'association ARIEE pour les protocoles			
0100 CHIRON	Catherine	15/11/1999	IP-EC	CASSENNE	Suivi du champ visuel sous Vigabatrine			
0100 CHIRON	Catherine	15/11/1999	IP-RE	CASSENNE	Expert pédiatrique pour l'essai de suivi du champ visuel sous Vigabatrine			
0100 CHIRON	Catherine	15/11/1999	IP-CF	JANSSEN CILAG	Formation sur les épilepsies de l'enfant			
0100 CHIRON	Catherine	01/01/1999	LD	BIOCODEX	2 essais pour le Stiripentol dans les épilepsies de l'enfant - contrat pour un an			
0100 CHIRON	Catherine	01/01/1999	IP-EC	BIOCODEX	Contrat de travail transitoire pour 2 essais contrôlés			
0100 CHIRON	Catherine	01/01/1999	IP-EC	HMR	Mise au point d'un protocole multicentrique en monothérapie			
0100 CHIRON	Catherine	01/01/1999	IP-CF	HMR	Rémunération pour la réalisation d'une cassette vidéo sur les spasmes infantiles			
0100 CHIRON	Catherine	01/01/1999	IP-AUT	HMR	Rémunération sous forme de prise en charge de frais de congrès à l'étranger 1 à 2 fois par an			
0100 CHIRON	Catherine	01/01/1999	IP-AUT	SANOFI WINTHROP				
0100 CHIRON	Catherine	01/01/1999	IP-CF	HMR	Rémunération à venir pour la collaboration à un livre sur les épilepsies			
0100 CHIRON	Catherine	01/01/1999	IP-EC	CASSENNE	Coordination d'un essai clinique (en projet)			
0100 CHIRON	Catherine	01/01/1999	IP-AC	CASSENNE	dépistage des anomalies du champ visuel éventuelles chez les enfants sous Satril et autres anti-épileptiques (en préparation)			
0100 CHIRON	Catherine	01/01/1999	IP-AUT	SANOFI	Prise en charge des frais de congrès à l'étranger			
0100 CHIRON	Catherine	01/01/1999	VB		Essais thérapeutiques - versement à ARIEE (St Vincent de Paul)			
0100 CHIRON	Catherine	01/01/1999	VB	BIOCODEX	Essai clinique du Stiripentol, versement sur ARIEE			
0100 CHIRON	Catherine	01/01/1998	IP-AUT	Cassenne				
0100 CHIRON	Catherine	01/01/1998	IP-AUT	CILAG		note d'honoraire		
						versement à une association :		
0100 CHIRON	Catherine	01/01/1998	VB		Suivi de patient sous protocole thérapeutique	ARIEE - St Vincent de Paul		
						Service D'Anesthésie-Réanimation, HEGP		
6009 CHOLLEY	Bernard	20/11/2010	VB	PHILIPS	investigation mentionnée plus haut			
				INSTITUT DE RECHERCHES INTERNATIONALES		Service D'Anesthésie-Réanimation, HEGP		
6009 CHOLLEY	Bernard	20/11/2010	VB	SERVIER	protocole mentionné plus haut (role de coordonnateur + Dossiers patients)			
6009 CHOLLEY	Bernard	20/11/2010	CF-AUD	FRESENIUS	ISICEM Bruxelles/ Intensive Care/ Voluven	Rémunération personnelle	03/2010	03/2010
6009 CHOLLEY	Bernard	20/11/2010	IP-AC	COVIDIEN	Monitorage en anesthésie-réanimation	expérimentateur principal	07/2009	
6009 CHOLLEY	Bernard	20/11/2010	EC-INV	PHILIPS	Essais pré-clinique d'une nouvelle plateforme ultrasonore destinée à la réanimation	Investigateur coordonnateur	01/2011	02/2011
				INSTITUT DE RECHERCHES INTERNATIONALES		Rémunération personnelle	07/2010	
6009 CHOLLEY	Bernard	20/11/2010	EC-INV	SERVIER	Protocole multicentrique de phase IV sur l'Ivabradine intraveineuse	Rémunération personnelle	01/2008	
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	BASILEA PHARMA	Board international / Board français	Rémunération personnelle	01/2008	
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	SERVIER	Board d'experts	Rémunération personnelle	01/2007	
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	ANACONDA PHARMA	Consultant	Rémunération personnelle		
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	SANOFI AVENTIS	Board Français	Rémunération personnelle		
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	BAYER	Board Français	Rémunération personnelle	01/2007	
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	PIERRE FABRE	Consultant	Rémunération personnelle	01/2009	
0104 CHOSIDOW	Olivier	23/04/2010	LD-AR	BMS	Board Français	Investigateur principal	01/2006	
0104 CHOSIDOW	Olivier	23/04/2010	EC-INV	BAILLEUL BIORGA	Isotretinoine dans la rosacée: étude randomisée. Aciclovir Lauriad dans l'herpes buccal. Doxycycline dans le	Investigateur principal	01/2008	
0104 CHOSIDOW	Olivier	23/04/2010	EC-INV	BIOALLIANCE	sotretinoine dans la rosacée: étude randomisée. Aciclovir Lauriad dans l'herpes buccal. Doxycycline dans le	Investigateur principal	01/2007	
0104 CHOSIDOW	Olivier	23/04/2010	EC-INV	ROCHE	sotretinoine dans la rosacée: étude randomisée. Aciclovir Lauriad dans l'herpes buccal. Doxycycline dans le	Investigateur principal	01/2008	
0104 CHOSIDOW	Olivier	23/04/2010	EC-INV	PIERRE FABRE	sotretinoine dans la rosacée: étude randomisée. Aciclovir Lauriad dans l'herpes buccal. Doxycycline dans le	Investigateur principal	01/2007	
0104 CHOSIDOW	Olivier	23/04/2010	EC-INV	DUCRAY	sotretinoine dans la rosacée: étude randomisée. Aciclovir Lauriad dans l'herpes buccal. Doxycycline dans le	Co-investigateur	01/2008	
0104 CHOSIDOW	Olivier	23/04/2010	EC-CO	PIERRE FABRE	Dermatologie, Vamis à l'Urée	Co-investigateur	01/2008	
0104 CHOSIDOW	Olivier	23/04/2010	EC-CO	LEO	Antipsoriasis du visage	Rémunération personnelle	01/2009	
0104 CHOSIDOW	Olivier	23/04/2010	IP-RE	ASTELLAS	Orbenine nouveau RCP	Rémunération personnelle	01/2009	
0104 CHOSIDOW	Olivier	23/04/2010	RE-AUT	ALMIRALL	Evaluation de la possibilité de remboursement par la HAS de Solaraze	Rémunération personnelle	01/2007	
0104 CHOSIDOW	Olivier	23/04/2010	IP-AC	GENEVRIER	Conseils pour analyse d'un essai randomisé Dermagen	Rémunération personnelle	01/2010	
0104 CHOSIDOW	Olivier	23/04/2010	IP-AC	MEDA	Conseils pour analyse d'un essai randomisé Aldara	Rémunération personnelle	01/2010	
0104 CHOSIDOW	Olivier	23/04/2010	IP-AC	ROCHE	Analyse de photographies d'effets secondaires du Tarceva dans un essai randomisé	Rémunération personnelle	01/2010	
0104 CHOSIDOW	Olivier	23/04/2010	IP-AC	BIOALLIANCE	Conseils pour analyse d'un essai randomisé Acyclovir Lauriad	Rémunération personnelle	01/2009	
0104 CHOSIDOW	Olivier	23/04/2010	CF-INT	BASILEA	Académie européenne de dermatologie, Berlin, qualité de vie Toctino		01/2009	
0104 CHOSIDOW	Olivier	23/04/2010	CF-INT	GALDERMA/ CELGENE/ JANSSEN CILAG	Journée dermatologiques de Paris. Paris. Observance en dermatologie. Formations des VM sur l'utilisation du thalidomide en dermatologie.		01/2010	
0104 CHOSIDOW	Olivier	23/04/2010	CF-AUD	GALDERMA	Académie Américaine de Dermatologie		01/2010	
0104 CHOSIDOW	Olivier	23/04/2010	CF-AUD	BASILEA	Académie Européenne de Dermatologie		01/2008	
0104 CHOSIDOW	Olivier	12/02/2009	EC-INV	PIERRE FABRE DERMATOLOGIE	efficacité et tolérance pommade RV410AA vs Amycor onychosel dans l'onychomycose des gros orteils	investigateur	01/2004	12/2005
0104 CHOSIDOW	Olivier	21/09/2007	EC-CO	DUCRAY	Essai randomisé évaluant l'efficacité de la tolérance de l'Hydroquinone vs excipient dans le mélasma de l'adulte (co-investigateur)		01/2005	12/2005
0104 CHOSIDOW	Olivier	21/09/2007	IP-EC	JOHNSON/JOHNSON	Essai randomisé comparant l'invermectine par os en 2 prises à 15 j d'intervalle à la lotion malathion dans la pédiculose de cuir chevelu : orga	coordinnateur	01/2006	12/2006
0104 CHOSIDOW	Olivier	21/09/2007	EC-INV	PIERRE FABRE DERMATOLOGIE	Essai randomisé d'intervention évaluant l'impact d'une campagne d'information sur la bonne prescription d'is		01/2006	12/2006
0104 CHOSIDOW	Olivier	21/09/2007	IP-EC	GALDERMA	Mise au point d'un outil évaluant l'observance des traitements locaux et généraux dans l'acné : organisation et interprétation de l'essai		01/2006	12/2006
0104 CHOSIDOW	Olivier	21/09/2007	IP-EC	3M DERMATOLOGIE	Revue systématique des essais thérapeutiques sur la prise en charge des kératoses actiniques	pas de rémunération depuis 2007	01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	EC-CO	LABCATAL	Essai pilote d'utilisation du gluconate de zinc dans la maladie de Verneuil : organisation et interprétation de l		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	EC-INV	BIOGA-BAILLEUL	Essai randomisé comparant isotrétinoine faible dose au placebo dans la rosacée résistante (investigateur pr		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	EC-INV	BIOALLIANCE	Aciclovir lauriad dans l'herpes labial : essai randomisé : en cours d'élaboration (investigateur principal - franc		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	EC-CO	ROCHE	Doxycycline en prévention ou traitement des lésions cutanées induites par le Tarceva : essai randominé (en		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	EC-INV	GENEVRIER	Dermagen dans les ulcères de diabétique : essai randomisé (comité scientifique et coordination)		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	IP-EC	ANACONDA PHARMA	CondyClin dans les condylomes ano-génitaux : essai randomisé (en cours d'élaboration), comité scientifique		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	EC-INV	DUCRAY	Malathion dans la pédiculose du cuir chevelu : coordinateur		01/2007	
0104 CHOSIDOW	Olivier	21/09/2007	IP-EC	LABCATAL	Zinc dans la maladie de Verneuil : membre du comité scientifique et investigateur,			
0104 CHOSIDOW	Olivier	21/09/2007	EC-INV	PIERRE FABRE DERMATOLOGIE	Rosiced dans la rosacée : essai 3 bras (vs excipient et vs métronidazole 0,75 %			

	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
104	CHOSIDOW	Olivier	21/09/2007	IP-RE	GLAXOSMITHKLINE	Demande d'AMM du Valaciclovir dans l'herpès génital du sujet immunodéprimé		01/2004	12/2004
104	CHOSIDOW	Olivier	21/09/2007	IP-RE	THERAPLIX (AVENTIS)	Evaluation de l'intérêt d'un produit pédiculicide		01/2005	12/2005
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	GLAXOSMITHKLINE	Essai randomisé européen évaluant l'efficacité et la tolérance de la pleuromutiline dans les pyodermites superficielles		01/2005	12/2005
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	PIERRE FABRE DERMATOLOGIE	Aide à la réalisation des essais cliniques en dermatologie		01/2005	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	EXPANSCIENCE	Bon usage des médicaments de l'acné et les visages rouges		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	GALDERMA	Participation au goupe d'experts acné (plusieurs réunions par an) + symposium satellite aux journées dermatologiques de Paris 2006 (démis		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	URGO	Produits OTC/Pansements		01/2005	12/2005
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	3M	Dossier de ré-inscription condylomes ano-génitaux plus inscription carcinomes baso-cellulaires	Aucune rémunération		
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	AVENTIS MSD	Rédaction d'un livre sur la zona	Aucune rémunération	01/2007	
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	VALEANT	Efudix	Aucune rémunération	01/2007	
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	JOHN LIBBEY EUROTEXT	Rédaction d'un ouvrage sur les onychomycoses en partenariat avec GALDERMA	Aucune rémunération	01/2007	
104	CHOSIDOW	Olivier	21/09/2007	IP-CF	ALMIRALL	EPU dermatoses bactériennes : association dermatologique Bordeaux (ADVSO)		11/2005	
104	CHOSIDOW	Olivier	21/09/2007	IP-CF	EXPANSCIENCE	Controverse sur l'acné (Lisbonne)		09/2005	09/2005
104	CHOSIDOW	Olivier	21/09/2007	IP-CF	GALDERMA	Actualités sur l'acné (Rabat et Casablanca)		05/2005	05/2005
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	ALTANA PHARMA	The french pricing/reimbursement process : the transparence (Zurich : 5 conférences en 2006)		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	LEO PHARMA	Formation des dermatologues aux essais thérapeutiques et aux bonnes pratiques : la Baule (mois de mars) et Paris (mois de septembre)		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	3M DERMATOLOGIE	Préparation et mise en place d'un programme de formation sur les carcinomes baso-cellulaires cutanés		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	MERCK	Rédaction d'un fascicule sur la prise en charge des effets secondaires cutanés liés aux inhibiteurs du récepteur à l'EGF et réunions de mise		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	COOPER	Exposé sur la résistance des poux aux insecticides		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	IP-AC	LEO PHARMA	Compte rendu de l'Académie de Dermatologie 2007, en partenariat avec MVS production		01/2007	12/2007
104	CHOSIDOW	Olivier	21/09/2007	CF-AUD	DUCRAY	Congrès mondial sur les pédiculoses		01/2006	12/2006
104	CHOSIDOW	Olivier	21/09/2007	CF-AUD	BIOALLIANCE	ICAAC		01/2007	12/2007
104	CHOSIDOW	Olivier	21/09/2007	CF-AUD	EXPANSCIENCE / PIERRE FABRE DERMATOLOGIE	Congrès mondial de dermatologie		01/2007	12/2007
104	CHOSIDOW	Olivier	21/09/2007	(Autre)	GALDERMA / MERCK / LEO / GSK / PIERRE FABRE DERMATOLOGIE / FUJISAWA	Versement d'une subvention à l'association Naturalia Biologia pour la réalisation épidémiologique sur les facteurs de risque de la dermite séi		01/2005	12/2007
104	CHOSIDOW	Olivier	20/05/2006	LD-AR	3 M	Aldaro - Board cancer Basocellulaire	rémunération personnelle	01/2006	
104	CHOSIDOW	Olivier	20/05/2006	LD-AR	MERCK	Board Erbitux	rémunération personnelle	01/2006	
104	CHOSIDOW	Olivier	20/05/2006	LD-AR	PIERRE FABRE DERMATOLOGIE	tous produits concernant la dermatologie et la réalisation d'essai clinique	rémunération personnelle	01/2006	
104	CHOSIDOW	Olivier	20/05/2006	LD-AR	ROCHE	Board Tarceva	rémunération personnelle	01/2006	
104	CHOSIDOW	Olivier	20/05/2006	EC-INV	PFD	Essai multicentrique d'intervention Isotrétinoïne	investigateur principal	01/2005	12/2006
104	CHOSIDOW	Olivier	20/05/2006	RE-DE	GSK	Herpès génital du sujet immunodéprimé - Zelitrex	rémunération personnelle	01/2006	12/2006
104	CHOSIDOW	Olivier	20/05/2006	IP-AC	GENEVRIER	essai thérapeutique ULCAR du diabétique réflexion sur un protocole	rémunération personnelle	01/2006	
104	CHOSIDOW	Olivier	20/05/2006	CF-INT	ALTANA PHARMA	Zurich - "Comment fonctionne la commission de la transparence?"	rémunération personnelle	01/2006	12/2006
104	CHOSIDOW	Olivier	20/05/2006	CF-INT	GSK	Pleuromutiline - Londres	rémunération personnelle	01/2006	12/2006
104	CHOSIDOW	Olivier	20/05/2006	CF-INT	LEO	formation sur les bonnes pratiques - La Baule - Paris	rémunération personnelle	01/2006	12/2006
104	CHOSIDOW	Olivier	19/12/2005	CF-INT	BIORGA	Symposium aux Journées Dermatologiques de Paris sur les actualités concernant la rosacée		12/2004	12/2004
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	3M France	Board France sur la prise en charge des kératoses actiniques (début en 2005, en cours)			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	3M Europe	Participation à un conseil scientifique sur une synthèse des données de la littérature sur la prise en charge des kératoses actiniques			
104	CHOSIDOW	Olivier	19/12/2005	CF-INT	EXPANSCIENCE	Orateur à un symposium sur l'acné à Lisbonne		09/2005	09/2005
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	EXPANSCIENCE	Avis ponctuel concernant le bon usage des médicaments dans l'acné et les visages rouges		07/2005	07/2005
104	CHOSIDOW	Olivier	19/12/2005	IP-CF	GALDERMA	Participation au groupe d'expert acné (4 réunions par an + symposium satellite aux Journées Dermatologiques de Paris		12/2005	12/2005
104	CHOSIDOW	Olivier	19/12/2005	CF-INT	GALDERMA	Exposé à Casablanca et à Rabat sur les actualités bibliographiques sur l'acné		06/2005	06/2005
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	GENEVRIER	Avis ponctuel à propos des substituts cutanés de thérapie cellulaire		10/2005	10/2005
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	GLAXO SMITHKLINE International et France	Conseil sur le développement (phase III) de la pleuromutiline topique dans les pyodermites superficielles			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	JOHNSON & JOHNSON	2 réunions sur le développement de l'ivermectine dans la pédiculose du cuir chevelu			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	MERCK	Aide à la prise en charge de la toxicité cutanée de l'Erbitux (réunions en janvier, juin et décembre 2005			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	PIERRE FABRE	Coordinateur du protocole sur l'impact des réunions d'information sur l'isotrétinoïne et exposé dans 2 FMC			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	PIERRE FABRE	Aide au développement de produits en dermatologie (consultations régulières dans l'année)			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	THERAPLIX	Evaluation d'un produit pédiculicide		02/2005	02/2005
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	URGO	Stratégie cicatrisation mai 2005			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	ALMIRALL	Actualités sur les dermatoses infectieuses, FMC, Bordeaux, nov. 2005			
104	CHOSIDOW	Olivier	19/12/2005	IP-AC	DUCRAY	Développement hydroquinone dans le melasma			
104	CHOSIDOW	Olivier	30/01/2004	IP-EC	P. FABRE				
104	CHOSIDOW	Olivier	30/01/2004	IP-EC	JOHNSON-JOHNSON	Ivermectine poux			
104	CHOSIDOW	Olivier	30/01/2004	IP-EC	LFD	Sphingogel acné			
104	CHOSIDOW	Olivier	30/01/2004	IP-RE	EXPANSCIENCE	Demande d'AMM Zinc acné			
104	CHOSIDOW	Olivier	30/01/2004	IP-AC	PFD	Stratégies médicaments			
104	CHOSIDOW	Olivier	30/01/2004	IP-AC	SERONO	Board France			
104	CHOSIDOW	Olivier	30/01/2004	IP-AC	URGO	Stratégie cicatrisation			
104	CHOSIDOW	Olivier	30/01/2004	IP-AC	3M	Aldara expertise dossier européen cancer cutané			
104	CHOSIDOW	Olivier	30/01/2004	IP-CF	EXPANSCIENCE	Conférence acné, Venise			
104	CHOSIDOW	Olivier	30/01/2004	IP-CF	GALDERMA	Enquête acné			
104	CHOSIDOW	Olivier	30/01/2004	IP-CF	YAMANOUCHI	Résultats enquête ORPIC			
104	CHOSIDOW	Olivier	30/01/2004	PAR	PIERRE FABRE	Essai AMEMPH			
104	CHOSIDOW	Olivier	21/08/2003	IP-EC	PIERRE FABRE	Essais randomisés Cyclo DS			
104	CHOSIDOW	Olivier	21/08/2003	IP-EC	LILLY-3M	Résiquimod Herpès			
104	CHOSIDOW	Olivier	21/08/2003	IP-EC	LEO	Essai randomisé sphingogel Acné			
104	CHOSIDOW	Olivier	21/08/2003	IP-EC	JOHNSON & JOHNSON	Essai randomisé Ivermectine Poux			
104	CHOSIDOW	Olivier	21/08/2003	IP-EC	PHARMHYGIEN	Essai randomisé Spraypax			
104	CHOSIDOW	Olivier	21/08/2003	IP-RE	GLAXO SMITHKLINE	Demande d'AMM Zelitrex herpès			
104	CHOSIDOW	Olivier	21/08/2003	IP-RE	SANOFI SYNTHELABO	Demande d'AMM Dermochrome			
104	CHOSIDOW	Olivier	21/08/2003	IP-AC	BIOGEN	Données européennes Alefacyl			
104	CHOSIDOW	Olivier	21/08/2003	IP-AC	SERONO	Raptiva			
104	CHOSIDOW	Olivier	21/08/2003	IP-AC	ALTANAPHARMA	Corticoïdes inhalés			
104	CHOSIDOW	Olivier	21/08/2003	IP-AC	URGO	Stratégie Cicatrisation			
104	CHOSIDOW	Olivier	21/08/2003	IP-AC	LABCATAL	Préparation d'un essai randomisé dans la maladie de Verneuil			
104	CHOSIDOW	Olivier	21/08/2003	IP-CF	3M	Conférence Québec			
104	CHOSIDOW	Olivier	21/08/2003	IP-CF	GALDERMA	Rédaction d'un ouvrage chez John Libbey sur l'acné			
104	CHOSIDOW	Olivier	21/08/2003	VB	3M	AREMPH (Association 1901 de recherche)			
104	CHOSIDOW	Olivier	15/10/2002	IP-EC	PIERRE FABRE				
104	CHOSIDOW	Olivier	15/10/2002	IP-EC	YAMANOUCHI				
104	CHOSIDOW	Olivier	15/10/2002	IP-EC	LILLY, 3 M				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10104	CHOSIDOW	Olivier	15/10/2002	IP-EC	PHARHYPREX				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	GLAXO SMITHKLINE				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	PHARMAFARM				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	LOPTOL				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	JOHNSON & JOHNSON				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	PHARHYPREX				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	NOVARTIS				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	WHITEHALL				
10104	CHOSIDOW	Olivier	15/10/2002	IP-RE	BIOGEN				
10104	CHOSIDOW	Olivier	15/10/2002	IP-AC	ETHYPHARM				
10104	CHOSIDOW	Olivier	15/10/2002	IP-AC	URGO				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	BIORGA				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	3 M				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	GLAXO SMITHKLINE				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	GLADERMA				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	LEO				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	JOHN LIBBEY				
10104	CHOSIDOW	Olivier	15/10/2002	IP-CF	LILLY				
10104	CHOSIDOW	Olivier	16/12/2000	IP-EC	AVENTIS	Essai ?			
10104	CHOSIDOW	Olivier	16/12/2000	IP-EC	PIERRE FABRE	Essai ?			
10104	CHOSIDOW	Olivier	16/12/2000	IP-EC	3 M	Essai ?			
10104	CHOSIDOW	Olivier	16/12/2000	IP-EC	LABCATAL	Essai ?			
10104	CHOSIDOW	Olivier	16/12/2000	IP-RE	MSD	Ivermectine AMM			
10104	CHOSIDOW	Olivier	16/12/2000	IP-AC	PHARHYGIEN	Produit Antipoux/Gah			
10104	CHOSIDOW	Olivier	16/12/2000	IP-AC	GALDERMA	Nad. Floxecine			
10104	CHOSIDOW	Olivier	16/12/2000	IP-AC	FOURNIER/URGO	Achat nouvelles molécules			
10104	CHOSIDOW	Olivier	16/12/2000	IP-AC	INNOTHERA	Vaginox			
10104	CHOSIDOW	Olivier	16/12/2000	IP-AC	YAMANOUCHI	Préparation fiche Ortérine			
10104	CHOSIDOW	Olivier	16/12/2000	IP-CF	GLAXO WELLCOME	Dermocorticoïdes			
10104	CHOSIDOW	Olivier	16/12/2000	IP-CF	3 M	Virologie cutanée			
10104	CHOSIDOW	Olivier	16/12/2000	IP-CF	LEO	Rédaction d'un article ectoparasitoses			
10104	CHOSIDOW	Olivier	16/12/2000	VB	MSD	Association 1901 AMENPH			
10104	CHOSIDOW	Olivier	01/07/2000	IP-EC	AVENTIS				
10104	CHOSIDOW	Olivier	01/07/2000	IP-RE	MSD				
10104	CHOSIDOW	Olivier	01/07/2000	IP-AC	3M				
10104	CHOSIDOW	Olivier	01/07/2000	IP-CF	GLAXO WELLCOME				
10104	CHOSIDOW	Olivier	01/07/2000	IP-EC	3M SANTE				
10104	CHOSIDOW	Olivier	01/07/2000	IP-EC	GLAXO WELLCOME				
10104	CHOSIDOW	Olivier	01/07/2000	IP-EC	SB				
10104	CHOSIDOW	Olivier	01/07/2000	IP-EC	PIERRE FABRE				
10104	CHOSIDOW	Olivier	01/07/2000	IP-EC	LABCATAL				
10104	CHOSIDOW	Olivier	01/07/2000	IP-RE	PARKE DAVIS				
10104	CHOSIDOW	Olivier	01/07/2000	IP-AC	GLAXO WELLCOME				
10104	CHOSIDOW	Olivier	01/07/2000	IP-AC	FOURNIER				
10104	CHOSIDOW	Olivier	01/07/2000	IP-AC	INNOTHERA				
10104	CHOSIDOW	Olivier	01/07/2000	IP-AC	PHARMAFARM				
10104	CHOSIDOW	Olivier	01/07/2000	IP-AC	GD DERMO				
10104	CHOSIDOW	Olivier	01/07/2000	IP-CF	LEO				
10104	CHOSIDOW	Olivier	15/01/2000	IP-EC	RPR	Pyostacine Phase IV			
10104	CHOSIDOW	Olivier	15/01/2000	IP-EC	PIERRE FABRE	Mycoster Phase III			
10104	CHOSIDOW	Olivier	15/01/2000	IP-EC	LABCATAL	Lithoderm			
10104	CHOSIDOW	Olivier	15/01/2000	IP-EC	SB	Fomciclovir Herpès Phase III			
10104	CHOSIDOW	Olivier	15/01/2000	IP-EC	GLAXO WELLCOME	Valaciclovir Herpès			
10104	CHOSIDOW	Olivier	15/01/2000	IP-RE	SB	AMM Fomciclovir Herpès			
10104	CHOSIDOW	Olivier	15/01/2000	IP-RE	MSD	Ivermectine AMM			
10104	CHOSIDOW	Olivier	15/01/2000	IP-RE	PARKE DAVIS	Rapport Neurontin/effets cutanés			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	WARNER LAMBERT	Stratégie Développement			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	3 M SANTE	Aldara Strategie Herpès			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	GLAXO WELLCOME	Stratégie Astodose			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	URGO	Développement			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	PHARMAFARM	Positionnement Dupyrocine			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	GALDERMA	Acné			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	INNOTHERA	Vaginox			
10104	CHOSIDOW	Olivier	15/01/2000	IP-CF	3 M SANTE	Aldare - Symposium			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AUT	ROCHE POSAY et BIODERMA	FMC Pitié-Salpétrière pour dermatologues de ville			
10104	CHOSIDOW	Olivier	15/01/2000	IP-AC	LABCATAL				
10104	CHOSIDOW	Olivier	01/01/1999	IP-EC	SmithKline Beecham				
10104	CHOSIDOW	Olivier	01/01/1999	IP-EC	Pierre Fabre				
10104	CHOSIDOW	Olivier	01/01/1999	IP-EC	Rhône-Poulenc Rorer				
10104	CHOSIDOW	Olivier	01/01/1999	IP-AC	SmithKline Beecham				
10104	CHOSIDOW	Olivier	01/01/1999	IP-AC	Labcatal				
10104	CHOSIDOW	Olivier	01/01/1999	IP-AC	Menarini				
10104	CHOSIDOW	Olivier	01/01/1999	IP-AC	Yamanouchi				
10104	CHOSIDOW	Olivier	01/01/1999	IP-CF	Lederle				
10104	CHOSIDOW	Olivier	01/01/1999	IP-CF	Bioderma				
10104	CHOSIDOW	Olivier	01/01/1999	IP-CF	Roche-Posay				
10104	CHOSIDOW	Olivier	01/01/1999	IP-CF	Roussel-Uclaf				
10104	CHOSIDOW	Olivier	01/01/1999	VB	Prise en charge de 6 jours : Lederlé				
10104	CHOSIDOW	Olivier	01/01/1999	VB	SmithKline Beecham				
10104	CHOSIDOW	Olivier	01/01/1999	VB	Janssen Cilag				
10104	CHOSIDOW	Olivier	01/01/1999	VB	Liphoderm				
10104	CHOSIDOW	Olivier	01/01/1998	LD	Servier				

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10104	CHOSIDOW	Olivier	01/01/1998	IP-AUT	Spécia				
10104	CHOSIDOW	Olivier	01/01/1998	IP-AUT	Roussel				
10104	CHOSIDOW	Olivier	01/01/1998	IP-AUT	Janssen				
10104	CHOSIDOW	Olivier	01/01/1998	IP-AUT	Lederlé				
10104	CHOSIDOW	Olivier	01/01/1998	IP-AUT	Beecham				
10104	CHOSIDOW	Olivier	01/01/1998	VB	Labcatal				
10104	CHOSIDOW	Olivier	01/01/1998	VB	Beecham				
10104	CHOSIDOW	Olivier	01/01/1998	VB	Lederlé				
10104	CHOSIDOW	Olivier	01/01/1998	VB	Servier				
61187	CLANET	Michel	05/05/2010	IP-EC	BAYER SCHERING	Membre du groupe MS FORVOL (enseignement, organisation colloques)	Rémunération personnelle	01/2007	12/2010
61187	CLANET	Michel	05/05/2010	IP-EC	BIOGEN IDEC	Membre du groupe International expert forum	Rémunération personnelle	01/2010	
61187	CLANET	Michel	05/05/2010	EC-INV	TEVA/SANOFI AVENTIS	Suivi de cohorte observationnelle. Etude demandée par la comm. Transparence)	Président du conseil scientifique	01/2007	12/2013
61187	CLANET	Michel	05/05/2010	EC-CO	GENZYME	ALEMTUZUMAB	Co-investigateur	01/2007	12/2011
61187	CLANET	Michel	05/05/2010	EC-CO	BIOGEN	DACLIZUMAB	Co-investigateur	01/2010	12/2014
61187	CLANET	Michel	05/05/2010	EC-CO	NOVARTIS	FINGOLIMAD	Co-investigateur	01/2007	12/2012
61187	CLANET	Michel	05/05/2010	EC-CO	ALMIRALL	SATIVEX	Co-investigateur	01/2005	12/2007
61187	CLANET	Michel	05/05/2010	EC-CO	GENMAB	OFATUMAB	Membre du comité de safety	01/2008	12/2010
61187	CLANET	Michel	05/05/2010	CF-INT	TEVA/AVENTIS	2009. BUDAPEST. Risks and benefits of treatments in multiple sclerosis	Rémunération personnelle	12/2009	12/2009
61187	CLANET	Michel	05/05/2010	CF-INT	AVENTIS/TEVA	Réunion France Catalanes Toulouse Juin 2009	aucune rémunération	06/2009	06/2009
61187	CLANET	Michel	05/05/2010	VB	BIOGEN-IDEC, NOVARTIS, BAYER-SCHERING, TEVA/AVENTIS/SANOFI, MERK SERONO	Subventions de recherche. Annuelles.	Ass Developt Recherche Neurologie- Réseau MPSEP		
61187	CLANET	Michel	29/05/2009	CF-AUD	EUTHERAPIE	American Academy Neurology - 2009	Coordonnateur du groupe de formation continue validé par la fédération française de Neurologie. Objectif: effectuer une couverture scientifique de cet évènement scientifique international avec des journalistes professionnels pour établis un document video	04/2009	05/2009
61187	CLANET	Michel	29/05/2009	EC-CO	GENZYME	Essai CAMMS323□□Phase III Alemtuzumab dans le traitement des formes rémittentes de la SEP	Coinvestigateur	07/2008	
61187	CLANET	Michel	29/05/2009	EC-INV	GENMAB	Membre de Independant Data Monitoring Committee de l'étude de phase II OFATUMUMAB dans la SEP.	Membre de ce comité indépendant dont l'objectif est la surveillance de la pharmacovigilance de l'essai avec possibilité d'interruption de l'essai si des problèmes d'EIG apparaissent dans l'étude	05/2009	
61187	CLANET	Michel	29/05/2009	EC-INV	AVENTIS TEVA	L'étude de cohorte dont il est question précédemment est une étude demandée par la DHOS et la commissi	J'assume la fonction de président du CS. Cette fonction n'est pas rémunérée. Elle est toujours en cours pendant 5 ans au moins de suivi.	01/2004	
61187	CLANET	Michel	03/03/2007	EC-CO	BIOGEN, IDEC	Participation à des essais cliniques / Natalizumab	co-investigateur	01/2002	12/2004
61187	CLANET	Michel	03/03/2007	EC-INV	SCHERING	Etude AFFIRM - Essai BEYOND, BENEFIT		01/2004	12/2006
61187	CLANET	Michel	03/03/2007	EC-INV	SANOFI	Xaliproden - essai thérapeutique	coordonateur principal	01/2002	12/2005
61187	CLANET	Michel	03/03/2007	EC-INV	AVENTIS,TEVA	Suivi de cohorte COPAXONE	Président du Conseil scientifique	01/2004	
61187	CLANET	Michel	03/03/2007	IP-AC	ALLMIRALL	Expert - réunion ponctuelle	rémunération personnelle	12/2006	
61187	CLANET	Michel	03/03/2007	CF-INT	SCHERING, SERONO, AVENTIS, TEVA, BIOGEN, IDEC	Plusieures interventions au cours des 3 dernières années, ponctuelles, lors de symposium ou de réunions c	Rémunération personnelle		
61187	CLANET	Michel	03/03/2007	CF-AUD	AVENTIS, TEVA	Congrès mondial de neurologie		11/2005	
61187	CLANET	Michel	03/03/2007	VB	BIOGEN, IDEC, SERONO, SCHERING, AVENTIS	Projets fondamentaux et cliniques de recherche hors champ des médicaments concernés (2005/2006/2007)	Association de recherche en neurologie		
61187	CLANET	Michel	18/04/2006	IP-EC	BIOGEN IDEC	NATALIZUMAB - INTERFERON B AVONEX	INVESTIGATEUR PRINCIPAL	01/2001	
61187	CLANET	Michel	18/04/2006	IP-EC	SANOFI - AVENTIS	XALIPRODEN - SCLEROSE EN P.LAQUES		01/2006	12/2006
61187	CLANET	Michel	18/04/2006	IP-EC	NOVARTIS	ETY	INVESTIGATEUR	01/2005	12/2007
61187	CLANET	Michel	18/04/2006	IP-EC	AVEENTIS	TERIFLUNOMITE	INVESTIGATEUR	01/2005	12/2007
61187	CLANET	Michel	18/04/2006	EC-CO	SERONO	CLADRIBINE	CO-INVESTIGATEUR	01/2005	12/2007
61187	CLANET	Michel	18/04/2006	EC-CO	EXELSIOR	MN 166	Membre du DSMB	01/2005	
61187	CLANET	Michel	18/04/2006	IP-AC	EISAI / CENTOCOR	Discussion méthodologique sur l'élaboration d'un essai dans la sclerose en plaques pour un anticorps monoclonal		01/2005	
61187	CLANET	Michel	18/04/2006	IP-CF	SCHERING SA	Neurologie de langue française : 10 ans de betaferon		04/2006	04/2006
61187	CLANET	Michel	18/04/2006	IP-CF	SERVIER	Académie Américaine de Neurologie : responsable du groupe qui assure la couverture scientifique dun congrès		01/2005	12/2005
61187	CLANET	Michel	18/04/2006	VB	BIOGEN - SCHERING SA	Programmes de recherche sur la génétique de la sclerose en plaques : association pour le développement et la recherche en Neurologie		01/2005	12/2006
61187	CLANET	Michel	17/01/2005	IF	BIOGEN, SCHERING, SERONO, TEVA, AVENTIS, SANOFI SYNTHELABO, CEPHALON-LAFFONT	Participation sporadique à des conseils ou rapports avec les laboratoires			
61187	CLANET	Michel	17/01/2005	IP-CF		Séances de formation continue soutenues par les laboratoires			
61187	CLANET	Michel	17/01/2005	IP-EC	BIOGEN	Interferon (1998-2002) participation à des essais thérapeutiques phase II ou III dans le domaine sclérose en plaques			
61187	CLANET	Michel	17/01/2005	IP-EC	BIOGEN	Antegren (en cours) participation a des essais thérapeutiques phase II et III dans le domaine sclérose en plaques			
61187	CLANET	Michel	17/01/2005	IP-EC	SANOFI	Xaliproden (en cours)			
61187	CLANET	Michel	17/01/2005	IP-EC	SCHERING	Interferon (en cours)			
61187	CLANET	Michel	17/01/2005	IP-EC	TEVA/AVENTIS	Copaxone (en cours)			
61187	CLANET	Michel	17/01/2005	IP-EC	CEPHALON	Modafinil (2000-2002)			
61187	CLANET	Michel	17/01/2005	VB	BIOGEN, SERONO, TEVA-AVENTIS, SANOFI SYNTHELABO	Programme de recherche et réseau de santé sur la sclérose en plaques (MIPSEP : Midi Pyrénées Sclérose En Plaques)			
10107	CLAUDE	Jean-Roger	25/01/2010	PAR	SERVIER	DIRECTEUR DE LA TOXICOLOGIE	CONJOINT	01/1993	
10107	CLAUDE	Jean-Roger	25/01/2010	CF-INT	MULTIPLES	Multiples tous les ans depuis 40 ans	Aucune rémunération	01/1967	

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat Rémunération	Date début	Date fin
07 CLAUDE	Jean-Roger	25/01/2010	RE-DE	SERVIER	PROTELOS / COVERSYL et dérivés	Rémunération personnelle	01/1987	01/2007
107 CLAUDE	Jean-Roger	25/01/2010	RE-DE	GUERBET	Produits de contraste IRM	Rémunération personnelle	01/1987	
07 CLAUDE	Jean-Roger	25/01/2010	LD-AR	PIERRE FABRE	Consultant tous produits	Rémunération personnelle	10/2007	
107 CLAUDE	Jean-Roger	25/01/2010	LD-AR	SERVIER	Consultant tous produits	Rémunération personnelle	01/1972	
107 CLAUDE	Jean-Roger	25/01/2010	LD-AR	GSK	Consultant tous produits	Rémunération personnelle	01/2001	01/2007
107 CLAUDE	Jean-Roger	25/01/2010	LD-AR	BAYER PHARMA	Consultant tous produits	Rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	25/01/2010	LD-AR	BMS	Consultant tous produits	Rémunération personnelle	02/1990	
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	BMS	Consultant tous produits	rémunération personnelle	02/1990	
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	BAYER PHARMA	Consultant tous produits	rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	GSK	Consultant tous produits	rémunération personnelle	01/2001	
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	SERVIER	Consultant tous produits	rémunération personnelle	01/1972	
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	MERCK THERAMEX	Consultant tous produits	rémunération personnelle	01/1989	06/2008
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	NEGMA	Consultant tous produits	rémunération personnelle	01/1999	12/2007
107 CLAUDE	Jean-Roger	02/03/2009	LD-AR	PIERRE FABRE	Consultant tous produits	rémunération personnelle	10/2007	
107 CLAUDE	Jean-Roger	02/03/2009	RE-DE	GUERBET	Produits de contraste IRM	rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	02/03/2009	RE-DE	SERVIER	PROTELOS - COVERSYL et dérivés	rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	02/03/2009	RE-DE	PIERRE FABRE	NAVELBINE	rémunération personnelle	01/1989	12/2007
107 CLAUDE	Jean-Roger	02/03/2009	CF-INT	MULTIPLES	Multiples : tous les ans depuis 40 ans	zucune rémunération	01/1967	
107 CLAUDE	Jean-Roger	02/03/2009	PAR	SERVIER	Directeur de la toxicologie	conjoint	01/1993	
107 CLAUDE	Jean-Roger	19/11/2007	RE-DE	PIERRE FABRE	NAVELBINE	Rémunération personnelle	01/1989	
107 CLAUDE	Jean-Roger	19/11/2007	RE-DE	GUERBET	Produits de contraste IRM	Rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	19/11/2007	RE-DE	SERVIER	PROTELOS / COVERSYL et dérivés	Rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	19/11/2007	CF-INT	MULTIPLES	Multiples tous les ans depuis 40 ans	Aucune rémunération	01/1967	
107 CLAUDE	Jean-Roger	19/11/2007	LD-AR	PIERRE FABRE	Consultant tous produits	Rémunération personnelle	10/2007	
107 CLAUDE	Jean-Roger	19/11/2007	LD-AR	NEGMA	Consultant tous produits	Rémunération personnelle	01/1999	
107 CLAUDE	Jean-Roger	19/11/2007	LD-AR	MERCK THERAMEX	Consultant tous produits	Rémunération personnelle	01/1989	
107 CLAUDE	Jean-Roger	19/11/2007	LD-AR	SERVIER	Consultant tous produits	Rémunération personnelle	01/1972	
107 CLAUDE	Jean-Roger	19/11/2007	LD-AR	GSK	Consultant tous produits	Rémunération personnelle	01/2001	
107 CLAUDE	Jean-Roger	19/11/2007	LD-AR	BAYER PHARMA	Consultant tous produits	Rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	12/02/2007	PAR	SERVIER	DIRECTEUR DE LA TOXICOLOGIE	CONJOINT	01/1993	
107 CLAUDE	Jean-Roger	12/02/2007	LD-AR	BMS	Consultant tous produits	Rémunération personnelle	02/1990	
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	BAYER-PHARMA	Consultant (toxicologie) tous produits	Rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	BEAUFOUR-IPSEN	Consultant tous produits	Rémunération personnelle	01/1998	12/2003
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	BRISTOL MYERS SQUIBB	Consultant tous produits	Rémunération personnelle	01/1990	12/2003
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	GLAXO SMITHKLINE	Consultant tous produits	Rémunération personnelle	01/2001	
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	HOFFMAN-LAROCHE	Consultant tous produits	Rémunération personnelle	01/2005	01/2006
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	MERCK-THERAMEX	Consultant tous produits	Rémunération personnelle	01/1989	
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	LAFON-CEPHALON	Consultant tous produits	Rémunération personnelle	01/1975	12/2002
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	NEGMA LERADS	Consultant tous produits	Rémunération personnelle	01/1999	
107 CLAUDE	Jean-Roger	21/11/2005	LD-AR	SERVIER	Consultant tous produits	Rémunération personnelle	01/1972	
107 CLAUDE	Jean-Roger	21/11/2005	RE-DE	GUERBET	Produits de contraste IRM - Toxicologie	Rémunération personnelle	01/1987	
107 CLAUDE	Jean-Roger	21/11/2005	RE-DE	PIERRE FABRE	Naveliase - Toxicologie	Rémunération personnelle	01/1989	
107 CLAUDE	Jean-Roger	21/11/2005	RE-DE	SERVIER	Protelos, Pretarax, Locabiotal, Coversyl, etc. - Toxicologie	Rémunération personnelle	01/1972	
107 CLAUDE	Jean-Roger	21/11/2005	RE-DE	MERCK-THERAMEX	Estreva, Nomax - Toxicologie	Rémunération personnelle	01/1989	
107 CLAUDE	Jean-Roger	21/11/2005	IP-AC	CIT	Président du Conseil scientifique	Rémunération personnelle	01/1990	10/2006
107 CLAUDE	Jean-Roger	21/11/2005	IP-AC	PFIZER	Membre de l'International Expert Panel Pregabalin	Rémunération personnelle	01/2000	12/2004
107 CLAUDE	Jean-Roger	21/11/2005	IP-AC	BIOGEN	peptide original - membre de l'IEP :	Rémunération personnelle	01/1999	12/2003
107 CLAUDE	Jean-Roger	21/11/2005	CF-INT		Trop nombreuses (1 par mois). Europe, USA, Chine - exposés - cours - conférences sur des sujets en rappo	Rémunération personnelle	01/1980	
107 CLAUDE	Jean-Roger	21/11/2005	CF-AUD		Voir ci-dessus		01/1980	
107 CLAUDE	Jean-Roger	03/06/2004	IP-RE	LABORATOIRE SERVIER	rapport expert PROTELOS COVERSYL (2001-2004)			
107 CLAUDE	Jean-Roger	03/06/2004	IP-RE	LABORATOIRE GUERBET	rapport expert VISTAREM 2003			
107 CLAUDE	Jean-Roger	03/06/2004	IP-RE	LABORATOIRE MERCK THERAMEX	rapport expert LUTENYL NAEMIS 2002			
107 CLAUDE	Jean-Roger	03/06/2004	IP-AC	BAYER PHARMA	secunte non clinique des produits			
107 CLAUDE	Jean-Roger	03/06/2004	IP-AC	IPSEN BEAUFOUR	secunte non clinique des produits			
107 CLAUDE	Jean-Roger	03/06/2004	IP-AC	BRISTOLS MYERS SQUIBB	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/06/2004	IP-AC	NEGMA LERADS	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/06/2004	IP-AC	PFIZER	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/06/2004	IP-CF	Centre International de Toxicologie (CIT)	Président du Conseil Scientifique international			
107 CLAUDE	Jean-Roger	03/09/2003	IP-RE	SERVIER	Rapport expertise AERODIOL, PROTELOS, COVERSYL (2000-2003)			
107 CLAUDE	Jean-Roger	03/09/2003	IP-RE	GUERBET	Rapport expertise VISTAREM (2003)			
107 CLAUDE	Jean-Roger	03/09/2003	IP-RE	MERCK-THERAMEX	Rapport expertise LUTENYL (2002)			
107 CLAUDE	Jean-Roger	03/09/2003	IP-RE	PIERRE FABRE	Rapport expertise NAVELBINE (2000)			
107 CLAUDE	Jean-Roger	03/09/2003	IP-AC	BAYER PHARMA	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/09/2003	IP-AC	IPSEN BEAUFOUR	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/09/2003	IP-AC	BRISTOL MYERS SQUIBB	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/09/2003	IP-AC	NEGMA-LERADS	Sécurité non clinique des produits			
107 CLAUDE	Jean-Roger	03/09/2003	IP-CF	CENTRE INTERNATIONAL DE TOXICOLOGIE (CIT)	Président du Conseil Scientifique International			
107 CLAUDE	Jean-Roger	03/09/2003	PAR	SERVIER	Conjoint	DPI dans le domaine des DM, pour les médicaments : se reporter à DPI pour AMM (datée du même jour)		
107 CLAUDE	Jean-Roger	15/11/2000	PAR	LAFON	Conjoint			
107 CLAUDE	Jean-Roger	15/11/2000	IP-EC	LAFON	Travaux en toxicologie			
107 CLAUDE	Jean-Roger	15/11/2000	IP-RE	GUERBET	Sinerem-Dotarem			
107 CLAUDE	Jean-Roger	15/11/2000	IP-RE	PIERRE FABRE	Noveibine oral			
107 CLAUDE	Jean-Roger	15/11/2000	IP-RE	SERVIER	Aérodiol			
107 CLAUDE	Jean-Roger	15/11/2000	IP-RE	THERAMEX	Lutenyl			
107 CLAUDE	Jean-Roger	15/11/2000	IP-AC	BMS	Taxol : purification et évaluation du Crémophore			
107 CLAUDE	Jean-Roger	15/11/2000	IP-CF	IFIP	Séminaires de formation à la toxicologie du médicament			
107 CLAUDE	Jean-Roger	15/11/2000	PAR	LABORATOIRE LAFON	Conjoint			
107 CLAUDE	Jean-Roger	15/05/2000	IP-EC	LAFON	Travaux en Toxicologie ; toute autre précision serait juridiquement attaquable (atteinte à la clause de confidentialité du contrat)			
107 CLAUDE	Jean-Roger	15/05/2000	IP-RE	GUERBET	Sinerem - Dotarem			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10107	CLAUDE	Jean-Roger	15/05/2000	IP-RE	PIERRE FABRE	Navelbine orale			
10107	CLAUDE	Jean-Roger	15/05/2000	IP-RE	SERVIER	Aérodiol			
10107	CLAUDE	Jean-Roger	15/05/2000	IP-RE	THERAMEX	Lutenyl			
10107	CLAUDE	Jean-Roger	15/05/2000	IP-AC	BMS	Taxol : purification et évaluation du Crémophore			
10107	CLAUDE	Jean-Roger	15/05/2000	IP-CF	IFIP	Séminaires formation à la Toxicologie du médicament			
10107	CLAUDE	Jean-Roger	15/05/2000	PAR	LAFON	Conjoint			
10107	CLAUDE	Jean-Roger	01/01/1999	IP-EC	LAFON				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-RE	GUERBET				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-RE	PIERRE FABRE				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-RE	SERVIER				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-RE	THERAMEX				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-AC	BAYER PHARMA				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-AC	BRISTOL MYERS SQUIBB				
10107	CLAUDE	Jean-Roger	01/01/1999	IP-CF	IFIP				
10107	CLAUDE	Jean-Roger	01/01/1999	PAR		Compagne dans l'industrie Pharmaceutique			
10107	CLAUDE	Jean-Roger	01/01/1999	PAR	GIRCOR	Président			
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Lafon				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Guerbet				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Pierre Fabre				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Servier				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Théramex				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Asta Médica				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Hybridon				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	Bayer-Pharma				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	BMS				
10107	CLAUDE	Jean-Roger	01/01/1998	IP-AUT	IFIP				
10107	CLAUDE	Jean-Roger	01/01/1998	PAR	compagne dans l'industrie pharmaceutique				
10107	CLAUDE	Jean-Roger	01/01/1998	PAR	Président du GIRCOR				
55659	CLEDES	Jacques	25/05/1999	IP-CF	PFIZER	Colloque FMC HTA			
55659	CLEDES	Jacques	25/05/1999	IP-CF	BRISTOL MYERS SQUIBB	Colloque FMC HTA			
55659	CLEDES	Jacques	25/05/1999	VB	HOESCHT MARION ROUSSEL	Essai clinique (phases II et III) : Association finistérienne pour la prévention et le traitement des maladies rénales et métaboliques			
55659	CLEDES	Jacques	01/01/1999	IP-EC	Laboratoires Servier : essai d'un anti-hypertenseur				
55659	CLEDES	Jacques	01/01/1999	IP-CF		Actions de formation médicale continue en collaboration avec diverses firmes			
55659	CLEDES	Jacques	01/01/1999	IP-AUT	MSD	Prise en charge de la participation au congrès de l'APH, New-York			
10110	CONORT	Ornella	13/07/2000	IP-CF	SERVIER	Conférence Moissan, préparation de pharmaciens au concours de Praticien Hospitalier			
10110	CONORT	Ornella	15/01/2000	IP-CF	SERVIER	Conférence Moissan, préparation au concours de PH en pharmacie			
10110	CONORT	Ornella	15/01/2000	PAR	UPJOHN PHARMACIA Orlando pour ACCP	Prise en charges de frais de congrès en 1999			
10110	CONORT	Ornella	15/01/2000	PAR	GLAXO WELLCOME	Prise en charge séminaire en pharmacie hospitalière (Jordanie)			
10110	CONORT	Ornella	01/01/1999	IP-AUT	SCHERING PLOUGH	Prises en charge des frais du 19th Annual Pharmacy Symposium of Cancer Chemotherapy, le 10/10/97 à Huston			
10110	CONORT	Ornella	01/01/1999	IP-AUT	GLAXO WELLCOME	Participation aux séminaires d'actualités en Pharmacie Hospitalière, 8 et 9 mars 1997 en Tunisie			
10110	CONORT	Ornella	01/01/1999	VB	SERVIER	Séances de formation au concours de PH, conférences Moisean, en 1997, sous forme de versements à une association SETOP			
10110	CONORT	Ornella	01/01/1998	IP-AUT	Servier				
10110	CONORT	Ornella	01/01/1998	IP-AUT	Bristol				
10110	CONORT	Ornella	01/01/1998	IP-AUT	Beecham				
10110	CONORT	Ornella	01/01/1998	VB	formations pédagogiques Servier				
10110	CONORT	Ornella	01/01/1998	VB	association SETOP				
63366	CORBE	Christian	27/06/2006	EC-INV	INSTITUT SERVIER	Trimétazidine 35	coordinnateur	01/1998	12/2007
63366	CORBE	Christian	27/06/2006	EC-INV	INSTITUT SERVIER	Ivabradine	membre du Safety committee en ophtalmologie	01/2000	12/2007
63366	CORBE	Christian	27/06/2006	CF-INT	IPSEN	Royaumont	rémunération personnelle	01/2004	12/2006
63366	CORBE	Christian	27/06/2006	CF-INT	OPTIC 2000	Djerba	rémunération personnelle	01/2005	12/2005
62656	CORDIER	Catherine	26/04/2007	EC-CO	SERVIER		co-investigateur	01/1997	12/2006
62656	CORDIER	Catherine	26/04/2007	EC-CO	LILLY		co-investigateur	01/2004	12/2006
62656	CORDIER	Catherine	26/04/2007	CF-INT	LILLY, SERVIER	2 à 3/an	rémunération personnelle		
62656	CORDIER	Catherine	26/04/2007	CF-AUD	PROCTER	Congrès Ostéoporose		01/2006	12/2006
62656	CORDIER	Catherine	15/10/2002	IP-EC	NOVARTIS	Essai ac-zoledunique			
62656	CORDIER	Catherine	15/10/2002	IP-CF	PIERRE FABRE	Formation médicale			
61774	CORMIER	Catherine	10/05/2004	IP-EC	SERVIER	Essai clinique ranelate de strontium			
61774	CORMIER	Catherine	10/05/2004	IP-EC	LILLY	Essai clinique teriparatide			
61774	CORMIER	Catherine	10/05/2004	IP-EC	NOVARTIS	Essai clinique			
61774	CORMIER	Catherine	10/05/2004	IP-EC	PHARMACIA	Essai clinique GH			
61774	CORMIER	Catherine	10/05/2004	IP-RE	ANAES	recommandation			
61774	CORMIER	Catherine	10/05/2004	IP-CF	AVENTIS	Formation personnel			
61774	CORMIER	Catherine	10/05/2004	IP-CF		Formation			
61774	CORMIER	Catherine	05/07/2002	VB	MSD	Protocole 037/024 Alendunate : Association			
61774	CORMIER	Catherine	05/07/2002	VB	MSD	Protocole Alendunate prévention orthico : Association			
62706	CORNIER	Catherine	15/06/2006	EC-CO	SERVIER	RANELATE DE STRONTIUM	Co-investigateur	01/1998	12/2006
62706	CORNIER	Catherine	15/06/2006	EC-CO	LILLY	TERIPARATIDE	Co-investigateur	01/2004	12/2006
62706	CORNIER	Catherine	15/06/2006	EC-CO	NOVARTIS	ZOLEDRONIQUE	Co-investigateur	01/2003	12/2006
62706	CORNIER	Catherine	15/06/2006	IP-RE	ROCHE	IBANDRONATE	Rémunération personnelle	01/2005	12/2006
62706	CORNIER	Catherine	15/06/2006	IP-AC	NOVARTIS	Groupe de travail Paget	Rémunération personnelle	01/2005	12/2006
62706	CORNIER	Catherine	15/06/2006	CF-INT	LILLY	Conférence sur XXX	Rémunération personnelle	06/2006	06/2006
62706	CORNIER	Catherine	15/06/2006	CF-INT	LILLY	Conférence sur le XXX	Rémunération personnelle	03/2006	03/2006
62706	CORNIER	Catherine	15/06/2006	CF-INT	LILLY	Conférence sur les BISPHOSPHATE	Rémunération personnelle	06/2006	06/2006
62706	CORNIER	Catherine	15/06/2006	CF-INT	SERVIER	Conférence sur les traitements de l'ostéoporose	Rémunération personnelle	01/2006	12/2006
62706	CORNIER	Catherine	15/06/2006	CF-INT	THERAMEX	Conférence sur les traitements de l'ostéoporose	Rémunération personnelle	05/2006	05/2006
62706	CORNIER	Catherine	15/06/2006	CF-AUD	SERVIER	ECCEO		05/2006	05/2006
62706	CORNIER	Catherine	10/05/2004	IP-EC	SERVIER	Essai clinique ranelate de strontium			
62706	CORNIER	Catherine	10/05/2004	IP-EC	LILLY	Essai clinique Teriparatide			
62706	CORNIER	Catherine	10/05/2004	IP-EC	PHARMACIA	GH			
62706	CORNIER	Catherine	10/05/2004	IP-EC	NOVARTIS	Zometa			
62706	CORNIER	Catherine	10/05/2004	IP-RE	Anaes				

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
706 CORNIER	Catherine	10/05/2004	IP-CF	AVENTIS	Formation personnel			
706 CORNIER	Catherine	10/05/2004	IP-CF		Formation à la desliométrie			
706 CORNIER	Catherine	18/02/2003	IP-EC	SERVIER	Essai ranelate de strontium			
706 CORNIER	Catherine	18/02/2003	IP-EC	NOVARTIS	Essai a zoledunique			
706 CORNIER	Catherine	18/02/2003	IP-EC	LILLY	Essai terapaxide			
706 CORNIER	Catherine	18/02/2003	IP-CF	LILLY	EPU			
706 CORNIER	Catherine	18/02/2003	IP-CF	PIERRE FABRE	Formation médicale			
706 CORNIER	Catherine	18/02/2003	IP-CF	PROCTER	EPU			
716 CORRUBLE	Emmanuelle	07/04/2010	EC-INV	LILLY	Duloxetine	investigateur coordonnateur	01/2005	12/2007
716 CORRUBLE	Emmanuelle	07/04/2010	EC-INV	JANSSEN CILAG	Paliperidone	investigateur coordonnateur	01/2006	12/2008
716 CORRUBLE	Emmanuelle	07/04/2010	EC-INV	SERVIER	Agomelatine (en cours)	investigateur coordonnateur	01/2007	
716 CORRUBLE	Emmanuelle	07/04/2010	IP-AC	SERVIER	Dépression - troubles anxieux (en cours)	rémunération personnelle	01/2005	
716 CORRUBLE	Emmanuelle	07/04/2010	IP-AC	BMS	Troubles bipolaires - troubles dépressifs (en cours)	rémunération personnelle	01/2009	
716 CORRUBLE	Emmanuelle	07/04/2010	IP-AC	LUNDBECK	Troubles dépressifs (en cours)	rémunération personnelle	01/2009	
716 CORRUBLE	Emmanuelle	07/04/2010	IP-AC	SANOFI	Cohorte SAGES de pharmaco-épidémiologie du sujet âgé (en cours)	rémunération personnelle	01/2009	
716 CORRUBLE	Emmanuelle	07/04/2010	CF-INT	WYETH	Dépression : formation interne, congrès Strasbourg	rémunération personnelle	01/2007	12/2007
716 CORRUBLE	Emmanuelle	07/04/2010	CF-INT	SERVIER	Déprsseion : interventions congrès	rémunération personnelle	01/2007	12/2010
716 CORRUBLE	Emmanuelle	07/04/2010	CF-INT	BMS	Séminaire Campus Psy	rémunération personnelle	01/2007	12/2010
716 CORRUBLE	Emmanuelle	03/03/2009	LD-AR	EUTHERAPIE	Conseil	rémunération personnelle	01/2006	
716 CORRUBLE	Emmanuelle	03/03/2009	EC-INV	SERVIER INTERNATIONAL	Coordination d'essai	coordonateur	01/2007	12/2010
716 CORRUBLE	Emmanuelle	03/03/2009	EC-INV	LILLY France	Coordianation d'essai		01/2003	12/2007
716 CORRUBLE	Emmanuelle	03/03/2009	CF-INT	SERVIER	ECNP-Environnement dépression	Rémunération personnelle	09/2008	09/2008
716 CORRUBLE	Emmanuelle	03/03/2009	CF-INT	BMS	Symposium lancement Aripiprazole	Rémunération personnelle	05/2008	05/2008
716 CORRUBLE	Emmanuelle	03/03/2009	CF-INT	EUTHERAPIE	Encéphale-Agomélatine + environnement dépression	Rémunération personnelle	05/2009	05/2009
716 CORRUBLE	Emmanuelle	03/03/2009	CF-AUD	UCB-Pharma	American Psychiatric Association		05/2008	05/2008
716 CORRUBLE	Emmanuelle	25/03/2008	EC-INV	LILLY	DULOXETINE	investigateur coordonateur	01/2005	12/2007
716 CORRUBLE	Emmanuelle	25/03/2008	EC-INV	JANSSEN CILAG	Paliperidone	investigateur coordonateur	01/2006	12/2008
716 CORRUBLE	Emmanuelle	25/03/2008	EC-INV	SERVIER	AGOMELATINE	investigateur coordonateur	01/2007	12/2009
716 CORRUBLE	Emmanuelle	25/03/2008	IP-AC	SERVIER	Dépression - troubles anxieux	rémunération personnelle	01/2005	
716 CORRUBLE	Emmanuelle	25/03/2008	IP-AC	JANSSEN	Troubles bipolaires	rémunération personnelle	01/2007	
716 CORRUBLE	Emmanuelle	25/03/2008	CF-INT	LILLY	Dépression - congrès de l'Encéphale - Paris	rémunération personnelle	01/2006	12/2006
716 CORRUBLE	Emmanuelle	25/03/2008	CF-INT	WYETH	Dépression : formation interne, congrès - Strasbourg	rémunération personnelle	01/2007	12/2007
716 CORRUBLE	Emmanuelle	25/03/2008	CF-INT	SERVIER	Dépression : interventions congrès	rémunération personnelle	01/2007	12/2008
716 CORRUBLE	Emmanuelle	25/03/2008	CF-INT	BMS	Séminaire Campus Psy	rémunération personnelle	01/2006	12/2007
716 CORRUBLE	Emmanuelle	09/06/2006	EC-INV	LILLY	Duloxétine	Investigateur Coordinnateur	01/2004	12/2006
716 CORRUBLE	Emmanuelle	09/06/2006	EC-INV	JOHNSON & JOHNSON	Paliperidone	Investigateur coordinnateur	01/2005	12/2008
716 CORRUBLE	Emmanuelle	09/06/2006	IP-AC	SERVIER	Groupes de travail Agomélaline et Tianeptine	Rémunération personnelle	01/2005	
716 CORRUBLE	Emmanuelle	09/06/2006	CF-AUD	PFIZER	APA - Toronto		05/2006	05/2006
716 CORRUBLE	Emmanuelle	09/06/2006	CF-AUD	GSK	ECNP - Amsterdam		10/2005	10/2005
716 CORRUBLE	Emmanuelle	09/06/2006	CF-AUD	LILLY	CINP - Chicago		07/2006	07/2006
716 CORRUBLE	Emmanuelle	04/04/2005	IP-AC	SERVIER	Tianeptine			
716 CORRUBLE	Emmanuelle	04/04/2005	IP-AC	UCB PHARMA	CREA (Centre de Recherche et d'Etudes sur l'Anxiété)			
716 CORRUBLE	Emmanuelle	04/04/2005	IP-EC	LILLY	Duloxétine (2004-2005)			
716 CORRUBLE	Emmanuelle	04/04/2005	IP-CF	ARDIX	Tianeptine			
716 CORRUBLE	Emmanuelle	04/04/2005	IP-CF	PFIZER	Sertraline			
716 CORRUBLE	Emmanuelle	04/04/2005	IP-AUT	LILLY, SERVIER, GSK, JANSSEN				
716 CORRUBLE	Emmanuelle	04/04/2005	LD	BMS	Aripiprazole, consultant (2003-2004)			
716 CORRUBLE	Emmanuelle	04/02/2005	LD	BMS	Aripiprazole, consultant (2003 et 2004)			
716 CORRUBLE	Emmanuelle	04/02/2005	IP-AC	SERVIER	Tianeptine			
716 CORRUBLE	Emmanuelle	04/02/2005	IP-AC	UCB	CREA			
716 CORRUBLE	Emmanuelle	04/02/2005	IP-EC	LILLY	Duloxetine			
716 CORRUBLE	Emmanuelle	04/02/2005	IP-CF	ARDIX	Tianeptine			
716 CORRUBLE	Emmanuelle	04/02/2005	IP-CF	PFIZER	Sertraline			
716 CORRUBLE	Emmanuelle	04/02/2005	IP-AUT	LILLY				
716 CORRUBLE	Emmanuelle	04/02/2005	IP-AUT	SERVIER				
716 CORRUBLE	Emmanuelle	04/02/2005	IP-AUT	GSK				
716 CORRUBLE	Emmanuelle	04/02/2005	IP-AUT	JANSSEN				
716 CORRUBLE	Emmanuelle	21/06/2000	IP-CF	LILLY	(2 formations/année) : sérotonine			
716 CORRUBLE	Emmanuelle	21/06/2000	IP-CF	SB	Dépression, trouble de la personnalité et mécanisme de défense			
716 CORRUBLE	Emmanuelle	21/06/2000	IP-AUT	ARDIX	Enregistrement de 2 videos sur "Dépression et Libido" et rédaction d'un document sur "Dépression et Libido"			
716 CORRUBLE	Emmanuelle	11/01/2000	IP-CF	LILLY	Formations pour les psychiatres			
716 CORRUBLE	Emmanuelle	11/01/2000	IP-CF	WYETH	Formation pour les psychiatres			
716 CORRUBLE	Emmanuelle	11/01/2000	IP-CF	LUNDBECK	Formation pour les médecins généralistes			
716 CORRUBLE	Emmanuelle	11/01/2000	IP-CF	SMITH KLINE BEECHAM	Formation pour les psychiatres			
1897 CORTET	Bernard	10/02/2010	CF-AUD	PROCTER & GAMBLE	SFR 2009		01/2009	12/2009
1897 CORTET	Bernard	10/02/2010	CF-AUD	SERVIER	ASBMR 2009 ASBMR 2010		01/2009	12/2010
1897 CORTET	Bernard	10/02/2010	CF-INT	SERVIER	SFR 2009-symposium-Aclasta	Rémunération personnelle	01/2009	12/2009
1897 CORTET	Bernard	10/02/2010	CF-INT	NOVARTIS	SFR 2009-symposium-Aclasta	Rémunération personnelle	01/2009	12/2009
1897 CORTET	Bernard	10/02/2010	EC-INV	MSD	MK-5442 (calcilytique): phase II (ostéoporose post-ménopausique)	investigateur	01/2010	
1897 CORTET	Bernard	10/02/2010	EC-INV	AMGEN	Denosumab ostéoporose de l'homme : phase III	Investigateur	09/2009	
1897 CORTET	Bernard	10/02/2010	IP-AC	NOVARTIS	Aclasta	rémunération personnelle	01/2005	
1897 CORTET	Bernard	10/02/2010	IP-AC	SERVIER	Protélos	Rémunération personnelle	01/2005	12/2009
1897 CORTET	Bernard	10/02/2010	IP-AC	NYCOMED	Preotact	Rémunération personnelle	01/2006	12/2008
1897 CORTET	Bernard	10/02/2010	IP-AC	ROCHE-GSK	Bonviva	Rémunération personnelle	01/2005	
1897 CORTET	Bernard	10/02/2010	IP-AC	MSD	Fosavance	Rémunération personnelle	11/2007	
1897 CORTET	Bernard	10/02/2010	IP-AC	AMGEN	Prolia (Denosumab)	Rémunération personnelle	01/2009	
1897 CORTET	Bernard	26/05/2008	IP-AC	MSD	FOSAVANCE	Rémunération personnelle	11/2007	
1897 CORTET	Bernard	26/05/2008	IP-AC	ROCHE GSK	Bonviva	rémunération personnelle - activités de conseil 2/3 réunions annuelles et par laboratoire	01/2005	

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
1897 CORTET	Bernard	26/05/2008	IP-AC	NYCOMED	Preotact	rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire	01/2006	12/2008
1897 CORTET	Bernard	26/05/2008	IP-AC	SERVIER	Protelos	rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire	01/2005	12/2009
1897 CORTET	Bernard	26/05/2008	IP-AC	NOVARTIS	Aclasta	rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire	01/2005	
1897 CORTET	Bernard	01/05/2007	IP-AC	NOVARTIS	Aclasta	rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire	01/2005	
1897 CORTET	Bernard	01/05/2007	IP-AC	SERVIER	Protelos	rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire	01/2005	
1897 CORTET	Bernard	01/05/2007	IP-AC	NYCOMED	Preotact	rémunération personnelle - activité de conseil 2/3 réunions annuelles et par laboratoire	01/2006	
1897 CORTET	Bernard	01/05/2007	IP-AC	ROCHE GSK	Bonviva	rémunération personnelle - activités de conseil 2/3 réunions annuelles et par laboratoire	01/2005	
1897 CORTET	Bernard	01/05/2007	CF-INT	PROCTER & GAMBLE/ NYCOMED	Symposium satellite SFR - Paris	rémunération personnelle	01/2005	12/2006
1897 CORTET	Bernard	01/05/2007	CF-INT	ROCHE	Symposium Satellite SFR - Paris	rémunération personnelle	01/2005	12/2005
1897 CORTET	Bernard	15/05/2006	LD-AR	ROCHE-GSK	Ibandronate consultant Strontium	rémunération personnelle	01/2005	
1897 CORTET	Bernard	15/05/2006	LD-AR	NOVARTIS	Zoledronate consultant strontium	rémunération personnelle	01/2005	
1897 CORTET	Bernard	15/05/2006	LD-AR	SERVIER	Ranelate consultant strontium	rémunération personnelle	01/2005	
1897 CORTET	Bernard	15/05/2006	LD-AR	NYCOMED	PTH (1,84) consultant strontium	rémunération personnelle	01/2006	
1897 CORTET	Bernard	15/05/2006	EC-CO	KYPHON	étude FREE	co-investigateur	01/2005	12/2008
1897 CORTET	Bernard	15/05/2006	EC-CO	LILLY	Forstéo	co-investigateur	01/2003	12/2007
1897 CORTET	Bernard	15/05/2006	EC-CO	AMGEN	DENOSUMAB	co-investigateur	01/2006	12/2007
1897 CORTET	Bernard	15/05/2006	IP-AC	AMGEN - MSD - LILLY	sollicitation ponctuelle pour avis (FOSOVANCE® - DENOSUMAB - FORSTEO®)	rémuneration personnelle	01/2005	
1897 CORTET	Bernard	15/05/2006	CF-INT	SERVIER	Medec ; journée		10/2005	03/2006
1897 CORTET	Bernard	15/05/2006	CF-INT	GSK-ROCHE	SFR, journées réflexions		03/2006	03/2006
1897 CORTET	Bernard	11/08/2005	LD	SERVIER	Consultant : Protelos	rémunération personnelle	01/2005	12/2006
1897 CORTET	Bernard	11/08/2005	LD	GSK/ROCHE	Consultant : Bonviva	Rémunération personnelle	01/2005	12/2006
1897 CORTET	Bernard	11/08/2005	LD	NOVARTIS	Consultant Aclasta	Rémunération personnelle		
1897 CORTET	Bernard	11/08/2005	IP-EC	LILLY	Etude Forsteo	Co-investigateur	01/2003	12/2006
1897 CORTET	Bernard	11/08/2005	IP-EC	GSK/ROCHE	Etude comparative Ibandronate 150 - 1 fois par mois vs Alendronate hebdomadaire	Co-investigateur	01/2005	12/2006
1897 CORTET	Bernard	11/08/2005	IP-EC	TYPHOON	Kyphoplastie au cours des fractures vertébrales	co-investigateur	01/2005	12/2008
1897 CORTET	Bernard	11/08/2005	IP-RE	GSK/ROCHE	Ibandronate - Boniva		01/2005	
1897 CORTET	Bernard	11/08/2005	IP-RE	NOVARTIS	Lumiracoxib		01/2005	
1897 CORTET	Bernard	11/08/2005	IP-RE	NICOMED	Preotact		01/2005	
1897 CORTET	Bernard	11/08/2005	IP-AC	PROCTER & GAMBLE, AMGEN, MSD	Avis ponctuels			
1897 CORTET	Bernard	11/08/2005	IP-CF	SERVIER	Société Française de Rhumatologie (SFR) 2004			
1897 CORTET	Bernard	11/08/2005	IP-CF	GSK/ROCHE	Société Française de Rhumatologie (SFR) 2005			
31640 CORTET	Etienne	22/12/2003	Néant					
31897 CORTET	Bernard	19/10/2002	IP-EC	PROCTER & GAMBLE	Participation ponctuelle à des essais thérapeutiques			
31897 CORTET	Bernard	19/10/2002	IP-CF	PROCTER & GAMBLE, LILLY, MSD	Formations ponctuelles et conférences locales ou nationales			
31897 CORTET	Bernard	19/10/2002	IP-EC	LILLY	Participation ponctuelle à des essais thérapeutiques			
31640 CORTET	Etienne	10/09/2002	LD	PEIGNAGE DE LA TOSSEE	PDG			
31640 CORTET	Etienne	18/06/2001	LD	PEIGNAGE DE LA TOSSEE	PDG			
31897 CORTET	Bernard	04/01/2001	LD		Rédacteur en chef adjoint d'une revue de FMC en Rhumatologie (Réflexions Rhumatologiques)			
31897 CORTET	Bernard	04/01/2001	IP-EC	PROCTER & GAMBLE	Risedronate (impact)			
31897 CORTET	Bernard	04/01/2001	IP-CF	LILLY	Participation pnctuelle à la formation des délégués médicaux			
31897 CORTET	Bernard	04/01/2001	IP-RE	GSK/ROCHE	2005			
31897 CORTET	Bernard	04/01/2001	IP-RE	NOVARTIS	2005			
31897 CORTET	Bernard	04/01/2001	IP-CF	SERVIER	SFR (2004)			
65589 CORVOL	Jean-Christophe	04/01/2010	EC-INV	SOCIETE FRANCAISE DE CARDIOLOGIE	Etude observationnelle sur la prévalence des valvulopathies sous pergolide - étude monocentrique Pilié sal	investigateur principal	01/2005	12/2007
65589 CORVOL	Jean-Christophe	04/01/2010	EC-INV	APHP	Etude des effets du polymorphisme de la COMT sur l'efficacité de l'entacapone dans la maladie de Parkinso	investigateur principal	01/2006	12/2009
65589 CORVOL	Jean-Christophe	04/01/2010	EC-INV	IMPAX LABORATORY	Etude pour l'évaluation de la sécurité et de l'efficacité de l'IPX066 dans la maladie de Parkinson avancée - é	investigateur coordonnateur France	01/2009	12/2010
65589 CORVOL	Jean-Christophe	04/01/2010	EC-INV	INSERM/DHOS	Etude du transcriptome dans les cellules périphériques dans la maladie de Parkinson (appel d'offre INSERM	investigateur principal	01/2009	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-INV	APHP	Etude de l'interaction gène-médicament dans la maladie de Parkinson (PHRC régional 2008) - étude multice	investigateur coordonnateur	01/2009	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	APHP	Efficacité et tolérance de la 3-4 amidopyridine dans la sclérose en plaques	co-investigateur	01/2005	12/2007
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	NOVARTIS-ORION PHARMA	Evaluation de l'effet du STAVELO (lévodopa/carbidopa /entacapone) vs lévodopa/carbidopa chez des patier	co-investigateur	01/2005	12/2008
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	HOPITAUX DE TOULOUSE	Evaluation des effets à long terme de l'amantadine chez le parkinsonien souffrant de dyskinésies induites pa	co-investigateur	01/2008	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	WYETH PHARMACEUTICALS INC	A Phase IIA, multicenter, randomized, third-party unblinded, adjuvant and placebo-controlled, multiple ascen	co-investigateur	01/2008	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	SERVIER	Effect of agomelatine (25mg) given orally once a day for 7 days on cerebral activity measured by functional I	co-investigateur	01/2008	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	FOLDRX PHARMACEUTICALS INC	The effects of Fx-1006A on Transthyretin Stabilization and clinical outcome measures in patients with Non-V	co-investigateur	01/2008	12/2009
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	THE GLAXOSMITHKLINE group of companies	A single and repeat dose escalation study of the safety, pharmacokinetics and pharmacodynamics of GSK 1	co-investigateur	01/2008	12/2008
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	INSERM/APHP	Caractérisation clinique, moléculaire et par neuroimagerie des formes monogéniques du syndrome parkinso	co-investigateur	01/2009	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	ROCHE	An open-label, multicentre, non randomized, dose-escalating phase I/II study, with a randomized phase II pa	co-investigateur	01/2009	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	APHP	Etude de l'effet sur la survie et le phénotype des syndromes Parkinson plus des variants génétiques des gèr	co-investigateur	01/2009	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	SANOFI AVENTIS	Etude randomisée, en double aveugle, contrôlée versus placebo, aux groupes parallèles, évaluant sur 14 se	co-investigateur	01/2009	
65589 CORVOL	Jean-Christophe	04/01/2010	EC-CO	INSERM	Etude clinico-génétique des pathologies des noyaux gris centraux	co-investigateur	01/2008	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
65589	CORVOL	Jean-Christophe	04/01/2010	EC-CO	PEPTIMMUNE INC	The effect of the dose of PI-2301 on safety, tolerability, and pharmacokinetics in subjects with the secondary	Responsable de l'étude ancillaire sur le transcriptome	01/2008	12/2009
65589	CORVOL	Jean-Christophe	04/01/2010	EC-CO	GENZYME CORPORATION	Etude randomisée, de phase III, avec évaluateur en aveugle, comparant 2 cycles annuels à forte dose ou fa	co-investigateur	01/2009	
65589	CORVOL	Jean-Christophe	04/01/2010	RE-AUT	APHP/DHOS	Appels d'offre PHRC régional ou national	aucune rémunération	01/2008	
65589	CORVOL	Jean-Christophe	04/01/2010	RE-AUT	INSERM	Appels d'offre (recherche translationnel, ANR réseaux)	aucune rémunération	01/2008	
65589	CORVOL	Jean-Christophe	04/01/2010	CF-AUD	BAYER SCHERING PHARMA	Congrès de pharmacologie, physiologie et thérapeutique (P2T)		01/2008	
65589	CORVOL	Jean-Christophe	04/01/2010	CF-AUD	BOEHRINGER INGELHEIM	Congrès de la Mouvement Disorder Society		01/2008	12/2008
65589	CORVOL	Jean-Christophe	04/01/2010	CF-AUD	BOEHRINGER INGELHEIM	Congrès de la Mouvement Disorder Society		01/2009	12/2009
65589	CORVOL	Jean-Christophe	04/01/2010	CF-AUD	BIOGEN	Congrès de phamacologie, physiologie et thérapeutique (P2T)		01/2009	12/2009
65589	CORVOL	Jean-Christophe	04/01/2010	VB	APHP	Etude des effets du polymorphisme de la COMT sur l'efficacité de l'entacapone dans la maladie de Parkinso	APHP	01/2006	12/2009
65589	CORVOL	Jean-Christophe	04/01/2010	VB	INSERM/DHOS	Etude du transcriptome dans les cellules périphériques dans la maladie de Parkinson (appel d'offre INSERM	APHP, INSERM	01/2009	12/2011
65589	CORVOL	Jean-Christophe	04/01/2010	VB	ANR	Mécanismes moléculaires des dyskinésies induites par la L-DOPA dans la maladie de Parkinson	INSERM	01/2010	12/2014
65589	CORVOL	Jean-Christophe	04/01/2010	VB	APHP	Etude de l'interaction gène-médicament dans la maladie de Parkinson	APHP, INSERM	01/2009	12/2012
64601	COSTENTIN	Jean	10/07/2010	Néant					
64601	COSTENTIN	Jean	10/07/2010	CF-AUD	JANSSEN CILAG	membre du comité scientifique de la revue INERPSY			
64601	COSTENTIN	Jean	10/07/2010	CF-INT	LUNDBECK	conférence sur la physiopathologie de la dépression en octobre 2010	Rémunération personnelle/institution		
64601	COSTENTIN	Jean	10/07/2010	IP-AC	LUNDBECK	analyse du dossier scientifique d'un produit utilisable dans la dépendance à l'alcool	Aucune rémunération		
64601	COSTENTIN	Jean	13/02/2009	EC-INV	P FABRE	co-dépositaire d'un brevet sur la paraxanthine		01/2007	07/2010
64601	COSTENTIN	Jean	13/02/2009	LD-AR	JANSSEN CILAG	membre d'un groupe d'expert sur les AntiPsychotique d'Action prolongée	Aucune rémunération	01/2008	01/2009
64601	COSTENTIN	Jean	12/06/2007	LD-AR	PFIZER	Membre d'un groupe d'experts ; ZIPRASIDONE	rémunération personelle / institution	01/2000	12/2004
64601	COSTENTIN	Jean	12/06/2007	LD-AR	BMS	Membre d'un groupe d'experts ; ARIPIPRAZOLE	rémunération personnelle / institution	01/2005	
64601	COSTENTIN	Jean	12/06/2007	LD-AR	LUNDBECK	ESCITALOPRAM	rémunération personnelle / institution	01/2004	01/2005
64601	COSTENTIN	Jean	12/06/2007	EC-INV	SERVIER	Agomélatine, inducteurs de la TH	expérimentateur	01/2005	01/2008
64601	COSTENTIN	Jean	12/06/2007	EC-INV	PIERRE FABRE	METHYLXANTHINE	expérimentateur	01/2006	
64601	COSTENTIN	Jean	12/06/2007	CF-INT	BMS	ARIPIPRAZOLE (Rouen - Lyon - La Baule)	rémunération personnelle		
64601	COSTENTIN	Jean	12/06/2007	CF-INT	LUNDBECK	ESCITALOPRAM	rémunération personnelle / institution		
64601	COSTENTIN	Jean	12/06/2007	CF-AUD	JANSSEN - CILAG	Membre conseil scientifique de la revue "INTERPSY" et antérieurement 3 helopsy 3			
64601	COSTENTIN	Jean	12/06/2007	IP-AUT	PIERRE FABRE	Dépot d'un brevet sur la paraxanthine		01/2006	
64113	COTTIN	Yves	30/12/2008	CF-INT	PFIZER	CNCF	Rémunération personnelle		
64113	COTTIN	Yves	30/12/2008	CF-INT	SANOFI	AHA	Rémunération personnelle		
64113	COTTIN	Yves	30/12/2008	CF-INT	PFIZER	CNCF	Rémunération personnelle		
64113	COTTIN	Yves	30/12/2008	CF-INT	SANOFI	AHA	Rémunération personnelle		
64113	COTTIN	Yves	30/12/2008	IP-AC	SERVIER	Procoralan	Rémunération personnelle	12/2007	
64113	COTTIN	Yves	30/12/2008	RE-AUT	NON		Aucune rémunération		
64113	COTTIN	Yves	30/12/2008	IP-AC	SERVIER	Procoralan	Rémunération personnelle	12/2007	
64113	COTTIN	Yves	30/12/2008	RE-AUT	NON		Aucune rémunération		
64113	COTTIN	Yves	30/12/2008	RE-DE	NON		Aucune rémunération		
64113	COTTIN	Yves	30/12/2008	RE-DE	NON		Aucune rémunération		
64113	COTTIN	Yves	30/12/2008	EC-INV	SANOFI	Rimonabant		12/2005	
64113	COTTIN	Yves	30/12/2008	EC-INV	SANOFI BMS	Anto Xa		12/2006	
64113	COTTIN	Yves	30/12/2008	EC-INV	SANOFI	Rimonabant		12/2005	
64113	COTTIN	Yves	30/12/2008	EC-INV	LILLY	prasugel		12/2006	
64113	COTTIN	Yves	30/12/2008	EC-INV	SANOFI BMS	Anto Xa		12/2006	
64113	COTTIN	Yves	30/12/2008	EC-INV	LILLY	prasugel		12/2006	
64113	COTTIN	Yves	30/12/2008	LD-AR	NON		Aucune rémunération		
64113	COTTIN	Yves	30/12/2008	LD-AR	NON		Aucune rémunération		
64113	COTTIN	Yves	30/12/2008	LD-ODE	NON				
64113	COTTIN	Yves	30/12/2008	LD-ODE	NON				
64113	COTTIN	Yves	30/12/2008	IF	NON		<5000 € ou <5% du capital		
64113	COTTIN	Yves	30/12/2008	IF	NON		<5000 € ou <5% du capital		
64113	COTTIN	Yves	10/12/2007	CF-INT	PFIZER	CNCF	Rémunération personnelle		
64113	COTTIN	Yves	10/12/2007	CF-INT	SANOFI	AHA	Rémunération personnelle		
64113	COTTIN	Yves	10/12/2007	IP-AC	SERVIER	Procoralan	Rémunération personnelle	12/2007	
64113	COTTIN	Yves	10/12/2007	RE-AUT	NON		Aucune rémunération		
64113	COTTIN	Yves	10/12/2007	RE-DE	NON		Aucune rémunération		
64113	COTTIN	Yves	10/12/2007	EC-INV	SANOFI	Rimonabant		12/2005	
64113	COTTIN	Yves	10/12/2007	EC-INV	SANOFI BMS	Anto Xa		12/2006	
64113	COTTIN	Yves	10/12/2007	EC-INV	LILLY	prasugel		12/2006	
64113	COTTIN	Yves	10/12/2007	LD-AR	NON		Aucune rémunération		
64113	COTTIN	Yves	10/12/2007	LD-ODE	NON				
64113	COTTIN	Yves	10/12/2007	IF	NON		<5000 € ou <5% du capital		
64113	COTTIN	Yves	10/12/2007	CF-INT	PFIZER	CNCF	Rémunération personnelle		
64113	COTTIN	Yves	10/12/2007	CF-INT	SANOFI	AHA	Rémunération personnelle		
64113	COTTIN	Yves	10/12/2007	IP-AC	SERVIER	Procoralan	Rémunération personnelle	12/2007	
64113	COTTIN	Yves	10/12/2007	RE-AUT	NON		Aucune rémunération		
64113	COTTIN	Yves	10/12/2007	RE-DE	NON		Aucune rémunération		
64113	COTTIN	Yves	10/12/2007	EC-INV	SANOFI	Rimonabant		12/2005	
64113	COTTIN	Yves	10/12/2007	EC-INV	LILLY	prasugel		12/2006	
64113	COTTIN	Yves	10/12/2007	EC-INV	SANOFI BMS	Anto Xa		12/2006	
64113	COTTIN	Yves	10/12/2007	LD-ODE	NON				
64113	COTTIN	Yves	10/12/2007	LD-AR	NON		Aucune rémunération		
64113	COTTIN	Yves	10/12/2007	IF	NON		<5000 € ou <5% du capital		
64113	COTTIN	Yves	15/04/2006	EC-CO	SANOFI	Rimonabant	Co-investigateur	04/2005	04/2006
64113	COTTIN	Yves	15/04/2006	EC-CO	LILLY	Prasugril	Co-investigateur	04/2006	12/2006
64113	COTTIN	Yves	15/04/2006	CF-INT	SANOFI	Cœur et diabète / plavix	Rémunération personnelle	02/2006	02/2006
64113	COTTIN	Yves	15/04/2006	CF-INT	LILLY	Congrès Thrombose coronaire	Rémunération personnelle	03/2006	03/2006
63305	COUET	Charles	28/07/2008	IF	SANOFI AVENTIS	Actions	< 5000 € ou < 5 % du capital		

Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
305 COUET	Charles	28/07/2008	EC-CO	TAKEDA	Recherche clinique - Pioglitazone	co-investigateur	01/2004	01/2006
305 COUET	Charles	28/07/2008	EC-CO	NOVO NORDISK	Recherche clinique - Insuline Détémir	co-investigateur	01/2005	01/2006
305 COUET	Charles	28/07/2008	EC-CO	LILLY	Recherche clinique - insuline inhalée	co-investigateur	01/2006	09/2008
305 COUET	Charles	28/07/2008	EC-CO	NOVO NORDISK	Recherche clinique - Insuline inhalée	co-investigateur	01/2006	06/2008
305 COUET	Charles	28/07/2008	EC-CO	GSK	Recherche clinique - rosiglitazone	co-investigateur	01/2005	
305 COUET	Charles	28/07/2008	EC-CO	MSD	Recherche clinique - Januvia	co-investigateur	01/2007	
305 COUET	Charles	28/07/2008	CF-INT	SERVIER	Coeur et diabète - Tours	rémunération institution	01/2006	01/2006
305 COUET	Charles	28/07/2008	CF-INT	SANOFI AVENTIS	Le système xx - Tours	rémunération institution	03/2007	03/2007
305 COUET	Charles	28/07/2008	CF-INT	SANOFI AVENTIS	La Baule	Rémunération institution	06/2007	06/2007
305 COUET	Charles	28/07/2008	CF-AUD	SANOFI AVENTIS	Formation Acomplia - Cannes		01/2007	01/2007
305 COUET	Charles	28/07/2008	CF-AUD	SERVIER	European Society of Cardiology - Vienne		09/2007	09/2000
305 COUET	Charles	28/07/2008	CF-AUD	SERVIER	Rencontres Franco-Italiennes de l'HTA - Rome		10/2007	10/2007
305 COUET	Charles	28/07/2008	CF-AUD	TAKEDA	ALFEDIAM - Bruxelles		03/2008	03/2008
305 COUET	Charles	28/07/2008	CF-AUD	ASTRA ZENECA	5th Metabolic syndrome Congress , type II Diabetes and Arthroselosis - Marrakech		05/2008	05/2008
305 COUET	Charles	28/07/2008	CF-AUD	SANOFI AVENTIS	EASD - Rome		09/2008	09/2008
305 COUET	Charles	28/07/2008	CF-AUD	NOVO NORDISK	Diabetes European Meeting - St Jacques de Compostelle		10/2008	10/2008
305 COUET	Charles	07/06/2004	IP-EC	TAKEDA	Participation essai clinique			
305 COUET	Charles	07/06/2004	IP	AVENTIS	Actions			
305 COUET	Charles	07/06/2004	IP-EC	SANOFI-SYNTHELABO	Participation essai clinique			
305 COUET	Charles	07/06/2004	IP-RE	CEDUS	Conseil			
305 COUET	Charles	07/06/2004	IP-RE	NUTRI-HEALTH	Conseil			
0122 CRETON	Bernard	20/05/1999	IP-EC	HOECHST	Etude Diabhicam			
0122 CRETON	Bernard	01/01/1999	IP-EC	HOECHST				
0122 CRETON	Bernard	01/01/1998	IP-AUT	Sandoz				
0122 CRETON	Bernard	01/01/1998	IP-AUT	Servier				
0122 CRETON	Bernard	01/01/1998	IP-AUT	Astra				
0122 CRETON	Bernard	01/01/1998	IP-AUT	Hoechst				
0122 CRETON	Bernard	01/01/1998	IP-AUT	FMC				
0631 CROCHET	Pierre-Dominique	08/12/2010	EC-INV	MEDTRONIC	Etude ENDEAVOR	Investigateur principal	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	08/12/2010	EC-INV	TERUMO	Etude KARE	Investigateur principal	01/2010	
0631 CROCHET	Pierre-Dominique	08/12/2010	EC-CO	CORDIS	Stent CYPHER	Investigateur	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	08/12/2010	CF-AUD	MEDTRONIC	Congrès AHA Chicago (USA)		11/2010	
0631 CROCHET	Pierre-Dominique	02/12/2009	EC-INV	MEDTRONIC	Etude Endeavor (stent actif)	Investigateur principal	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	02/12/2009	EC-CO	CORDIS	Stent Cypher	Investigateur	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	02/12/2009	CF-INT	MENARINI	Imagerie cardiologique	Rémunération personnelle	11/2005	11/2005
0631 CROCHET	Pierre-Dominique	02/12/2009	CF-AUD	SORIN	Congrès Hitech Cardio		01/2007	01/2007
0631 CROCHET	Pierre-Dominique	02/12/2009	CF-AUD	SERVIER	ESC		09/2008	09/2008
0631 CROCHET	Pierre-Dominique	02/12/2009	CF-AUD	MEDITRONIC	Hitech Cardio		11/2009	11/2009
0631 CROCHET	Pierre-Dominique	09/01/2009	CF-AUD	SERVIER	ESC - Munich		09/2008	09/2008
0631 CROCHET	Pierre-Dominique	09/01/2009	CF-AUD	MEDTRONIC	HITECH cardio - Marseille		01/2009	01/2009
0631 CROCHET	Pierre-Dominique	09/01/2009	CF-AUD	TERUMO	HITECH cardio - Marseille		01/2008	01/2008
0631 CROCHET	Pierre-Dominique	08/01/2008	EC-INV	MEDTRONIC	Etude Endeavor (Stent actif)	investigateur principal	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	08/01/2008	EC-CO	CORDIS	Stent Cypher	investigateur	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	08/01/2008	CF-INT	MENARINI	Imagerie cardiaque	rémunération personnelle	11/2005	11/2005
0631 CROCHET	Pierre-Dominique	08/01/2008	CF-AUD	SORIN	Congrès HI-TECH Cardio		01/2007	01/2007
0631 CROCHET	Pierre-Dominique	20/11/2006	EC-CO	MEDTRONIC	Stent ENDEAVOR	co-investigateur	01/2002	12/2004
0631 CROCHET	Pierre-Dominique	20/11/2006	CF-INT	MENARINI	scanner des artères coronaires	rémunération personnelle	09/2006	09/2006
0631 CROCHET	Pierre-Dominique	20/11/2006	CF-INT	SANOFI AVENTIS	prise en charge cardio vasculaire du diabétique	rémunération personnelle	10/2006	10/2006
0631 CROCHET	Pierre-Dominique	20/11/2006	CF-AUD	SERVIER	Barcelone - congrès européen de cardiologie		09/2006	09/2006
0631 CROCHET	Pierre-Dominique	06/12/2005	EC-INV	MEDTRONIC	Etude Endeavor	Investigateur principal	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	06/12/2005	EC-CO	CORDIS	Stent Cypher	Investigateur	01/2003	12/2005
0631 CROCHET	Pierre-Dominique	06/12/2005	EC-CO	GUIDANT	Stent passif - étude Trend	Investigateur	01/2002	12/2004
0631 CROCHET	Pierre-Dominique	06/12/2005	EC-CO	GUIDANT	Etude ICARUS 2	Investigateur	01/2001	12/2003
0631 CROCHET	Pierre-Dominique	06/12/2005	CF-INT	MENARINI	Imagerie cardiaque	Rémunération personnelle	11/2005	11/2005
0631 CROCHET	Pierre-Dominique	06/12/2005	CF-AUD	MEDTRONIC	Etude Endeavor		11/2005	11/2005
0631 CROCHET	Pierre-Dominique	07/03/2004	IP-EC	CORDIS	Etude Typhoon			
0631 CROCHET	Pierre-Dominique	07/03/2004	IP-EC	MEDTRONIC	Etude Endeavor			
0631 CROCHET	Pierre-Dominique	04/02/2002	IP-EC	HERACATH	Etude Hellstent TI			
0631 CROCHET	Pierre-Dominique	04/02/2002	IP-EC	GUIDANT	Etude ULTRA			
0631 CROCHET	Pierre-Dominique	05/07/2000	IP-AC	SOCIETE BOSTON SCIENTIFIQUE	Filtres cavas	Rémunération personnelle		
55634 CUCHERAT	Michel	14/09/2006	IP-AC	BéSINS	conseils méthodo et stat pour le développement (depuis le 1/9/2006)			
55634 CUCHERAT	Michel	14/09/2006	IP-AUT	NOVARTIS	membre du comité scientifique de l'étude DGC Glaevec			
55634 CUCHERAT	Michel	14/09/2006	IP-AUT	SANOFI AVENTIS	membre du comite scientifique de l'étude DGS copaxone			
55634 CUCHERAT	Michel	14/09/2006	CF-INT	BMS	séminaire méthodologie Anesthésie Top Performer Biarritz septembre 2006	Rémunération personnelle		
55634 CUCHERAT	Michel	14/09/2006	CF-INT	SANOFI AVENTIS	séminaire de méthodologie en neurologie Lyon juin 2006	Rémunération personnelle		
55634 CUCHERAT	Michel	14/09/2006	RE-AUT	SANOFI AVENTIS	docetaxel	Rémunération personnelle	08/2006	10/2006
55634 CUCHERAT	Michel	14/09/2006	RE-AUT	LAB MANARINI	nebivolol	Rémunération personnelle		12/2006
55634 CUCHERAT	Michel	12/09/2006	IP-AC	LAB MENARINI	analyse méthodologique de publications	Rémunération personnelle		12/2006
55634 CUCHERAT	Michel	12/09/2006	RE-AUT	LAB SERVIER	Ivabradine			12/2001
55634 CUCHERAT	Michel	15/05/2000	IP-CF	SANOFI SYNTHELABO	Méta analyse			12/2001
55634 CUCHERAT	Michel	15/05/2000	IP-CF	VIDENDI	Méthodologie des essais			12/2004
55634 CUCHERAT	Michel	15/05/2000	VB	GUERBET	Service de Pharmacologie clinique, Lyon			
55634 CUCHERAT	Michel	01/01/1999	IP-CF	RHONE POULENC RORER	1997-1998			
55634 CUCHERAT	Michel	01/01/1999	IP-CF	SANOFI	1996-1995			
55634 CUCHERAT	Michel	01/01/1999	IP-CF	LIPHA	1997			
55634 CUCHERAT	Michel	01/01/1999	IP-AUT	RHONE POULENC RORER	(1996), Société européenne de cardiologie			
55634 CUCHERAT	Michel	01/01/1999	VB	GUERBET	Université Lyon I - EZUS.			
55634 CUCHERAT	Michel	01/01/1999	VB	Laboratoires LIPHA	Association APRET (1997).	Université Lyon I		
55634 CUCHERAT	Michel	01/01/1999	VB	Laboratoires Sanofi :	Université Lyon I - EZUS (1997-1998).			
55634 CUCHERAT	Michel	01/01/1998	IP-CF	Rhône Poulence Rorer				
55634 CUCHERAT	Michel	01/01/1998	IP-CF	LIPHA		Université Lyon I		
55634 CUCHERAT	Michel	01/01/1998	VB	Laboratoires Sanofi ; Université Lyon I - EZUS				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61131	CUILLERIER	Emmanuel	16/10/2000	IP-EC	NOVARTIS	Traitement troubles fonctionnels intestinaux			
61131	CUILLERIER	Emmanuel	16/10/2000	IP-EC	FERRING	Préparation à la coloscopie			
61131	CUILLERIER	Emmanuel	16/10/2000	PAR	SERVIER	Conjoint			
63795	D'AZEMAR DE FABREGUES	Pascal	13/04/2005	LD	LABORATOIRE SERVIER	S18866, phase II (mars 2002)			
63795	D'AZEMAR DE FABREGUES	Pascal	13/04/2005	LD	LABORATOIRE SERVIER	Salarié			
60510	DAMIEN	Gérard	02/04/2009	LD-AR	GROUPE DE RECHERCHE SERVIER	CONSULTANT CMC	Rémunération personnelle	04/2008	
60510	DAMIEN	Gérard	02/04/2009	LD-AR	GROUPE DE RECHERCHE SERVIER	CONSULTANT CMC	Aucune rémunération	04/2008	04/2008
60510	DAMIEN	Gérard	08/09/2006	LD-ODE	TECHNOLOGIE SERVIER	salarié		01/1974	04/2008
60510	DAMIEN	Gérard	08/09/2006	IP-AUT	I.F.I.S	module 3 du CTD			
60510	DAMIEN	Gérard	25/05/2005	LD	TECHNOLOGIE SERVIER	Salarié			
60510	DAMIEN	Gérard	25/05/2005	IP-CF	IFIS	Module 3 du CTD			
60510	DAMIEN	Gérard	15/03/2004	LD	SERVIER	Salarié			
60510	DAMIEN	Gérard	15/03/2004	IP-CF	INSTITUT FORMATION DES INDUSTRIES DE SANTE (IFIS)	Le dossier d'AMM			
60510	DAMIEN	Gérard	30/11/1999	IP-CF	IFIP	Formation : la partie II du dossier d'AMM			
60510	DAMIEN	Gérard	08/11/1999	IP-CF	IFIP	Partie II du dossier d'AMM			
60251	DANCHIN	Nicolas	11/08/2008	PAR	SERVIER	Médecin direction scientifique France	épouse		12/2005
60251	DANCHIN	Nicolas	11/08/2008	CF-INT	ASTRA-ZENECA, BAYER, BMS, BOEHRINGER INGELHEIM, GSK, LILLY, MSD, NEGMA, NOVARTIS, PFIZER, SANOFI AVENTIS, SERVIER		Rémunération personnelle		
60251	DANCHIN	Nicolas	11/08/2008	EC-INV	PFIZER, SERVIER	Pas de produit	Pfizer et Servier ont fourni des grants pour le registre d'infarctus de la SFC FAST-MI, dont je suis investigateur principal		
60251	DANCHIN	Nicolas	11/08/2008	EC-INV	SERVIER	Trimetazidine □□Ivabradine	trimetazidine : (investigateur - coordonateur étude VASCO)□ ivabradine : (coordonateur national étude BEAUTIFUL)	01/2005	
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	BAYER	Nifédipine	Rémunération personnelle		
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	SERVIER	S-18886	Rémunération personnelle		
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	SERVIER	Trimétazidine	Rémunération personnelle		
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	SERVIER	Ivabradine	Rémunération personnelle		
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	SANOFI AVENTIS	Clopidogrel	Rémunération personnelle		
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	MERCK LIPHA	Nicorandil	Rémunération personnelle		12/2006
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	HOECHST	Canporide	Aucune rémunération		12/2005
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	ASTRA ZENECA	Ximélagatran	Aucune rémunération		12/2006
60251	DANCHIN	Nicolas	13/04/2005	IP-EC	ASTRA ZENECA	Rosuvastatine			
60251	DANCHIN	Nicolas	13/04/2005	EC-INV	SERVIER	Trimétazidine			
60251	DANCHIN	Nicolas	13/04/2005	IP-RE	BAYER	Acarbose			12/2007
60251	DANCHIN	Nicolas	13/04/2005	IP-CF	ASTRA ZENECA, BMS, BAYER,GSK, MSD, NOVARTIS, PFIZER, SANOFI AVENTIS, SERVIER, MERCK LIPHA				
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	BMS	Pravastatine	Rémunération personnelle		
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	PFIZER	Amlodipine	Rémunération personnelle		12/2007
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	PFIZER	Atorvastatine	Rémunération personnelle		12/2007
60251	DANCHIN	Nicolas	13/04/2005	IP-AC	SANOFI AVENTIS	Clopidogrel	Aucune rémunération		
60251	DANCHIN	Nicolas	13/04/2005	IP-CF	ASTRA ZENECA, GSK, SERVIER				
60251	DANCHIN	Nicolas	10/04/2005	IP-RE	SERVIER	Mission d'expertise et participation au Comité directeur de l'étude VASCO (propriétés antiangineuses de la li			
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	BOSTON SCIMED				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	CORDIS JOHNSON & JOHNSON				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	BRISTOL MYERS SQUIBB				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	BAYER				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	NOVARTIS				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	MERCK LIPHA				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	ASTRA ZENECA				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	SCHERING PLOUGH				
60251	DANCHIN	Nicolas	09/09/2003	IP-EC	SERVIER				
60251	DANCHIN	Nicolas	09/09/2003	IP-AC	PFIZER				
60251	DANCHIN	Nicolas	09/09/2003	IP-AC	PIERRE FABRE				
60251	DANCHIN	Nicolas	09/09/2003	IP-CF	SANOFI SYNTHELABO				
60251	DANCHIN	Nicolas	09/09/2003	IP-CF	SERVIER				
60251	DANCHIN	Nicolas	09/09/2003	IP-AC	PFIZER				
60251	DANCHIN	Nicolas	09/09/2003	PAR	SERVIER	Epouse salariée			
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	AVENTIS				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	ASTRA ZENECA				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	BRISTOL MYERS SQUIBB				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	BOSTON SCIMED				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	LIPHA				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	PFIZER				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	PIERRE FABRE				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	SANOFI				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	SERVIER				
60251	DANCHIN	Nicolas	20/08/2003	IP-EC	SCHERING PLOUGH				
60251	DANCHIN	Nicolas	20/08/2003	IP-AC	PFIZER				
60251	DANCHIN	Nicolas	20/08/2003	IP-AC	LIPHA				
60251	DANCHIN	Nicolas	20/08/2003	IP-AC	MERCK SHARP & DOHME				
60251	DANCHIN	Nicolas	20/08/2003	IP-AC	BRISTOL MYERS SQUIBB				
60251	DANCHIN	Nicolas	20/08/2003	IP-CF	AVENTIS				
60251	DANCHIN	Nicolas	20/08/2003	IP-CF	ASTRA ZENECA				
60251	DANCHIN	Nicolas	20/08/2003	IP-CF	BRISTOL MYERS SQUIBB				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60251	DANCHIN	Nicolas	20/08/2003	IP-CF	BOEHRINGER INGELHEIM				
60251	DANCHIN	Nicolas	20/08/2003	IP-CF	PFIZER				
60251	DANCHIN	Nicolas	20/08/2003	IP-CF	SERVIER				
60251	DANCHIN	Nicolas	20/08/2003	PAR	SERVIER	Epouse salariée			
60251	DANCHIN	Nicolas	06/11/2001	IP-EC	CORDIS	Coordination registre			
60251	DANCHIN	Nicolas	06/11/2001	IP-EC	GUIDANT	Coordination registre			
60251	DANCHIN	Nicolas	06/11/2001	IP-CF	JOHNSON et JOHNSON	Conférence			
60251	DANCHIN	Nicolas	06/11/2001	VB	BOSTON SCIENTIFIC	Soutien à l'Association Claude Bernard pour organisation d'un séminaire d'enseignement			
60251	DANCHIN	Nicolas	01/03/2001	IP-EC	GUIDANT				
60251	DANCHIN	Nicolas	01/03/2001	IP-EC	CORDIS				
60251	DANCHIN	Nicolas	01/03/2001	IP-EC	MEDTRONIC				
60251	DANCHIN	Nicolas	01/03/2001	IP-EC	SERVIER				
60251	DANCHIN	Nicolas	01/03/2001	IP-EC	AVENTIS				
60251	DANCHIN	Nicolas	01/03/2001	IP-AC	MSD				
60251	DANCHIN	Nicolas	01/03/2001	IP-AC	LILLY				
60251	DANCHIN	Nicolas	01/03/2001	IP-AC	SERVIER				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	MSD				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	BMS				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	SCHERING PLOUGH				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	AVENTIS				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	GLAXO WELLCOME				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	SERVIER				
60251	DANCHIN	Nicolas	01/03/2001	IP-CF	FOURNIER				
60251	DANCHIN	Nicolas	01/03/2001	VB		Divers protocoles d'études cliniques			
60251	DANCHIN	Nicolas	01/03/2001	PAR	SERVIER	Conjoint			
61344	DANY	François	28/01/2010	LD-AR	ICARLIM :RESEAU D INSUFFISANTS CARDIAQUES 4 AVE DE LA REVOLUTION 87000 LIMOGES	RESEAU DE SANTE VILLE HOPITAL. UNE VACATION HEBDOMADAIRE (EN COURS)	RÉMUNERATION PERSONNELLE	01/2005	
61344	DANY	François	28/01/2010	EC-CO	ASTRA ZENECA	ETUDES DE PHASE IV... (IMPACT RECO)...		01/2006	12/2007
61344	DANY	François	28/01/2010	EC-CO	MSD CHIBRET	EZETIMIBE	CO-INVESTIGATEUR	01/2005	12/2006
61344	DANY	François	28/01/2010	EC-CO	MSD CHIBRET	EZETIMIBE	CO-INVESTIGATEUR	01/2008	12/2009
61344	DANY	François	28/01/2010	EC-CO	MERCK SERONO	ETUDES PHASE IV (OLMECONTROL)..		01/2005	12/2009
61344	DANY	François	28/01/2010	EC-CO	BOEHRINGER...INGELHEIM	ETUDES DE PHASE IV...(TELETENSION,CARAVAGE)...	CO-INVESTIGATEUR	01/2008	12/2009
61344	DANY	François	28/01/2010	EC-CO	TAKEDA	ETUDE PHASE IV SYSTOLA.		01/2008	12/2009
61344	DANY	François	28/01/2010	EC-CO	INSERM	ETUDE SUFOLOM 3	CO-INVESTIGATEUR	01/2005	
61344	DANY	François	28/01/2010	EC-CO	BMS SANOFI ADVENTIS	ETUDE I-SYSPRES	CO-INVESTIGATEUR	01/2008	12/2009
61344	DANY	François	28/01/2010	IP-RE	ANAES	NOMENCLATURE DES ACTES MEDICAUX CPAM 12 ACTES CARDIOVASCULAIRES	RÉMUNERATION PERSONNELLE	01/2001	12/2001
61344	DANY	François	28/01/2010	IP-AC	ASTRA ZENECA	INTERVENTIONS PERIODIQUES SUR LE PROJET ICARE..INSUFFISANCE CARDIAQUE ET EDUCATIOI	ANIMATEUR	03/2004	06/2009
61344	DANY	François	28/01/2010	IP-AC	MENARINI	JOURNEE DE FORMATION DE DELEGUES MEDICAUX...FORMATION REMUNEREE PAR LE LABORAT(	EXPERT	11/2006	11/2006
61344	DANY	François	28/01/2010	CF-INT	SANOFI AVENTIS	BIARRITZ : JOURNEES ATLANTIQUES DE CARDIOLOGIE : ATELIER SUR L ARTERITE DES MEMBRES	AUCUNE REMUNERATION	11/2007	
61344	DANY	François	28/01/2010	CF-INT	ASTRA ZENECA	REUNION DU PROJET ICARE	AUCUNE REMUNERATION	01/2006	12/2007
61344	DANY	François	28/01/2010	CF-INT	PFIZER	EPU SUR LES HYPERLIPIDEMIES	RÉMUNERATION PERSONNELLE	11/2008	
61344	DANY	François	28/01/2010	CF-INT	BOUCHARA RECORDATI	EPU HYPERTENSION ARTERIELLE : CORDES DU CIEL	RÉMUNERATION PERSONNELLE	03/2009	
61344	DANY	François	28/01/2010	CF-INT	MSD	NOUVEAUTES SUR LES HYPERLIPIDEMIES LIMOGES	RÉMUNERATION PERSONNELLE	04/2009	
61344	DANY	François	28/01/2010	CF-INT	BAYER	HTA DANS LE CONTEXTE A RISQUE LIMOGES	RÉMUNERATION PERSONNELLE	06/2009	
61344	DANY	François	28/01/2010	CF-INT	ASTRA ZENECA	COLLOQUE ICARLIM TULLE OCTOBRE 2009	RÉMUNERATION PERSONNELLE	10/2009	
61344	DANY	François	28/01/2010	CF-AUD	MERCK SERENO	1/CONGRES HEART FAILURE MILAN JUIN 2008 2/2/REUNION FRANCO UKRAINIENNE DE CARDIOLOGIE KIEV 11 OCTOBRE 2008		10/2008	
61344	DANY	François	28/01/2010	CF-AUD	BOUCHARA RECORDATI	INVITATION AUX JOURNEES SCIENTIFIQUES DE L AHA ORLANDO		11/2007	
61344	DANY	François	28/01/2010	CF-AUD	BAYER PHARMA	REUNION PARIS FORMATION SUR LE TELMISARTAN (ONTARGET)		03/2008	
61344	DANY	François	28/01/2010	CF-AUD	ASTRA ZENECA	INVITATION AUX JOURNEES EUROPEENNES DE CARDIOLOGIE PARIS 16 JANVIER 2009		01/2009	
61344	DANY	François	28/01/2010	CF-AUD	TAKEDA	SYMPOSIUM CANDESRTAN ET RISQUE VASCULAIRE MILAN JANVIER 2009		01/2009	
61344	DANY	François	28/01/2010	IP-AUT	SERVIER	INVITATION AU CONGRES HEART FAILURE 2009 EN MAI A NICE		05/2009	06/2009
61344	DANY	François	28/01/2010	IP-AUT	ASTRA ZENECA	JOURNEES FRANCAISES D INSUFFISANCE CARDIAQUE. LA BAULE 22 SEPTEMBRE 2009		09/2009	09/2009
61344	DANY	François	06/01/2009	LD-AR	ICARLIM	Réseau de santé	rémunération personnelle	01/2005	
61344	DANY	François	06/01/2009	EC-CO	ASTRA ZENECA	Etude de phase IV (impact reco)	co-investigateur	01/2006	12/2007
61344	DANY	François	06/01/2009	EC-CO	MSD CHIBRET	Ezetimibe	co-investigateur	01/2005	12/2006
61344	DANY	François	06/01/2009	EC-CO	MERCK SERONO	Etudes phase IV (Olmecontrol)	co-investigateur	01/2008	12/2009
61344	DANY	François	06/01/2009	EC-CO	BOEHRINGER INGELHEIM	Etudes de phase IV (télétension, caravage)	co-investigateur	01/2005	12/2006
61344	DANY	François	06/01/2009	EC-CO	BOEHRINGER INGELHEIM	Etudes de phase IV (télétension, caravage)	co-investigateur	01/2008	12/2009
61344	DANY	François	06/01/2009	EC-CO	TAKEDA	Etude phase IV - Systola	co-investigateur	01/2008	12/2008
61344	DANY	François	06/01/2009	RE-DE	ANAES	Nomenclature des actes médicaux CPAM 12 actes cardiovasculaires	rémunération personnelle	01/2001	12/2001
61344	DANY	François	06/01/2009	IP-AC	ASTRA ZENECA	Interventions périodiques sur le projet ICARE Insuffisance cardiaque et éducation thérapeutique	aucune rémunération - animateur	03/2004	06/2007
61344	DANY	François	06/01/2009	IP-AC	MENARINI	Journée de formation de délégués médicaux - formation rémunérée par le laboratoire	expert	11/2006	11/2006
61344	DANY	François	06/01/2009	CF-INT	SANOFI AVENTIS	Journées atlantiques de cardiologie : atelier sur l'artérite des membres inférieurs	aucune rémunération	11/2007	11/2007
61344	DANY	François	06/01/2009	CF-INT	ASTRA ZENECA	Réunion du projet ICARE	aucune rémunération	01/2006	12/2007
61344	DANY	François	06/01/2009	CF-INT	PFIZER	EPU sur les hyperlipidemies	rémunération personnelle	11/2008	11/2008
61344	DANY	François	06/01/2009	CF-AUD	MERCK SERONO	Congrès Heart Failure - Milan		06/2008	06/2008
61344	DANY	François	06/01/2009	CF-AUD	MERCK SERONO	Réunion franco ukrainienne de cardiologie - Kiev		10/2008	10/2008
61344	DANY	François	06/01/2009	CF-AUD	MERCK SERONO	L'Europe du coeur - Talinn (Estonie)		10/2006	10/2006
61344	DANY	François	06/01/2009	CF-AUD	BOUCHARA RECORDATI	invitation aux journées scientifiques de l'AHA - Orlando		11/2007	11/2007
61344	DANY	François	06/01/2009	CF-AUD	BAYER PHARMA	Réunion Paris Formation sur le telmisartan (on target)		03/2008	03/2008
61344	DANY	François	20/03/2008	EC-CO	CEPHALON	étude LIMB buflomédil.	co-investigateur	01/2000	12/2005
61344	DANY	François	20/03/2008	EC-CO	MSD	étude RUN HTAFA	co-investigateur	01/2007	12/2007
61344	DANY	François	20/03/2008	EC-CO	CHIESI	étude eveil XXX	co-investigateur	01/2007	12/2007
61344	DANY	François	20/03/2008	EC-CO	PFIZER	étude DECIC AMCR	co-investigateur	01/2002	12/2007
61344	DANY	François	20/03/2008	EC-CO	SANOFI	étude ISYPRESS (en cours)	co-investigateur	01/2008	

d	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
1344	DANY	François	20/03/2008	EC-CO	TAKEDA	étude SISTOLA (XXX) : en cours	co-investigateur	01/2008	
1344	DANY	François	20/03/2008	CF-INT	AVENTIS	Journée cardiologie AquitaineXXX - Biarritz : intervention sur cas cliniques en XXX	rémunération personnelle	11/2007	11/2007
1344	DANY	François	20/03/2008	CF-INT	MSD	Diabetes et HTA	rémunération personnelle	11/2008	11/2008
1344	DANY	François	20/03/2008	CF-AUD	SANOFI	Journées de l'insuffisance cardiaque - Deauville		09/2008	09/2008
1344	DANY	François	20/03/2008	CF-AUD	BOUCHARA RECORDATI	American Heart Association - Orlando (USA)		11/2007	11/2007
1344	DANY	François	20/03/2008	CF-AUD	BAYER	Journée de formation - Paris		01/2008	01/2008
1344	DANY	François	17/05/2007	EC-CO	PFIZER	Etudes Phase IV - CADUET	Experimentateur non principal	01/2005	12/2006
1344	DANY	François	17/05/2007	EC-CO	LAFON	Etude LIMB BUFLOMEDIL	Experimentateur non principal	01/2002	12/2005
1344	DANY	François	17/05/2007	EC-CO	ASTRA ZENECA	Etudes de pratique	Co-investigateur	01/2004	12/2007
1344	DANY	François	17/05/2007	IP-AC	MENARINI	Alleis	rémunération personnelle	10/2006	10/2006
1344	DANY	François	17/05/2007	CF-INT	ASTRA ZENECA	Projet ICARE - réunions périodiques depuis 2004	rémunération personnelle	01/2004	
1344	DANY	François	17/05/2007	CF-INT	MSD	Réunions de FMC	rémunération personnelle	01/2005	12/2005
1344	DANY	François	17/05/2007	CF-INT	MSD	Ateliers de formation	rémunération personnelle	01/2007	12/2007
1344	DANY	François	17/05/2007	CF-AUD	SANOFI	Congrès des cardiologues du Sud Ouest - Biarritz		01/2006	12/2006
1344	DANY	François	17/05/2007	CF-AUD	LIPHA	Journées Franco-Estoniennes de cardiologie		01/2006	12/2006
1344	DANY	François	17/05/2007	CF-AUD	BMS	Journée insuffisance cardiaque - La Baule		01/2006	12/2006
1344	DANY	François	17/05/2007	CF-AUD	SANOFI	Réunion Acomplia - Paris		11/2006	11/2006
1344	DANY	François	17/05/2007	VB	ICARLIM	Versements pour □□- URCAM□□- ARH		01/2005	12/2007
1344	DANY	François	17/05/2007	VB	ICARLIM	Quelques dons des labos (Astra Zeneca) pour l'organisation d'un colloque		10/2006	10/2006
1344	DANY	François	17/05/2007	(Autre)	ICARLIM	Président - réseau Limousin d'insuffisance cardiaque			
1344	DANY	François	15/05/2006	EC-CO	PFIZER	CADUET étude RIGHT	co-investigateur		
1344	DANY	François	15/05/2006	EC-CO	SERVIER (EUTHE RAPK)	Etude MERCURE	co-investigateur		
1344	DANY	François	15/05/2006	EC-CO	MERCK CLEVENOT	Etude PUNCH (NIACINE)	co-investigateur		
1344	DANY	François	15/05/2006	EC-CO		Plusieurs Phases IV - Nice	co-investigateur	01/2005	12/2005
1344	DANY	François	15/05/2006	IP-AC	ANAES	Recommandations TEHA	aucune rémunération	01/1997	
1344	DANY	François	15/05/2006	IP-AC	AFFSAPS	Elévation Tensionnelles aigues	aucune rémunération	01/2002	12/2002
1344	DANY	François	15/05/2006	IP-AC	ANAES	- Nomenclature des actes médicaux (12 actes) charge de travail	rémunération personnelle	01/2002	12/2002
1344	DANY	François	15/05/2006	CF-INT	MSD	Erude TWICE - Réunion M6 Limoges	rémunération personnelle	01/2004	12/2004
1344	DANY	François	15/05/2006	CF-INT	ASTRA ZENECA	Groupe ICARE (Insuffisance cardiaque) 2 Week-end de Formation - Paris	aucune rémunération	01/2005	12/2005
1344	DANY	François	15/05/2006	CF-AUD	MERCK CLEVENOT	Journées ERASCO de Cardiologie - Talinn		09/2005	09/2005
1344	DANY	François	15/05/2006	CF-AUD	MSD	Journées ERASCO Roumaines de Cardiologie - Bucarest		01/2005	01/2005
1344	DANY	François	15/05/2006	IP-AC	ANAES	- Angioplasties Carotidiennes	aucune rémunération	01/2000	
5468	DAUBIN	Claire	30/06/2009	PAR	SERVIER	Pharmacien responsable projet internet	Conjoint	01/2008	
2667	DE GROOTE	Pascal	31/03/2010	LD-AR	SANOFI BMS	Expert insuffisance cardiaque à FEVG préservé / IRBESARTAN	Rémunération personnelle	01/2005	12/2009
2667	DE GROOTE	Pascal	31/03/2010	LD-AR	SANOFI BMS	Expert fibrillation auriculaire / IRBESARTAN	Rémunération personnelle	01/2007	12/2009
2667	DE GROOTE	Pascal	31/03/2010	LD-AR	SANOFI BMS	Expert fibrillation auriculaire / DRONEDARONE	Rémunération personnelle	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	LD-AR	ACTELION	Expert HTAP Sclérodermie, Echocardiographie	Rémunération personnelle	01/2004	
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	ASTRA - ZENECA	Etude IMPACT I, II et III / CANDESARTAN	Comité scientifique	01/2004	12/2010
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	BMS SANOFI	Etude I-SYPRESS / IRBESARTAN	Comité Scientifique	01/2007	12/2009
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	BMS SANOFI	Etude I-SYPRESS / IRBESARTAN	Comité d' adjudication	01/2008	12/2009
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	ABBOTT	Etude Observe / CLOPIDOGREL	Comité d'adjudication	01/2008	12/2009
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	ABBOTT	Etude Calypso / post IDM	Comité scientifique	01/2007	
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	MENARINI	Etude observationnelledu post infarctus / TRANDOLAPRIL	Comité Scientifique	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	AMGEN	Etude Efficare	Investigateur	01/2006	
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	res MED SAS	Etude Red-HF / Erythropoiétine dans l'insuffisance cardiaque. Etude SERVE-HF / ventilation Servo Assistée	Investigateur	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	EC-CO	BAYER	Etude PATENT/ CHEST / BAY 63-2521. Etude BSP TRUST / descriptive	Investigteur	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	IP-RE		Herceptine	Rémunération personnelle		
2667	DE GROOTE	Pascal	31/03/2010	IP-RE	AB SCIENCE	Masitinib	Rémunération personnelle	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	IP-RE	BAYER	Riociguiat	Rémunération personnelle	01/2010	
2667	DE GROOTE	Pascal	31/03/2010	IP-RE	NOVARTIS	Imatinib	Rémunération personnelle	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	IP-RE	LUNGRC	Béraprost	Rémunération personnelle	01/2009	
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	ACTELION	HTAP, échocardiographie	Rémunération personnelle / Aucune rémunération		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	ASTRA - ZENECA	Insuffisance cardiaque, recommandations	Rémunération personnelle / Aucune rémunération		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	MENARINI	Insuffisance cardiaque	Rémunération personnelle / Aucune rémunération		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	ABBOTT	Insuffisance cardiaque	Rémunération personnelle / Aucune rémunération		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	PFIZER	HTAP	Rémunération personnelle / Aucune rémunération		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	TAKEDA	Insuffisance cardiaque	Rémunération personnelle / Aucune rémunération		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	MERCK - LIPHA	Insuffisance cardiaque	Parfois non rémunéré		
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	ROCHE	Insuffisance cardiaque			
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	SANOFI BMS	Insuffisance cardiaque			
2667	DE GROOTE	Pascal	31/03/2010	CF-INT	GLAXO	HTAP			
2667	DE GROOTE	Pascal	31/03/2010	CF-INT		Présentations générales, pas de produit, région Nord -Pas de Calais, parfois national			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	SERVIER	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	ASTRA - ZENECA	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	SANOFI - BMS	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	TAKEDA	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	MENARINI	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	ACTELION	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	31/03/2010	CF-AUD	PFIZER	Congrès de cardiologie en France ou à l' étranger (congrès Européen ou Américain (AHA)) (ces dernières années)			
2667	DE GROOTE	Pascal	20/03/2009	LD-AR	SANOFI BMS	Expert insuffisance cardiaque à FEVG préservée / Irbesartan	rémunération personnelle		
2667	DE GROOTE	Pascal	20/03/2009	LD-AR	SANOFI BMS	Expert fibrillation auriculaire / Irbesartan	rémunération personnelle		
2667	DE GROOTE	Pascal	20/03/2009	LD-AR	ACTELION	Expert HTAP Sclérodermie Echocardiographie	rémunération personnelle		
2667	DE GROOTE	Pascal	20/03/2009	EC-CO	ASTRA ZENECA	Etude Impact I, II et III / Candesartan	Comité Scientifique		
2667	DE GROOTE	Pascal	20/03/2009	EC-CO	BMS, SANOFI	Etude I-Sypress / Irbesartan	Comité d'Adjudication		
2667	DE GROOTE	Pascal	20/03/2009	EC-CO	BMS, SANOFI	Etude Observe / Clopidogrel			

d	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
2667	DE GROOTE	Pascal	20/03/2009	EC-CO	ABBOTT	Etude observationnelle du post infarctus / Trandolapril	Comité Scientifique		
2667	DE GROOTE	Pascal	20/03/2009	EC-CO	AMGEN	Etude Red-HF / Erythropoïétine	investigateur principal		
2667	DE GROOTE	Pascal	20/03/2009	RE-DE		Herceptine	rémunération personnelle		
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	ACTELION	HTAP, échocardiographie			
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	ASTRA ZENECA	Insuffisance cardiaque, recommandations			
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	MENARINI	Insuffisance cardiaque			
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	ABBOTT	Insuffisance cardiaque			
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	PFIZER	HTAP			
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	TAKEDA	Insuffisance cardiaque			
2667	DE GROOTE	Pascal	20/03/2009	CF-INT	MERCK LIPHA	Présentations générales, pas de produit, région Nord - pas de Calais - parfois national	Parfois non rémunéré		
2667	DE GROOTE	Pascal	20/03/2009	CF-AUD	SERVIER, ASTRA ZENECA, SANOFI BMS, TAKEDA, MENARINI, ACTELION, PFIZER	Congrès de cardiologie en France ou à l'étranger - Congrés Européen ou Américain (AHA)	Ces dernières années		
0129	DE JONG	Hendrik-Jan	15/02/2009	LD-ODE	SERVIER	Conseiller scientifique	CDI		11/2008
0129	DE JONG	Hendrik-Jan	09/05/2006	LD	SCIENCE UNION - IRIS SERVIER	Directeur	CDI		
0129	DE JONG	Hendrik-Jan	26/04/2005	LD	INSTITUT DE RECHERCHES INTERNATIONALES	CDI			
0129	DE JONG	Hendrik-Jan	26/04/2005	LD	SCIENCE UNION (SERVIER)	CDI			
0129	DE JONG	Hendrik-Jan	26/04/2005	(Autre)	UNIVERSITE DE LEIDEN - Pays Bas	Professeur extraordinaire			
0129	DE JONG	Hendrik-Jan	26/04/2005	(Autre)	IUP - ingénierie de la santé - UNIVERSITE MONTPELLIER 1	Président conseil au perfectionnement			
0129	DE JONG	Hendrik-Jan	26/04/2005	(Autre)	UNIVERSITE HOSHI - Tokio - Japon	"visiting professor"			
0129	DE JONG	Hendrik-Jan	22/09/2003	LD	INSTITUT DE RECH. INTERNATIONALE SERVIER	CDI - Directeur Relations Scientifiques Internationales			
0129	DE JONG	Hendrik-Jan	22/09/2003	LD	SCIENCE UNION (SERVIER)	CDI			
0129	DE JONG	Hendrik-Jan	22/09/2003	(Autre)	UNIVERSITE DE LEIDEN - Pays Bas	Professeur honoraire			
0129	DE JONG	Hendrik-Jan	22/09/2003	(Autre)	UNIVERSITE HOSHI - Tokio - Japon	Professeur honoraire			
0129	DE JONG	Hendrik-Jan	22/09/2003	(Autre)	IUP UNIVERSITE MONTPELLIER 1	Président Conseil au perfectionnement			
0129	DE JONG	Hendrik-Jan	14/05/2003	LD	INSTITUT DE RECHERCHE INTERNATIONAL SERVIER	CDI			
0129	DE JONG	Hendrik-Jan	14/05/2003	LD	SCIENCE UNION (SERVIER)	CDI			
0129	DE JONG	Hendrik-Jan	14/05/2003	IP-AUT	Université Leiden (Pays-Bas)	Cours en Développement pharmaceutique			
0129	DE JONG	Hendrik-Jan	14/05/2003	IP-AUT	Université Montpellier	Président Conseil ou perfectionnement UIP Santé			
0129	DE JONG	Hendrik-Jan	14/05/2003	IP-AUT	Université Hoshi (Japon)	Conférences : Formulation/Excipients			
0129	DE JONG	Hendrik-Jan	14/05/2003	(Autre)		Membre USP Convention 2000-2005			
0129	DE JONG	Hendrik-Jan	14/05/2003	IP-AUT		Président International Pharmaceutical Excipients Council (IPEC)			
0129	DE JONG	Hendrik-Jan	19/06/2001	LD	IRIS (SERVIER)	Contrat permanent - Directeur Relations Scientifiques Internationales			
0129	DE JONG	Hendrik-Jan	19/06/2001	(Autre)	Université de Montpellier	Président du Conseil de Perfectionnement IUP Ingénierie de santé			
0129	DE JONG	Hendrik-Jan	19/06/2001	(Autre)	Université de Leyde, Pays-Bas	Professeur chimie analytique			
0129	DE JONG	Hendrik-Jan	01/01/1999	LD	SERVIER	Directeur Général des affaires pharmaceutiques internationales.			
0129	DE JONG	Hendrik-Jan	01/01/1999	LD		Professeur en chimie analytique - Université de Leiden, Pays-Bas.			
0129	DE JONG	Hendrik-Jan	01/01/1998	IP-RE	SERVIER	Expert dossiers chimie/pharmacie.			
0129	DE JONG	Hendrik-Jan	01/01/1999	IP-CF		Président Conseil en perfectionnement Sup ingenierie en santé - Montpellier.			
0129	DE JONG	Hendrik-Jan	01/01/1999	IP-AUT	IPEC-Europe	Membre actif IPEC-Europe (Association au sujet des excipients pharmaceutiques)			
0129	DE JONG	Hendrik-Jan	01/01/1998	LD	Servier				
0129	DE JONG	Hendrik-Jan	01/01/1998	IP-AUT	Servier				
0129	DE JONG	Hendrik-Jan	01/01/1998	IP-AUT	membre suppléant à la Pharmacopée européenne				
0129	DE JONG	Hendrik-Jan	01/01/1998	IP-AUT	Professeur Université Leider - Pays Bas				
60386	DE KORWIN	Jean Dominique	27/09/2010	EC-CO	ACTELION	Etude ITINERAIR II□□Etude épidémiologique BOSENTAN (TRACLEER)	Expérimentateur non principal	01/2005	12/2008
60386	DE KORWIN	Jean Dominique	27/09/2010	EC-CO	PIERRE FABRE	Etude multicentrique internationale randomisée en double aveugle contre placebo du milnacipran (IXEL) dar	Expérimentateur non principal	01/2006	12/2008
60386	DE KORWIN	Jean Dominique	27/09/2010	EC-CO	BMS	Essai ADOPT □□Etude multicentrique de phase 3 randomisée en double aveugle d'évaluation de la toléran	Expérimentateur non principal	01/2007	10/2010
60386	DE KORWIN	Jean Dominique	27/09/2010	EC-CO	BIAL	Efficacité et tolérance de l'acétate d'eslicarbazepine dans le traitement des patients atteints de fibromyalgie	Expérimentateur non principal	01/2009	12/2010
60386	DE KORWIN	Jean Dominique	27/09/2010	IP-CF	BIOPROJET	Paris : Conférence délégués médicaux sur infection à H. pylori	rémunération personnelle	09/2009	09/2009
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	LFB	Paris : 6èmes journées d'immunothérapie "Complications neurologiques des maladies auto-immunes"		11/2008	11/2008
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	LFB	Paris : 7èmes journées d'immunothérapie "Déficits immunitaires"		11/2009	11/2009
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	LFB	8èmes journées d'immunothérapie "Infections et dysimmunité"		11/2010	11/2010
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	GSK	Florence : 1st Systemic Sclerosis World Congress		02/2010	02/2010
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	ASTRA ZENECA	Paris : 13èmes rencontres pluridisciplinaires en gastroentérologie, cardiologie, pneumologie et rhumatologie "Regards sur éthique et médeci		10/2007	10/2007
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	ASTRA ZENECA	Paris : Journées Francophones d'Hépato-Gastroentérologie et d'Oncologie digestive.		03/2010	03/2010
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	ASTRA ZENECA	New Orleans : Congrès AGA		05/2010	05/2010
60386	DE KORWIN	Jean Dominique	27/09/2010	CF-AUD	ASTRA ZENECA	Barcelone : 18th United European Gastroenterology Week (UEGW)		10/2011	10/2011
60386	DE KORWIN	Jean Dominique	27/09/2010	VB	LABORATOIRE PIERRE FABRE	Honoraires essai MILNACIPRAN	Association des Chefs de Services du CHU de Nancy	01/2007	12/2008
60386	DE KORWIN	Jean Dominique	27/09/2010	(Autre)	GROUPE D'ETUDES FRANCAIS DES HELICOBACTER	Membre du conseil d'administration□□En cours	Groupe français de recherche sponsorisé par l'industrie pharmaceutique	01/1992	
60386	DE KORWIN	Jean Dominique	27/09/2010	(Autre)	PRIMED	Membre du conseil scientifique français et président de symposia	Société internationale organisatrice d'actions de FMC	01/2007	12/2008
60386	DE KORWIN	Jean Dominique	27/09/2010	(Autre)	FMC-EPP-Université (FMC-U)	Président du conseil d'administration□□En cours	Fédération des départements universitaires de FMC et d'EPP	01/2006	
60386	DE KORWIN	Jean Dominique	15/12/2009	LD-AR	JANSSEN CILAG	membre du "board panel",□□activité de conseil et organisation de réunions de formation des professionnels	rémunération personnelle	01/2000	12/2006
60386	DE KORWIN	Jean Dominique	15/12/2009	EC-INV	ASTRA ZENECA	étude STARS II ESOMEPRAZOLE(INEXIUM)	coordinateur national	01/2003	12/2005
60386	DE KORWIN	Jean Dominique	15/12/2009	EC-INV	ACTELION	étude ITINERAIR II□□étude épidémiologique BOSENTAN (TRACLEER)	expérimentateur non principal	01/2005	12/2008
60386	DE KORWIN	Jean Dominique	15/12/2009	EC-CO	PIERRE FABRE	Etude multicentrique internationale randomisée en double aveugle contre placebo du milnacipran (IXEL) dar	Expérimentateur non principal	01/2006	12/2008
60386	DE KORWIN	Jean Dominique	15/12/2009	EC-CO	BMS	Essai ADOPT, étude multicentrique de phase 3 randomisée en double aveugle d'évaluation de la tolérance	Expérimentateur non principal	01/2007	
60386	DE KORWIN	Jean Dominique	15/12/2009	EC-CO	BIAL	efficacité et tolérance de l'acétate d'eslicarbazepine dans le traitement des patients atteints de fibromyalgie :	Expérimentateur non principal	01/2009	
60386	DE KORWIN	Jean Dominique	15/12/2009	IP-AC	MAYOLI SPINDLER	HELIKIT : conseil pour extension AMM	Rémunération personnelle	01/2005	12/2005
60386	DE KORWIN	Jean Dominique	15/12/2009	IP-AC	BIOHIT	GASTROPANEL : conseil pour utilisation expérimentation en France	rémunération personnelle	01/2005	12/2006
60386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	JANSSEN CILAG	ST PETERSBOURG : symposium JANSSEN CILAG "IPP nouvelles données pratiques " (PARIET)	Rémunération personnelle	01/2005	01/2005
60386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	JANSSEN CILAG	SORRENTE : symposium JANSSEN CILAG " IPP nouvelles données, nouvelles pratiques " (PARIET)	rémunération personnelle	03/2005	03/2005
60386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	JANSSEN CILAG	MARRAKECH : symposium JANSSEN CILAG "IPP nouvelles données, nouvelles pratiques" (PARIET)	rémunération personnelle	09/2005	09/2005
60386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	JANSSEN CILAG	COLMAR : symposium JANSSEN CILAG " le RGO en question" (PARIET)	rémunération personnelle	04/2006	04/2006
60386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	JANSSEN CILAG	BERLIN : symposium JANSSEN CILAG "situations difficiles dans le RGO" (PARIET)	Rémunération personnelle	10/2006	10/2006
60386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	ASTRA ZENECA	VARSOVIE :congrès preuves et pratiques sur le RGO	rémunération insititution	03/2007	03/2007

d	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	SANOFI AVENTIS	CHAMONIX : 1ère régionale SANOFI AVENTIS en gastroentérologie "AINS et infection à HP " (INIPOMP)	rémunération personnelle	04/2005	04/2005
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	SANOFI AVENTIS	NANCY : manisfestation extra digestives du RGO	rémunération personnelle	06/2007	06/2007
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	MERCK SHARP DOHM (MSD)	LYON : réunion "recettes en rhumatologie : la corticothérapie	rémunération personnelle	10/2007	10/2007
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-INT	BIOPROJET	PARIS : conférence délégués médicaux sur infection à h pylori	rémunération personnelle	09/2009	09/2009
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-AUD	LFB	PARIS : 6èmes journées d'immunothérapie "complications neurologiques des maladies auto-immunes"		01/2008	12/2008
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-AUD	LFB	PARIS : 7èmes journées d'immunothérapie "déficits immunitaires"		01/2009	12/2009
0386	DE KORWIN	Jean Dominique	15/12/2009	CF-AUD	ASTRA ZENECA	PARIS : 13èmes rencontres pluridisciplinaires en gastroentérologie, cardiologie, pneumologie et rhumatologie " regards sur éthique et méde		10/2007	10/2007
0386	DE KORWIN	Jean Dominique	15/12/2009	VB	SOCIETE BCA	solde 53ème congrès de nancy de la société nationale française de médecine interne 2006	association des chefs de services du chu de Nancy	06/2006	12/2006
0386	DE KORWIN	Jean Dominique	15/12/2009	VB	LABORATOIRE PIERRE FABRE	honoraires essai MILNACIPRAN	association des chefs de services du chu de nancy	01/2007	12/2008
0386	DE KORWIN	Jean Dominique	15/12/2009	(Autre)	SOPHIA FONDATION D'ENTREPRISE GENEVRIER	Président du conseil d'administration (en cours)	fondation dont l'objectif est de réaliser ou de financer des actions indépendantes d'EPP ou de FMC (enregistrement préfecture en 2006)	01/2006	12/2006
0386	DE KORWIN	Jean Dominique	15/12/2009	(Autre)	GROUPE D'ETUDES FRANCAIS DES HELICOBACTER	membre du conseil d'administration	groupe français de recherche sponsorisé par l'industrie pharmaceutique	01/1992	
0386	DE KORWIN	Jean Dominique	15/12/2009	(Autre)	PRIMED	membre du conseil scientifique français et president de symposia	société internationale organisatrice d'actions de FMC	01/2007	12/2008
0386	DE KORWIN	Jean Dominique	15/12/2009	(Autre)	FMC-EPP-UNIVERSITE (FMC-U)	Président du conseil d'administration (en cours)	Fédération des départements universitaires du FMC et d'EPP	01/2006	
0386	DE KORWIN	Jean Dominique	31/07/2009	LD-AR	JANSSEN CILAG	Membre du "Board Pariet" activité de conseil et organisation de réunions de formation des professionnels d	rémunération personnelle	01/2000	12/2006
0386	DE KORWIN	Jean Dominique	31/07/2009	EC-INV	ASTRAZENECA	Etude STARS II ESOMEPRAZOLE (Inexium)	coordinateur national	01/2003	12/2005
0386	DE KORWIN	Jean Dominique	31/07/2009	EC-CO	ACTELION	Etude ITINERAIR II - étude épidémiologique Bosentan	expérimentateur non principal	01/2005	12/2008
0386	DE KORWIN	Jean Dominique	31/07/2009	EC-CO	PIERRE FABRE	Essais thérapeutiques multicentriques internationaux GE302-GE304 randomisés en double aveugle contre p	expérimentateur non principal	01/2006	12/2008
0386	DE KORWIN	Jean Dominique	31/07/2009	EC-CO	BMS	Essai ADOPT : essai thérapeutique multicentrique de phase 3 randomisé en double aveugle d'évaluation de	expérimentateur non principal	01/2007	
0386	DE KORWIN	Jean Dominique	31/07/2009	EC-CO	BIAL	Essai thérapeutique BIA-2093-210 phase II, multicentrique international, de l'Eslicarbazepine Acétate dans l	expérimentateur non principal	01/2009	
0386	DE KORWIN	Jean Dominique	31/07/2009	IP-AC	MAYOLI SPINDLER	HELIKIT - conseil pour extension AMM	rémunération personnelle	01/2005	12/2005
0386	DE KORWIN	Jean Dominique	31/07/2009	IP-AC	BIOHIT	GASTROPANEL : conseil pour utilisation expérimentation en France	rémunération personnelle	01/2005	12/2006
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	JANSSEN CILAG	Symposium Janssen Cilag " Le RGO en question" (PARIET) - Colmar	rémunération personnelle	04/2006	04/2006
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	JANSSEN CILAG	Symposium Janssen Cilag " Situations difficiles dans le RGO" (PARIET) -Berlin	rémunération personnelle	10/2006	10/2006
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	ASTRAZENECA	Congrès Preuves et Pratiques sur le RGO - Varsovie	rémunération personnelle	03/2007	03/2007
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	SANOFI AVENTIS	Manifestations extra-digestives du RGO - Nancy	rémunération personnelle	06/2007	06/2007
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	MERCK SHARP DOHM	Réunions " Recettes en rhumatologie : la corticothérapie" - Lyon	rémunération personnelle	10/2007	10/2007
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	PRIMED	Organisation de deux réunions de FMC à Paris	rémunération personnelle	01/2007	12/2008
0386	DE KORWIN	Jean Dominique	31/07/2009	CF-INT	TERRE NEUVE	Organisation d'une réunion de FMC à Nancy	rémunération personnelle	01/2008	12/2008
0386	DE KORWIN	Jean Dominique	31/07/2009	VB	SOCIETE BCA	Solde 53ème congrès de Nancy de la Société Nationale Française de la Medecine Interne 2006	Associations des Chefs de services du CHU de Nancy	06/2006	06/2006
0386	DE KORWIN	Jean Dominique	31/07/2009	VB	PIERRE FABRE	Honoraires essai Milnacipran	Associations des Chefs de services du CHU de Nancy	01/2007	12/2008
0386	DE KORWIN	Jean Dominique	31/07/2009	(Autre)	SOPHIA FONDATION D'ENTREPRISE GENEVRIER	Président du conseil d'administration	Fondation dont l'objectif est de réaliser ou de financer des actions indépendantes d'EPP ou de FMC (enregistrement préfecture en 2006)	01/2006	12/2006
0386	DE KORWIN	Jean Dominique	31/07/2009	(Autre)	GROUPE D'ETUDES FRANCAIS DES HELICOBACTER	Membre du conseil d'administration	Groupe français de recherche sponsorisé par l'industrie pharmaceulique	01/1992	
0386	DE KORWIN	Jean Dominique	31/07/2009	(Autre)	PRIMED	Membre du conseil scientifique français	Société internationale organisatrice d'actions de FMC	01/2007	12/2008
0386	DE KORWIN	Jean Dominique	31/07/2009	(Autre)	FMC-EPP-UNIVERSITE	Président du conseil d'administration	Fédération des départements universitaires de FMC et d'EPP	01/2006	
0386	DE KORWIN	Jean Dominique	31/07/2009	(Autre)	UFR MEDECINE NANCY- DEPARTEMENT DE FORMATION PERMANENTE	Co-directeur	Organisation d'actions de FMC sponsorisées par l'industrie pharmaceutique	01/1992	
0386	DE KORWIN	Jean Dominique	09/03/2009	LD-AR	JANSSEN CILAG	MEMBRE DU " BOARD PARIET ". ACTIVITE DE CONSEIL ET ORGANISATION DE REUNIONS DE FORM	REMUNERATION PERSONNELLE	01/2000	12/2006
0386	DE KORWIN	Jean Dominique	09/03/2009	EC-INV	ASTRA ZENECA	ETUDE STARS II ESOMEPRAZOLE (INEXIUM)	COORDINATEUR NATIONAL	01/2003	12/2005
0386	DE KORWIN	Jean Dominique	09/03/2009	EC-CO	ACTELION	ETUDE ITINERAIR II. ETUDE EPIDEMIOLOGIQUE BOSENTAN	EXPERIMENTATEUR NON PRINCIPAL	01/2005	12/2008
0386	DE KORWIN	Jean Dominique	09/03/2009	EC-CO	PIERRE FABRE	ESSAIS THERAPEUTIQUES MULTICENTRIQUES INTERNATIONAUX GE302-GE304 RANDOMISES EN I	EXPERIMENTATEUR NON PRINCIPAL	01/2006	12/2008
0386	DE KORWIN	Jean Dominique	09/03/2009	EC-CO	BMS	ESSAI ADOPT : ESSAI THERAPEUTIQUE MULTICENTRIQUE DE PHASE 3 RANDOMISE EN DOUBLE A'	EXPERIMENTATEUR NON PRINCIPAL	01/2007	
0386	DE KORWIN	Jean Dominique	09/03/2009	EC-CO	BIAL	Essai thérapeutique BIA-2093-210 phase II, multicentrique international, de l'Eslicarbazepine Acétate dans l	Expérimentateur non principal	01/2009	
0386	DE KORWIN	Jean Dominique	09/03/2009	IP-AC	MAYOLI SPINDLER	HELIKIT. Conseil pour extension AMM	Rémunération personnelle	01/2005	12/2005
0386	DE KORWIN	Jean Dominique	09/03/2009	IP-AC	BIOHIT	GASTROPANEL. Conseil pour utilisation expérimentation en France	Rémunération personnelle	01/2005	12/2006
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	JANSSEN CILAG	COLMAR : Symposium JANSSEN CILAG "Le RGO en question" (PARIET)	Rémunération personnelle	04/2006	04/2006
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	JANSSEN CILAG	BERLIN : Symposium JANSSEN CILAG "situations difficiles dans le RGO"(PARIET)	Rémunération personnelle	10/2006	10/2006
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	ASTRA ZENECA	VARSOVIE : Congrès Preuves et Pratiques sur le RGO	Rémunération personnelle	03/2007	03/2007
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	SANOFI AVENTIS	NANCY : Manifestations extra-digestives du RGO	Rémunération personnelle	06/2007	06/2007
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	MERCK/SHARP/DOHM/(MSD)	LYON : Réunion "Recettes en Rhumatologie : la corticothérapie"	Rémunération personnelle	10/2007	
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	PRIMED	Organisation de deux réunions de FMC à Paris	Rémunération personnelle	01/2007	12/2008
0386	DE KORWIN	Jean Dominique	09/03/2009	CF-INT	TERRE NEUVE	Organisation d'une réunion de FMC à Nancy	Rémunération personnelle	01/2008	12/2008
0386	DE KORWIN	Jean Dominique	09/03/2009	VB	SOCIETE BCA	Solde 53ème congrès de Nancy de la Société Nationale Française de Médecine Interne 2006	Association des chefs de Services du CHU de Nancy	06/2006	12/2006

id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60386	DE KORWIN	Jean Dominique	09/03/2009	VB	PIERRE FABRE	Honoraires essai MILNACIPRAN	Association des chefs de Services du CHU de Nancy	01/2007	12/2008
60386	DE KORWIN	Jean Dominique	09/03/2009	(Autre)	SOPHIA Fondation d'entreprise Genevrier	Président du conseil d'administration	Fondation dont l'objectif est de réaliser ou de financer des actions indépendantes d'EPP ou de FMC (enregistrement préfecture en 2006	01/2006	12/2009
60386	DE KORWIN	Jean Dominique	09/03/2009	(Autre)	Groupe d 'Etude Français des Helicobacter	Membre du conseil d'administration (en cours)	Groupe français de recherche sponsorisé par l'industrie pharmaceutique	01/1992	
60386	DE KORWIN	Jean Dominique	09/03/2009	(Autre)	PRIMED	Membre du conseil scientifique français	Société internationale organisatrice d'actions de FMC	01/2007	12/2008
60386	DE KORWIN	Jean Dominique	09/03/2009	(Autre)	FMC-EPP-Université (FMC-U)	Président du conseil d'administration (en cours)	Fédération des départements universitaires de FMC et d'EPP	01/2006	
60386	DE KORWIN	Jean Dominique	09/03/2009	(Autre)	Département de formation permanente UFR Médecine Nancy	Co-directeur (en cours)	Oraganisation d'actions de FMC sponsorisées par l'industrie pharmaceutique	01/1992	
60386	DE KORWIN	Jean Dominique	10/11/2008	LD-AR	JANSSEN CILAG	Membre du "Board Pariet" activité de conseil et organisation de réunions de formation des professionnels de	rémunération personnelle	01/2000	12/2006
60386	DE KORWIN	Jean Dominique	10/11/2008	EC-INV	ASTRAZENECA	Etude STARS II ESOMEPRAZOLE (Inexium)	coordinateur principal	01/2003	12/2005
60386	DE KORWIN	Jean Dominique	10/11/2008	EC-CO	ACTELION	Etude ITINERAIR II - étude épidémiologique BOSENTAN (TRACLEER)	expérimentateur non principal	01/2005	12/2008
60386	DE KORWIN	Jean Dominique	10/11/2008	EC-CO	PIERRE FABRE	Etude multicentrique internationale randomisée en double aveugle contre placebo du milnacipran (IXEL) dar	expérimentateur non principal	01/2006	12/2008
60386	DE KORWIN	Jean Dominique	10/11/2008	EC-CO	BMS	Essai ADOPT : étude mullicentrique de phase 3 randomisée en double aveugle d'évaluation de la tolérance	expérimentateur non principal	01/2007	
60386	DE KORWIN	Jean Dominique	10/11/2008	IP-AC	MAYOLI SPINDLER	HELIKIT - Conseil pour extension AMM	rémunération personnelle	01/2005	12/2005
60386	DE KORWIN	Jean Dominique	10/11/2008	IP-AC	BIOHIT	Gastropanel - conseil pour utilisation expérimentation en France	rémunération personnelle	01/2005	12/2006
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	JANSSEN CILAG	Symposium JANSSEN CILAG " IPP nouvelles données, nouvelles pratiques" (PARIET) - St Petersbourg	rémunération personnelle	01/2005	01/2005
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	JANSSEN CILAG	Symposium JANSSEN CILAG "IPP nouvelles données, nouvelles pratiques " (PARIET) - Sorrente	rémunération personnelle	03/2005	03/2005
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	JANSSEN CILAG	Symposium JANSSEN CILAG " IPP nouvelles données, nouvelles pratiques" (PARIET) - Marrakech	rémunération personnelle	09/2005	09/2005
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	JANSSEN CILAG	Symposium JANSSEN CILAG " Le RGO en question " (PARIET) - Colmar	rémunération personnelle	04/2006	04/2006
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	JANSSEN CILAG	Symposium JANSSEN CILAG " Situations difficiles dans le RGO" (PARIET) - Berlin	rémunération personnelle	10/2006	10/2006
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	ASTRAZENECA	Congrès Preuves et pratiques sur le RGO - Varsovie	rémunération personnelle	03/2007	03/2007
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	SANOFI AVENTIS	1ère régionale SANOFI AVENTIS en gastroentérologie " AINS et infection à Hp" (INIPOMP) - Chamonix	rémunération Institution	04/2005	04/2005
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	SANOFI AVENTIS	Manifestations extra-digestives du RGO - Nancy	rémunération personnelle	06/2007	06/2007
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-INT	MERCK SHARP DOHM (MSD)	Réunion " Recettes en rhumatologie : la corticothérapie" - Lyon	rémunération personnelle	10/2007	10/2007
60386	DE KORWIN	Jean Dominique	10/11/2008	CF-AUD	ASTRAZENECA	13ème rencontres pluridisciplinaires en gastroentérologie, cardiologie, pneumologie et rhumatologie " Regards sur éthique et médecine" - Pa		10/2007	10/2007
60386	DE KORWIN	Jean Dominique	10/11/2008	VB	SOCIETE BCA	53ème congrès de Nancy de la Société Nationale Française de Médecine Interne 2006	Asssociation des chefs de Services du CHU de Nancy	06/2006	06/2006
60386	DE KORWIN	Jean Dominique	10/11/2008	VB	PIERRE FABRE	Honoraires essai MILNACIPRAN	Association des chefs de Services du CHU de Nancy	01/2007	12/2008
60386	DE KORWIN	Jean Dominique	10/11/2008	(Autre)	SOPHIA FONDATION D'ENTREPRISE GENEVRIER	Président du conseil d'administration	Fondation dont l'objectif est de réaliser ou de financer des actions indépendantes d'EPP ou de FMC (enregistrement préfecture en 2006)	01/2006	12/2006
60386	DE KORWIN	Jean Dominique	10/11/2008	(Autre)	Groupe d'Etudes Français des Helicobacter	Membre du conseil d'administration	Groupe Français de recherche sponsorisé par l'industrie pharmaceutique	01/1992	
60386	DE KORWIN	Jean Dominique	10/11/2008	(Autre)	PRIMED	Membre du conseil scientifique français et président de symposia	Société internationale organisatrice d'actions de FMC	01/2007	
60386	DE KORWIN	Jean Dominique	10/11/2008	(Autre)	FMC EPP-Université (FMC -U)	Président du conseil d'administration	Fédération des départements universitaires de FMC et d'EPP	01/2006	
60386	DE KORWIN	Jean Dominique	12/12/2007	CF-INT	SANOFI AVENTIS	Manifestations extra-digestives du RGO - Nancy	Aucune rémunération	06/2007	06/2007
60386	DE KORWIN	Jean Dominique	22/11/2007	CF-INT	MERCK SHARP DOHM (MSD)	LYON : Réunion "Recettes en Rhumatologie : la cortocothérapie"	Rémunération personnelle	10/2007	10/2007
60386	DE KORWIN	Jean Dominique	22/11/2007	CF-INT	ASTRA ZENECA	VARSOVIE : Congrès Preuves et Pratiques sur le RGO	Rémunération personnelle/institution	03/2007	03/2007
60386	DE KORWIN	Jean Dominique	22/11/2007	CF-INT	JANSSEN CILAG	ROME: Symposium satellite JFPD « nouvelle stratégie » (PARIET)	Aucune rémunération	01/2005	01/2005
60386	DE KORWIN	Jean Dominique	22/11/2007	CF-INT	JANSSEN CILAG	PARIS : Symposium satellite JFPD « Dyspepsie, RGO, Coxib» (PARIET)	Aucune rémunération	04/2004	04/2004
60386	DE KORWIN	Jean Dominique	22/11/2007	IP-AC	BIOHIT	GASTROPANEL□□Conseil pour utilisation expérimentation en France□□	Rémunération personnelle	01/2005	12/2006
60386	DE KORWIN	Jean Dominique	22/11/2007	CF-INT	JANSSEN CILAG	PARIS : Symposium satellite JFPD « Eradication de Hp et RGO : le pour » (PARIET)□□□□	Rémunération personnelle	03/2003	03/2003
60386	DE KORWIN	Jean Dominique	22/11/2007	IP-AC	MAYOLI SPINDLER	HELIKIT□□Conseil pour extension AMM□□	Rémunération personnelle	01/2005	12/2005
60386	DE KORWIN	Jean Dominique	22/11/2007	EC-CO	PIERRE FABRE	Etude multicentrique internationale randomisée en double aveugle contre placebo du milnacipran (IXEL) dar	Expérimentateur non principal	01/2006	12/2007
60386	DE KORWIN	Jean Dominique	22/11/2007	EC-CO	ACTELION	Etude ITINERAIR II□□Etude épidémiologique BOSENTAN□□(TRACLEER)□□	Expérimentateur non principal	01/2005	12/2007
60386	DE KORWIN	Jean Dominique	22/11/2007	EC-INV	ASTRA ZENECA□	Etude STARS II ESOMEPRAZOLE□□(INEXIUM)□□□	coordinateur national□	01/2003	12/2005
60386	DE KORWIN	Jean Dominique	22/11/2007	EC-INV	ASTRA ZENECA	Etude STARS II ESOMEPRAZOLE□□(INEXIUM)□□	coordinateur national	01/2003	12/2005
60386	DE KORWIN	Jean Dominique	22/11/2007	LD-AR	JANSSEN CILAG	Membre du "BOARD PARIET"□□Activité de conseil et organisation de réunions de formation des profession	Rémunération Institution	01/2000	12/2006
60386	DE KORWIN	Jean Dominique	27/04/2007	CF-INT	SANOFI-AVENTIS France	Les troubles induits dans les formes atypiques du RGO - Réunion "Manifestations extra-digestives du RGO", Nancy		06/2007	06/2007
60386	DE KORWIN	Jean Dominique	22/11/2006	VB	Société BCA	Solde 53ème congrès de Nancy de la Société Nationale Française de Médecine Interne 2006		06/2006	06/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	LD-AR	JANSSEN CILAG	Membre du « BOARD PARIET » Activité de conseil et organisation de réunions de formation des profession	Rémunération personnelle	01/2000	12/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	EC-INV	ASTRA ZENECA	Etude STARS II ESOMEPRAZOLE (INEXIUM) - coordinateur national		01/2003	12/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	EC-CO	ACTELION	Etude ITINERAIR II - Etude épidémiologique BOSENTAN (TRACLEER)	Expérimentateur non principal	01/2005	
60386	DE KORWIN	Jean Dominique	13/06/2006	EC-CO	PIERRE FABRE	Etude multicentrique internationale randomisée en double aveugle contre placebo du milnacipran (IXEL) dar	Expérimentateur non principal	01/2006	
60386	DE KORWIN	Jean Dominique	13/06/2006	IP-AC	MAYOLI SPINDLER	HELIKIT - Conseil pour extension d'AMM	Rémunération personnelle	01/2005	12/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	IP-AC	BIOHIT	GASTROPANEL - Conseil pour utilisation expérimentation en France	Rémunération personnelle	01/2005	12/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	PARIS : Symposium satellite JFPD « Eradication de Hp et RGO : le pour » (PARIET)	Rémunération personnelle	03/2003	03/2003
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	PARIS : Symposium satellite JFPD « Dyspepsie, RGO, coxib » (PARIET)	Rémunération personnelle	04/2004	04/2004
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	ROME : Symposium Janssen Cilag « Nouvelle stratégie » (PARIET)	Rémunération personnelle	03/2004	03/2004
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	ST PETERSBOURG : Symposium Janssen Cilag « IPP nouvelles données, nouvelles pratiques » (PARIET)	Rémunération personnelle	01/2005	01/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	SORRENTE : Symposium Janssen Cilag « IPP nouvelles données, nouvelles pratiques » (PARIET)	Rémunération personnelle	03/2005	03/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	MARRAKECH : Symposium Janssen Cilag « IPP nouvelles données, nouvelles pratiques » (PARIET)	Rémunération personnelle	09/2005	09/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	COLMAR : Symposium Janssen Cilag « Le RGO en question» (PARIET)	Rémunération personnelle	04/2006	04/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	JANSSEN CILAG	BERLIN : Symposium Janssen Cilag « Situations difficiles dans le RGO » (PARIET)	Rémunération personnelle	10/2006	10/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	ASTRA ZENECA	PARIS : Avancées en gastroentérologie « que surveiller après éradication de Hp » (INEXIUM)	Rémunération personnelle	12/2004	12/2004
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-INT	SANOFI AVENTIS	CHAMONIX : 1ère régionale SANOFI AVENTIS en gastroentérologie « AINS et infection à Hp » (INIPOMP)	Rémunération personnelle	04/2005	04/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	ASTRA ZENECA	PARIS : JFPD symposium satellite "symptômes digestifs hauts et lésions muqueuses : quelle relation ? » (INEXIUM)		04/2004	04/2004
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	ASTRA ZENECA	PARIS : Rencontre en gastroentérologie et rhumatologie workshop (INEXIUM)		10/2005	10/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	BIOHIT	PARIS : Réunion FMC « Diagnostic non invasif de l'atrophie gastrique »		03/2005	03/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	ALTANA	PARIS : JFPD symposium satellite (EUPANTOL)		04/2005	04/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	SANOFI SYNTHELABO	CHAMONIX : 1ères Régionales en gastro-entérologie en gastroentérologie « AINS et infection à Hp » (INIPOMP)		06/2005	06/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	SANOFI AVENTIS	NANTES : 52ème congrès français de Médecine Interne (SNFMI)		10/2005	10/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	ASTRA ZENECA	PARIS : XIIèmes Rencontres en Gastro-entérologie et Rhumatologie. Workshop « Autour du bénéfice – risque des médicaments en 2005 »			01/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	JANSSEN CILAG	MONTREAL : 11ème congrès mondial de gastroentérologie - symposium satellite (PARIET)		09/2005	09/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	JANSSEN CILAG	COPENHAGUE : 13ème United European Gastroenterology Week (UEGW)		10/2005	10/2005
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	BAXTER	PARIS : Symposium "Traitement par immunoglobulines, actualités thérapeutiques, indications et bonnes pratiques"		09/2006	09/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	LFB	PARIS : 4ème journée d'immunothérapie		10/2006	10/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	SANOFI AVENTIS	PARIS : 1ères Assises d'Oncologie Digestive		10/2006	10/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	CF-AUD	ASTRA ZENECA	PARIS : 13èmes rencontres pluridisciplinaires en gastroentérlogie, Cardiologie, Pneumologie et rhumatologie « Regards sur éthique et méde		10/2006	10/2006
60386	DE KORWIN	Jean Dominique	13/06/2006	(Autre)	SOPHIA Fondation d'entreprise Génévrier	Président du conseil d'administration (fondation dont l'objectif est de réaliser ou de financer des actions indépendantes d'EPP ou de FMC - e		01/2006	12/2006
60386	DE KORWIN	Jean Dominique	10/10/2005	RE-DE	AFSSAPS	groupe de travail NHG	titulaire		
60386	DE KORWIN	Jean Dominique	10/10/2005	RE-DE	AFSSAPS	groupe de travail DM	titulaire		
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-EC	ACTELION	essai thérapeutique en cours			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-EC	ASTRA ZENECA	essais thérapeutiques passés			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-EC	JANSSEN CILAG	essais thérapeutiques passés			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-EC	SANOFI AVENTIS	essais thérapeutiques passés			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AC	JANSSEN CILAG	groupe de travail Rabéprazole			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AC	MAYOLI SPINDLER	1 réunion conseil			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AC	BIOHIT	conseil GASTROPANEL			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-CF	ASTRA ZENECA	conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-CF	JANSSEN CILAG	conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-CF	SANOFI AVENTIS	conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-CF	ACTELION	financement réunions			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-CF	LFB	conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-CF	BIOHIT	conférence FMC			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AUT	ASTRA ZENECA	Frais de congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AUT	JANSSEN CILAG	Frais de congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AUT	SANOFI AVENTIS	Frais de congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	10/10/2005	IP-AUT	LFB	Colloques organisés par les laboratoires			
60386	DE KORWIN	Jean Dominique	10/10/2005	VB	ASTRA ZENECA	association des chefs de services du CHU de Nancy (essai thérapeutique)			
60386	DE KORWIN	Jean Dominique	10/10/2005	VB	ACTELION	association des chefs de services du CHU de Nancy			
60386	DE KORWIN	Jean Dominique	22/09/2005	IP-EC	ACTELION	Essai thérapeutique en cours			
60386	DE KORWIN	Jean Dominique	22/09/2005	IP-EC	SANOFI AVENTIS	essais thérapeutiques passés			
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-EC	ASTRA ZENECA	essais thérapeutiques passés			12/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-EC	JANSSEN CILAG	essais thérapeutiques passés			12/2004
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-RE		pas de projet en cours, ni au cours des 5 dernières années			
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AC	JANSSEN CILAG	Groupe de travail Rabéprazole (groupe renouvelable)			12/2006
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AC	MAYOU SPINDLER	1 réunion de conseil (extension d'AMM)			12/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AC	BIO-HIT	Conseil gastropanel			12/2006
60386	DE KORWIN	Jean Dominique	22/08/2005	CF-INT	ASTRA ZENECA	conférences, actions de formation			12/2004
60386	DE KORWIN	Jean Dominique	22/08/2005	CF-INT	JANSSEN CILAG	conférences, actions de formation (2003, 2004)			09/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	CF-INT	SANOFI AVENTIS	conférences, actions de formation			04/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-CF	ACTELION	Financement réunions (recherche)			
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-CF	LFB	conférences, actions de formation : myopathie inflammatoire			12/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	CF-AUD	BIOHIT	Conférence FMC : Atrophie gastrique			03/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AUT	ASTRA ZENECA	Frais de congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AUT	JANSSEN CILAG	Frais de congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AUT	SANOFI AVENTIS	Frais de congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	22/08/2005	IP-AUT	LFB	colloques organisés par les laboratoires			
60386	DE KORWIN	Jean Dominique	22/08/2005	VB	ASTRA ZENECA	Association des chefs de service du CHU de Nancy (essai thérapeutique Inexium)			12/2005
60386	DE KORWIN	Jean Dominique	22/08/2005	VB	ACTELION	Association des chefs de services du CHU de Nancy			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-EC	ASTRA ZENECA	Essais thérapeutiques passés ou en cours (INEXIUM)			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-EC	JANSSEN CILAG	Essais thérapeutiques projet en cours (PARIET)			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-RE		Pas de projet en cours, ni au cours des 5 dernières années			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-AC	JANSSEN CILAG	Groupe de travail PARIET			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-CF	ASTRA ZENECA	Conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-CF	JANSSEN CILAG	Conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	19/07/2004	IP-CF	SANOFI SYNTHELABO	Présidence symposiums			
60386	DE KORWIN	Jean Dominique	19/07/2004	(Autre)	ASTRA ZENECA	Frais congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	19/07/2004	(Autre)	JANSSEN CILAG	Frais congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	19/07/2004	(Autre)	TAKEDA - SERVIER - AVENTIS	FMC sponsorisée			
60386	DE KORWIN	Jean Dominique	19/07/2004	(Autre)	IPSEN	Colloque organisé par le laboratoire			
60386	DE KORWIN	Jean Dominique	19/07/2004	(Autre)	AVENTIS / LFB		Colloque organisé par le laboratoire		
60386	DE KORWIN	Jean Dominique	19/07/2004	PAR	AVENTIS	Essai thérapeutique n'ayant pas abouti à inclusion et rémunération			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-EC	ASTRA ZENECA	Essais thérapeutiques passés ou en cours (Inexium R)			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-EC	JANSSEN CILAG	Essais thérapeutiques projet en cours (Pariet R)			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-RE		Pas de projet en cours, ni au cours des 5 dernières années			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-AC	JANSSEN CILAG	Groupe de travail Pariet R			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-CF	ASTRA ZENECA	Conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-CF	JANSSEN CILAG	Conférences, actions de formation			
60386	DE KORWIN	Jean Dominique	04/05/2004	IP-CF	SANOFI SYNTHELABO	Présidence symposiums			
60386	DE KORWIN	Jean Dominique	04/05/2004	(Autre)	ASTRA ZENECA	Frais congrès, symposiums, FMC			
60386	DE KORWIN	Jean Dominique	04/05/2004	(Autre)	JANSSEN CILAG	Frais congrès, symposiums, FMC			

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#	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
0386	DE KORWIN	Jean Dominique	04/05/2004	(Autre)	TAKEDA - SERVIER - AVENTIS	FMC sponsorisé			
0386	DE KORWIN	Jean Dominique	04/05/2004	(Autre)	IPSEN	Colloque organisé par le laboratoire			
0386	DE KORWIN	Jean Dominique	04/05/2004	(Autre)	AVENTIS - LFB	Colloques organisés par les laboratoire			
0386	DE KORWIN	Jean Dominique	04/05/2004	VB	ASTRA ZENECA	Association chefs de services du CHU de Nancy			
0386	DE KORWIN	Jean Dominique	04/05/2004	(Autre)	AVENTIS	Essai thérapeutique n'ayant pas abouti à inclusion et rémunération			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-EC	ASTRA ZENECA	Essais thérapeutiques passés ou en cours - Inexium			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-EC	JANSSEN CILAG	Essais thérapeutiques - projet en cours - pariet			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-AC	JANSSEN CILAG	Groupe de travail Pariet			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-CF	ASTRA ZENECA	Conférences, actions de formation			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-CF	JANSSEN CILAG	Conférences, actions de formation			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-CF	SANOFI SYNTHELABO	Présidence symposium			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-AUT	ASTRA ZENECA	Frais congrès, symposiums, FMC			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-AUT	JANSSEN CILAG	Frais congrès, symposiums, FMC			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-AUT	TAKEDA/SERVIER/AVENTIS	FMC sponsorisées			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-AUT	IPSEN	Colloque organisé par le laboratoire;			
0386	DE KORWIN	Jean Dominique	18/09/2003	IP-AUT	AVENTIS/LFB	Colloques organisés par les laboratoires			
0386	DE KORWIN	Jean Dominique	18/09/2003	(Autre)	AVENTIS	Essai thérapeutique n'ayant pas abouti à inclusion et rémunération			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-EC	ASTRA ZENECA	(En cours) Essai multicentrique STARS II (ezomeprazole et dyspepsie) = coordonnateur national			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-EC	AVENTIS	(En cours) Essai multicentrique EXCLAIM (enoxaparine en prévention MTEU) = investigateur principal			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-RE		Actuellement non			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-RE		Membre conseil scientifique - Formation Rofensorwolle conventionnelle - évaluation des actions de formations régionales			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-AC	JANSSEN-CILAG	Membre d'un groupe d'experts			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-CF	JANSSEN-CILAG	Symposium médecine générale à Séville (1-2/02/2003) : les nouveaux IPP			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-CF	JANSSEN-CILAG	Symposium satellite Journées francophones de Pathologie digestive (29/03/2003) : Helicobacter pylori, controverses RGO			
0386	DE KORWIN	Jean Dominique	15/01/2003	IP-CF	Sociétés Savantes	Conférence H. Pylori, Pathologie digestive			
0386	DE KORWIN	Jean Dominique	15/01/2003	VB	ASTRA ZENECA	Essai (nouvel anti-thrombotique) - co-investigateur (terminé fin 2002)			
0386	DE KORWIN	Jean Dominique	05/07/2000	IP-EC	ASTRA ZENECA	Essai thérapeutique			
0386	DE KORWIN	Jean Dominique	05/07/2000	IP-EC	JANSSEN-CILAG	Essai thérapeutique			
0386	DE KORWIN	Jean Dominique	05/07/2000	IP-EC	AVENTIS	Essai thérapeutique			
0386	DE KORWIN	Jean Dominique	05/07/2000	IP-CF	ASTRA ZENECA	Pathologies digestives - H pylori			
0386	DE KORWIN	Jean Dominique	05/07/2000	IP-CF	JANSSEN-CILAG	Pathologies digestives - H Pylori			
0386	DE KORWIN	Jean Dominique	05/07/2000	IP-CF	AVENTIS	Pathologie digestive - Thrombose - Corticothérapie			
0386	DE KORWIN	Jean Dominique	05/07/2000	VB	ASTRA ZENECA	Association chef de service du CHU de Nancy			
0386	DE KORWIN	Jean Dominique	05/07/2000	VB	JANSSEN-CILAG	Association chef de service du CHU de Nancy			
0386	DE KORWIN	Jean Dominique	05/07/2000	VB	AVENTIS	Groupe d'études français des hélicobacters			
2345	DE KORWIN	Gérard							
2458	DE LA GASTINE	Blandine	22/03/2010	CF-INT	LUNDBECK	Fiers - FMC pour des médecins généralistes : "les médicaments Psychotropes en Gériatrie" . Pas de produit Aucune rémunération		06/2010	
2458	DE LA GASTINE	Blandine	22/03/2010	CF-AUD	SERVIER	Séminaire de Pharmacologie clinique sur la maladie Alzheimer en décembre 2010 (Vaux de Cernay)		12/2010	12/2010
2458	DE LA GASTINE	Blandine	30/04/2009	Néant					
2458	DE LA GASTINE	Blandine	21/04/2008	Néant					
2458	DE LA GASTINE	Blandine	16/04/2007	Néant					
2458	DE LA GASTINE	Blandine	09/01/2006	CF-AUD	NOVARTIS	formation de DESC de Gériatrie à Lille en mai 2006 · organisation par le Pr PUISIEUX □□(séminaire national)		05/2006	05/2006
2458	DE LA GASTINE	Blandine	21/10/2004	PAR	DOLISOS	1 soeur pharmacienne			
2458	DE LA GASTINE	Blandine	18/03/2004	PAR	DOLISOS (PIERRE FABRE)	Soeur pharmacien			
3025	DE LEERSNYDER	Hélène	06/01/2010	EC-INV	SERVIER	Agomélatine	Investigateur principal	01/2004	12/2008
1777	DE VERNEJOUL	Marie-Christine	14/12/2005	LD-AR	SERVIER	Expert Protelos	Rémunération personnelle	10/2005	10/2006
1777	DE VERNEJOUL	Marie-Christine	14/12/2005	EC-INV	PROCTER ET GAMBLE	Etude pré-clinique Actonel	Investigateur principal	09/2005	06/2007
1777	DE VERNEJOUL	Marie-Christine	14/12/2005	EC-CO	LILLY	Etude clinique Forsteo	Co-investigateur	01/2006	12/2008
1777	DE VERNEJOUL	Marie-Christine	14/12/2005	RE-AUT	NOVARTIS	Acide zoledronique omso (effets secondaires)	Rémunération personnelle	10/2004	10/2007
1777	DE VERNEJOUL	Marie-Christine	14/12/2005	CF-INT	PROCTER ET GAMBLE	SFR 2004 Paris	Rémunération personnelle	10/2004	10/2004
1777	DE VERNEJOUL	Marie-Christine	14/12/2005	CF-INT	SERVIER	Congrès contre l'ostéoporose Tunis	Rémunération personnelle	10/2005	10/2005
0131	DE VERNEJOUL	Dominique	01/01/1999	LD		Cardiologue à la Ville de Paris.			
0131	DE VERNEJOUL	Dominique	01/01/1999	IP-CF		Occasionels, pour des organismes professionnels.			
0131	DE VERNEJOUL	Dominique	01/01/1998	PAR		Interventions non rémunérées.			
0133	DEBRAY	Quentin	28/04/2004	LD	PFIZER	Comité de rédaction de la revue "Dépression"			
0133	DEBRAY	Quentin	16/11/2003	IP-AUT	GLAXO SMITHKLINE	Membre du Jury du prix Pelicier (sans rémunération régulière)			
0133	DEBRAY	Quentin	16/11/2003	IP-AUT	PFIZER	Membre du comité de rédaction de la revue " DEPRESSION" (sans rémunération)			
0133	DEBRAY	Quentin	11/07/2000	IP-CF	LILLY	23 mai 2000 - enseignement parauniversitaire			
0133	DEBRAY	Quentin	11/07/2000	IP-CF	BEECHAM	20 avril 2000 - enseignement post universitaire			
0133	DEBRAY	Quentin	11/07/2000	IP-AUT	PFIZER	Membre du comité de rédaction du Journal Dépression			
0133	DEBRAY	Quentin	11/07/2000	IP-AUT	SMITHKLINE BEECHAM	Membre du jury au prix Félicien			
0133	DEBRAY	Quentin	11/07/2000	IP-AUT	ORGANON	Prise en charge du voyage et congrès à l'ECNP (Londres, 1999)			
0133	DEBRAY	Quentin	11/07/2000	IP-AUT	PFIZER	Prise en charge du voyage et congrès de l'APA (Chicago, 2000)			
0133	DEBRAY	Quentin	11/07/2000	(Autre)	SKB, PFIZER, ORGANON, AVENTIS, PHARMACIA UPJOHN, LUNDBECK, NOVARTIS	J'ai présidé le comité d'organisation du 4° congrès européen sur les troubles de la personnalité (Paris, Juin 2000)			
0133	DEBRAY	Quentin	01/01/1999	IP-EC	PIERRE FABRE	Etude Oedipe			
0133	DEBRAY	Quentin	01/01/1999	IP-CF	ZENECA	Dysfonctions sexuelles et dépression (1997)			
0133	DEBRAY	Quentin	01/01/1999	IP-AUT	PFIZER	World Congress of biological Psychiatry, Nice - Juin 1997			
0133	DEBRAY	Quentin	01/01/1999	IP-AUT	KNOLL	European College of Biological Psychopharmacology, Vienne, sept. 1997			
0133	DEBRAY	Quentin	01/01/1999	VB	AROIX Médical	Journée scientifique à l'hôpital Laënnec - Fondation IPSEN	fondation ipsen		
0133	DEBRAY	Quentin	01/01/1999	VB	CIBA GEIGY	Fondation IPSEN			
0133	DEBRAY	Quentin	01/01/1999	VB	SYNTHELABO	Fondation IPSEN			
0133	DEBRAY	Quentin	01/01/1999	VB	WYETH-LEDERLE	Fondation IPSEN			
0133	DEBRAY	Quentin	01/01/1999	VB	VEDIM	Fondation IPSEN			
0133	DEBRAY	Quentin	01/01/1999	VB	SMITHKLINE BEECHAM	Fondation IPSEN			
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Lundbeck				
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Wyeth Lederle				
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Servier				
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Pierre Fabre				
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Sanofi				
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Lilly				
0133	DEBRAY	Quentin	01/01/1998	IP-AUT	Pfizer				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10133	DEBRAY	Quentin	01/01/1998	IP-AUT	UCB				
10133	DEBRAY	Quentin	01/01/1998	IP-AUT	Bristol Myers Squibb				
10133	DEBRAY	Quentin	01/01/1998	VB	Lederle		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Sanofi		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Ciba Geigy		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Eutherapie		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Organin		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Pfizer		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Zeneca		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Specia		journées scientifiques à l'Hôpital Laennec		
10133	DEBRAY	Quentin	01/01/1998	VB	Servier		journées scientifiques à l'Hôpital Laennec		
62178	DEBURE	Clélia	22/01/2002	IP-EC	SMITH NEPHEW	Essai ouvert - ... publié et en cours (2001)			
62178	DEBURE	Clélia	22/01/2002	IP-EC	ASTRA	Essai contrôlé EMLA - publié (1996)			
62178	DEBURE	Clélia	22/01/2002	IP-EC	BAYER	Essai contrôlé BAYW 9798 (1995)			
62178	DEBURE	Clélia	22/01/2002	IP-EC	SERVIER	Essai contrôlé Daflon publié (1993)			
62178	DEBURE	Clélia	22/01/2002	IP-CF	THUASNE	Pied diabétique - soins infirmiers (déc. 2001)			
62178	DEBURE	Clélia	22/01/2002	IP-CF	C.P.C.	Aspects cliniques des infections (2002)			
62178	DEBURE	Clélia	22/01/2002	IP-CF	CANTATER	Atelier et conférence ulcère, Montpellier, Réseau Lille-Hôpital			
62729	DEFEBVRE	Luc	30/01/2010	LD-AR	SOLVAY	participation au bord solvay	rémunération personnelle	01/2008	
62729	DEFEBVRE	Luc	30/01/2010	LD-AR	NOVARTIS	participation au bord novartis (en cours)	rémunération personnelle	01/2008	
62729	DEFEBVRE	Luc	30/01/2010	LD-AR	BOEHRINGER	présentation FMC	rémunération personnelle	01/2009	12/2010
62729	DEFEBVRE	Luc	30/01/2010	EC-CO	BOEHRINGER	étude SIFROL CP	co-investigateur	01/2008	12/2009
62729	DEFEBVRE	Luc	30/01/2010	EC-CO	NOVARTIS	étude patch EXELON	co-investigateur	01/2008	12/2009
62729	DEFEBVRE	Luc	30/01/2010	CF-INT	SOLVAY	présentation résultats nationaux sur DUODOPA Paris	rémunération personnelle	10/2008	
62729	DEFEBVRE	Luc	30/01/2010	CF-INT	GE HEALTHCARE	place investigation paracliniques MP	rémunération personnelle	10/2008	
62729	DEFEBVRE	Luc	30/01/2010	CF-INT	AGUETTANT	place apomorphine dans le traitement MP	rémunération personnelle	12/2009	
62729	DEFEBVRE	Luc	30/01/2010	CF-INT	BOEHRINGER	nouveautés thérapeuthiques MP	rémunération personnelle	12/2009	
62729	DEFEBVRE	Luc	30/01/2010	CF-AUD	SOLVAY	participation congrès : XXX en juin 2008			
62729	DEFEBVRE	Luc	18/09/2008	LD-AR	NOVARTIS	Réunions européennes programmes fluchobres	rémunération personnelle	01/2004	12/2006
62729	DEFEBVRE	Luc	18/09/2008	LD-AR	SOLVAY	Place du xx dans stratégie thérapeutique Parkinson	aucune rémunération	01/2008	
62729	DEFEBVRE	Luc	18/09/2008	EC-CO	BOEHRINGER	Etude	co-investigateur	01/2008	
62729	DEFEBVRE	Luc	18/09/2008	EC-CO	NOVARTIS	Etude patch Rivastigmine	co-investigateur	01/2008	12/2009
62729	DEFEBVRE	Luc	20/11/2007	LD-AR	NOVARTIS	Réunions Européennes pour établir un programme d'enseignement sur les Fluchobres 1 réunion/ an depuis	rémunération personnelle	01/2004	12/2006
62729	DEFEBVRE	Luc	20/11/2007	IP-EC	GSK	Etude sur le Requip LP	co-investigateur	01/2005	12/2008
62729	DEFEBVRE	Luc	20/11/2007	IP-EC	NOVARTIS	Comparaison effet Stalevo/Modopar - prévention des Fluchobres	co-investigateur	01/2005	12/2008
62729	DEFEBVRE	Luc	20/11/2007	IP-EC	SERVIER	Effet forme dispersible (protocole terminé)	co-investigateur	01/2006	12/2007
62729	DEFEBVRE	Luc	20/11/2007	IP-EC	ESSAI	Efficacité de XX sur les Fluchobres	co-investigateur	01/2007	12/2008
62729	DEFEBVRE	Luc	20/11/2007	IP-CF	BOEHRINGER INGELHEIM	Présentation le 08/11/07 : les fondamentaux du traitement	rémunération personnelle	11/2007	11/2007
62729	DEFEBVRE	Luc	20/11/2007	CF-AUD	SOLVAY	Participation au congrès international Parkinson's disease		12/2007	12/2007
62729	DEFEBVRE	Luc	16/05/2006	LD-AR	NOVARTIS	Réunions Européennes pour établir un programme d'enseignement sur les Fluchobres (1 réunion/ an depuis	rémunération personnelle	01/2004	12/2006
62729	DEFEBVRE	Luc	16/05/2006	EC-CO	GSK	Etude sur le Requip LP	co-investigateur	01/2005	12/2007
62729	DEFEBVRE	Luc	16/05/2006	EC-CO	SANOFI	Effet Neuroprotecteur	co-investigateur	01/2004	12/2006
62729	DEFEBVRE	Luc	16/05/2006	EC-CO	NOVARTIS	Comparaison effet STALEVO/ MODOPAR	co-expérimentateur	01/2005	12/2007
62729	DEFEBVRE	Luc	16/05/2006	EC-CO	SERVIER	Effet forme dispersible	co-investigateur	01/2006	12/2007
62729	DEFEBVRE	Luc	16/05/2006	CF-INT	SERVIER	Lille (présentation études sur le Trivastal)	rémunération personnelle	03/2006	03/2006
62729	DEFEBVRE	Luc	16/05/2006	CF-INT	BOEHRINGER	Lille (présentation études sur le Sifrol)	rémunération personnelle	11/2005	11/2005
62729	DEFEBVRE	Luc	16/05/2006	CF-AUD	SANTER	AAN - Prise en charge par Société SANTER - Site Internet indépendant Laboratoire Pharmaceutique		04/2006	04/2006
62729	DEFEBVRE	Luc	16/05/2006	CF-AUD	SANTER	AAN - Prise en charge par Société SANTER - Site Internet indépendant Laboratoire Pharmaceutique		04/2005	04/2005
62729	DEFEBVRE	Luc	16/05/2006	CF-AUD	LILLY	Congrès Parkinson Berlin - Prise en charge LILLY		06/2005	06/2005
62729	DEFEBVRE	Luc	06/06/2003	IP-EC	GLAXOSMITHKLINE				
63907	DEMOLIS	Jean-Louis	01/09/2005	EC-INV	HMR	Etudes cliniques / Télithromycine	Investigateur - expérimentateur principal	01/2000	12/2003
63907	DEMOLIS	Jean-Louis	01/09/2005	EC-INV	Etablissement pharmaceutique des hôpitaux de Paris (EPHP)	Etude clinique / 3-4 diaminopyridine	investigateur - expérimentateur principal	01/2002	12/2005
63907	DEMOLIS	Jean-Louis	01/09/2005	EC-INV	IRI SERVIER	Etude clinique / Agomélatine	investigateur - expérimentateur principal	01/2003	12/2004
63907	DEMOLIS	Jean-Louis	01/09/2005	IP-AC	IRI SERVIER	Analyses électrocardiographiques / produits divers	Rémunération perçue par l'expert	01/2000	12/2005
63907	DEMOLIS	Jean-Louis	01/09/2005	CF-INT	LUNDBECK	Mise en place d'un essai clinique / formation sur la mesure de la repolarisation ventriculaire/ Serdolect	Rémunération perçue par l'expert	01/2002	12/2003
60411	DEMOLIS	Pierre	11/04/2003	VB	ASTRA ZENECA - BOEHRINGER INGELHEIM - THERVAL MEDICAL - PFIZER - NOVARTIS - MENARINI - ORION	AEMSSI (Association loi 1901) Service Hématologie - Hôpital de Bicêtre			
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	SERONO				
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	NOVARTIS				
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	AMGEN				
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	UCB				
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	LILLY				
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	BMS				
60411	DEMOLIS	Pierre	05/03/2003	IP-EC	PFIZER				
60411	DEMOLIS	Pierre	05/03/2003	IP-AC	ORION PHARMA	Organisation d'études cliniques			
60411	DEMOLIS	Pierre	05/03/2003	IP-AC	SERONO	Organisation d'études cliniques			
60411	DEMOLIS	Pierre	05/03/2003	IP-AC	NOVARTIS	Organisation d'études cliniques			

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60411	DEMOLIS	Pierre	05/03/2003	IP-CF	SERVIER				
60411	DEMOLIS	Pierre	05/03/2003	IP-CF	ASTRA ZENECA				
60411	DEMOLIS	Pierre	05/03/2003	IP-CF	MENARINI				
60411	DEMOLIS	Pierre	05/03/2003	VB	Divers laboratoires mentionnés ci-dessus	Hôpital de Bicêtre AEMSSI (Association 1901)			
60411	DEMOLIS	Pierre	29/06/2000	VB	BIOCODEX France	1 Essai actuellement terminé - Analyse en cours : Association Claude Bernard			
60411	DEMOLIS	Pierre	29/06/2000	IP-AC	SCORPION - Agence de communication domaine pharmacologie cardiovasculaire	Conseil technique sur aspects pharmacologiques antihypertenseurs			
60411	DEMOLIS	Pierre	29/06/2000	IP-CF	ASTRA ZENECA, GLAXO WELLCOME, SANOFI SYNTHELABO	Diverses interventions Symposia : pharmacologie de anti-HTA, physipathologie de l'HTA			
10138	DENIS	François Alphonse	08/02/2002	IP-EC	GLAXO, GSK	Observatoire des pneumocoques			
10138	DENIS	François Alphonse	08/02/2002	IP-CF	AVENTIS	Conférence sur les vaccins			
10138	DENIS	François Alphonse	08/02/2002	IP-CF	GLAXO, SKB	Conférence sur les vaccins			
10138	DENIS	François Alphonse	10/01/2002	IP-CF	GLAXO - SK	2 conférences vaccins lexavalents (Paris, Nancy)			
10138	DENIS	François Alphonse	10/01/2002	IP-CF	BIOMERIEUX	Action de formation - Actualités cytomégalovirus			
10138	DENIS	François Alphonse	10/01/2002	IP-CF	MSD (Enseignement post universitaire)	Actualités vaccinations hépatites, VIH (Meaux)			
10138	DENIS	François Alphonse	10/01/2002	IP-CF	AVENTIS PASTEUR	Enquête taux couverture vaccinale adulte			
10138	DENIS	François Alphonse	16/01/2000	IP-CF	SMITHKLINE BEECHAM	Conférences sur vaccins hépatite B (sans rémunération)			
10138	DENIS	François Alphonse	16/01/2000	IP-CF	PASTEUR MERIEUX CONNAUGHT	Conférences sur vaccins (sans rémunération)			
10138	DENIS	François Alphonse	16/01/2000	IP-CF	MERCK SHARP DOHME	Colloque : l'A, B, C des hépatites (rémunéré)			
10138	DENIS	François Alphonse	16/01/2000	IP-CF	SMITHKLINE BEECHAM	Invitation congrès ICAAC (USA)			
10138	DENIS	François Alphonse	16/01/2000	VB	CILAG	Versement au budget de l'université - taxe d'apprentissage			
10138	DENIS	François Alphonse	16/01/2000	VB	SKB	Observatoire des pneumocoques - association			
10138	DENIS	François Alphonse	16/01/2000	VB	Diasorin	Association (évaluation des réactifs)			
10138	DENIS	François Alphonse	16/01/2000	VB	GLAXO WELLCOME	Association (études clinico-biologiques)			
10138	DENIS	François Alphonse	16/01/2000	VB	SERVIER IRIS	Association (études clinico-biologiques)			
10138	DENIS	François Alphonse	01/01/2000	VB	GLAXO WELLCOME	Association			
10138	DENIS	François Alphonse	01/01/2000	VB	SMITHKLINE BEECHAM	Association			
10138	DENIS	François Alphonse	01/01/2000	VB	ROUSSEL DIAMANT	Association			
10138	DENIS	François Alphonse	01/01/2000	VB	WYETH LEDERLE	Association			
10138	DENIS	François Alphonse	01/01/2000	VB	BIOMERIEUX	Association, Université			
10138	DENIS	François Alphonse	01/01/2000	VB	INGEN	Association, Université			
10138	DENIS	François Alphonse	01/01/2000	VB	DAKO	Association, Université			
10138	DENIS	François Alphonse	01/01/2000	(Autre)	ABBOTT	Invitation à des congrès			
10138	DENIS	François Alphonse	01/01/2000	(Autre)	BIOMERIEUX	Invitation à des congrès			
10138	DENIS	François Alphonse	01/01/2000	(Autre)	SMITH KLINE BEECHAM	Invitations à des congrès			
10138	DENIS	François Alphonse	01/01/2000	(Autre)	SMITH KLINE BEECHAM	Conférences sur les vaccins			
10138	DENIS	François Alphonse	01/01/2000	(Autre)	PASTEUR MERIEUX MSD	Conférences sur les vaccins			
65309	DESCAMPS	Vincent	13/04/2010	LD-ODE		Création en tant "auto enterpreneur," d'une entreprise, rédaction scientifique le 1er octobre 2009. Chef d'entreprise			
65309	DESCAMPS	Vincent	13/04/2010	LD-AR	SERVIER	Expertise	Rémunération personnelle	01/2008	12/2010
65309	DESCAMPS	Vincent	13/04/2010	LD-AR		Revue images en dematologie	Rémunération personnelle	01/2008	
65309	DESCAMPS	Vincent	13/04/2010	EC-INV	WYETH	Enbrel	investigateur principal	01/2005	12/2006
65309	DESCAMPS	Vincent	13/04/2010	EC-INV	SCHERING PLOUGH	Remicade	investigateur principal	01/2008	12/2010
65309	DESCAMPS	Vincent	13/04/2010	EC-INV	GSK	Mage 3 vaccination	investigateur principal	01/2009	
65309	DESCAMPS	Vincent	13/04/2010	EC-CO		Rituximab Mabthera	Co-investigateur	01/2007	12/2008
65309	DESCAMPS	Vincent	13/04/2010	EC-CO		Edratide Teva	Co-investigateur	01/2006	
65309	DESCAMPS	Vincent	13/04/2010	EC-CO		Regranex	Co-investigateur		
65309	DESCAMPS	Vincent	13/04/2010	CF-INT	WYETH	Réunions interface dermato / rhumato dns services de Bichat	Aucune rémunération	01/2009	
65309	DESCAMPS	Vincent	13/04/2010	CF-INT	SCHERING PLOUGH	CR de l'EADV à Berlin	Aucune rémunération	01/2009	
65309	DESCAMPS	Vincent	13/04/2010	CF-AUD	SCHERING PLOUGH	EADB Berlin		01/2009	
65309	DESCAMPS	Vincent	13/04/2010	CF-AUD	JANSSEN	Académie américaine de dermatologie		01/2010	
65309	DESCAMPS	Vincent	13/04/2010	CF-AUD	LEO	Académie américaine de dermatologie		01/2009	
65309	DESCAMPS	Vincent	02/09/2008	LD-AR	SERVIER	Expert syndrome d'hypersensibilité médicamenteuse DRESS au cours des traitements par Protelos	rémunération institution	05/2008	05/2009
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	WYETH	Biothérapie du psoriasis (étanercept) 3 études		01/2006	
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SERONO	Biothérapie du psoriasis (efalizumab)		01/2006	12/2007
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	Biothérapie du psoriasis (infliximab)		01/2008	
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	Vaccination cans le mélanome MAGE - mise en place prochaine			
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	Interféron dans le mélanome PEG Interféron, étude EADO		01/2003	12/2006
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	GLIVEC en préopératoire des tumeurs de Darier Ferrand		01/2005	12/2007
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	IgIV étude TEVA dans le traitement ds dermatomyosites		01/2008	
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	Regranex dans les angiodermites nécrosantes Protocole ERAN		01/2004	
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	IgIV (Tegeline) dans le traitement du DRESS		01/2008	
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	Rituximab (Mabthera) dans le traitement du pemphigus		01/2003	12/2004
65309	DESCAMPS	Vincent	02/09/2008	EC-CO	SCHERING PLOUGH	Imiquimod dans le traitement du carcinome basocellulaire		01/2003	12/2004
65309	DESCAMPS	Vincent	02/09/2008	CF-INT	SERVIER	Manifestations cutanées associées à l'administration de l'interféron bêta (REBIF dans la sclérose en plaques	rémunération personnelle	01/2008	12/2008
64755	DESCHENES	Georges	08/05/2010	LD-AR	NOVARTIS - TAKEDA	Expertise conseil	Rémunération personnelle		
64755	DESCHENES	Georges	08/05/2010	EC-INV	OXTHERA	Oxbacter	Investigateur principal		
64755	DESCHENES	Georges	08/05/2010	EC-INV	NOVARTIS	Valsartan	Investigateur principal		
64755	DESCHENES	Georges	08/05/2010	EC-INV	ROCHE	Mircera	Investigateur principal		
64755	DESCHENES	Georges	08/05/2010	EC-INV	AMGEN	Aranesp	Investigateur principal		
64755	DESCHENES	Georges	08/05/2010	EC-INV	ALEXION	Soliris	Investigateur principal		
64755	DESCHENES	Georges	08/05/2010	CF-AUD	ROCHE	ATC 2007-2010			
64755	DESCHENES	Georges	08/05/2010	CF-AUD	FRESENIUS	ASN 2008-2009			
64755	DESCHENES	Georges	16/05/2009	EC-INV	OXTHERA	Oxalobacter	investigateur principal	01/2008	12/2008
64755	DESCHENES	Georges	16/05/2009	EC-INV	NOVARTIS	Valsartan	investigateur principal	01/2008	12/2008
64755	DESCHENES	Georges	16/05/2009	EC-INV	ROCHE	Mircera	investigateur principal	01/2009	12/2009
64755	DESCHENES	Georges	16/05/2009	EC-INV	AMGEN	Arenesp	investigateur principal	01/2009	12/2009
64755	DESCHENES	Georges	16/05/2009	RE-AUT	TAKEDA	Hematide	rémunération personnelle	01/2009	12/2009
64755	DESCHENES	Georges	16/05/2009	CF-AUD	FRESENIUS	Réunion ASN 2008		11/2008	11/2008
64755	DESCHENES	Georges	16/05/2009	CF-AUD	FRESENIUS	Réunion ASN 2007		11/2007	11/2007
64755	DESCHENES	Georges	17/06/2008	EC-INV	NOVARTIS	VALSARTAN	investigateur principal	01/2008	12/2008
64755	DESCHENES	Georges	17/06/2008	EC-INV	OXTHERA	OXALOBACTER	investigateur principal	01/2008	01/2010
64755	DESCHENES	Georges	17/06/2008	EC-INV	ROCHE	MIRCERA	investigateur	09/2008	09/2009

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64755	DESCHENES	Georges	17/06/2008	EC-INV	DRC	NEPHROVIR	investigateur coordonateur	12/2007	06/2010
64755	DESCHENES	Georges	17/06/2008	RE-DE	ROCHE	MIRCERA	rémunération institution	06/2008	07/2008
64755	DESCHENES	Georges	17/06/2008	CF-AUD	FRESENIUS	ASN réunion annuelle 2007		11/2007	11/2007
64755	DESCHENES	Georges	17/06/2008	CF-AUD	FRESENIUS	ASN réunion annuelle 2008		11/2008	11/2008
64755	DESCHENES	Georges	17/06/2008	CF-AUD	ROCHE	ATC réunion 2007		04/2007	04/2007
64755	DESCHENES	Georges	09/07/2007	EC-INV	NOVARTIS	Valsartan	Investigateur principal	09/2007	09/2009
64755	DESCHENES	Georges	09/07/2007	EC-CO	SERVIER (IRIS)	Coversyl	co-investigateur	09/2003	09/2006
64755	DESCHENES	Georges	09/07/2007	CF-AUD	FRESENIUS	ASN réunion annuelle		11/2006	11/2006
64755	DESCHENES	Georges	09/07/2007	CF-AUD	ROCHE	Congrès ATC		04/2007	04/2007
64755	DESCHENES	Georges	09/07/2007	VB	ROCHE	Séminaire	ASRD	03/2007	03/2007
64755	DESCHENES	Georges	09/07/2007	VB	NOVARTIS	Séminaire	ASRD	03/2007	03/2007
64755	DESCHENES	Georges	09/07/2007	VB	FERRING	Séminaire	ASRD	03/2007	03/2007
61407	DESCOTES	Jacques	16/02/2010	RE-DE	TILOCOR	Expert toxicologue	Rémunération personnelle	02/2010	
61407	DESCOTES	Jacques	16/02/2010	RE-DE	SERVIER	Expert immunotoxicologue	Rémunération personnelle	02/2009	04/2009
61407	DESCOTES	Jacques	16/02/2010	RE-DE	MERIEUX ALLIANCE	Expert toxicologue	Rémunération personnelle	04/2009	05/2010
61407	DESCOTES	Jacques	16/02/2010	EC-INV	ROCHE	Expert immunotoxicologue	Conseil	02/2010	
61407	DESCOTES	Jacques	16/02/2010	LD-AR	WITTYCELL	Expert toxicologue	Rémunération personnelle	09/2009	
61407	DESCOTES	Jacques	16/02/2010	EC-INV	ENDOTIS	Expert Toxicologue	Conseil	09/2008	
61407	DESCOTES	Jacques	16/02/2010	EC-INV	DBV TECHNOLOGIES	Expert toxicologue	Conseil	09/2008	
61407	DESCOTES	Jacques	16/02/2010	EC-INV	CELLECTIS	Expert toxicologue	Conseil	02/2010	
61407	DESCOTES	Jacques	16/02/2010	LD-AR	FLUOPTICS	Expert toxicologue	Rémunération personnelle	10/2009	
61407	DESCOTES	Jacques	16/02/2010	LD-AR	BAYER-SCHERING	Expert toxicologue	Rémunération personnelle	01/2009	
61407	DESCOTES	Jacques	16/02/2010	LD-AR	ALFACT	Expert toxicologue	Rémunération personnelle	01/2009	
61407	DESCOTES	Jacques	16/02/2010	LD-AR	CIT	Expert toxicologue	Rémunération personnelle	10/2008	
61407	DESCOTES	Jacques	16/02/2010	LD-AR	ADOCIA	Expert toxicologue	Rémunération personnelle	12/2009	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	XI-GEN	Expertise toxicologique : XG-102		09/2007	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	JOHNSON & JOHNSON	Expertise toxicologique : doripenem		02/2007	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	RICORDATI	Expertise toxicologique : silodosin		09/2007	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	PIERRE FABRE MEDICAMENT	Expertise toxicologique: diphencyprone		01/2008	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	PIERRE FABRE MéDICAMENT	Avis effet indésirable : Eludril		12/2007	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	PIERRE FABRE MéDICAMENT	Avis effet indésirable : Eludril		12/2007	01/2008
61407	DESCOTES	Jacques	12/02/2008	EC-INV	PIERRE FABRE MéDICAMENT	Expertise pharmacovigilance		12/2007	01/2008
61407	DESCOTES	Jacques	12/02/2008	EC-INV	PIERRE FABRE MéDICAMENT	Expertise pharmacovigilance : Eludril		10/2007	01/2008
61407	DESCOTES	Jacques	12/02/2008	EC-INV	ORPHAN EUROPE	Expertise toxicologique : Vedrop		02/2007	
61407	DESCOTES	Jacques	12/02/2008	LD-AR	MILLENIUM	Expert toxicologue	Rémunération personnelle	05/2007	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	MEDIOPHARM	Expertise toxicologique		11/2007	12/2007
61407	DESCOTES	Jacques	12/02/2008	EC-INV	GE HEALTHCARE	Expertise toxicologique : Omnipaque		04/2007	05/2007
61407	DESCOTES	Jacques	12/02/2008	EC-INV	GE HEALTHCARE	Expertise toxicologique : Omnipaque		04/2007	05/2007
61407	DESCOTES	Jacques	12/02/2008	EC-INV	GE HEALTHCARE	Expertise Toxicologique : Omnipaque		04/2007	05/2007
61407	DESCOTES	Jacques	12/02/2008	EC-INV	GE HEALTHCARE	Expertise toxicologique : Omnipaque		04/2007	05/2007
61407	DESCOTES	Jacques	12/02/2008	LD-AR	FLAMEL	Expert toxicologue	Rémunération personnelle	05/2007	
61407	DESCOTES	Jacques	12/02/2008	EC-INV	EFFIK	Expertise toxicologique (		05/2008	12/2008
61407	DESCOTES	Jacques	12/02/2008	EC-INV	BT PHARMA	Expertise toxicologique : ProCervix		06/2007	
61407	DESCOTES	Jacques	12/02/2008	LD-AR	EFFIK	Expert toxicologue	Rémunération personnelle	02/2008	12/2008
61407	DESCOTES	Jacques	12/02/2008	LD-AR	ERYTECH PHARMA	Expert Toxicologue	Rémunération personnelle	05/2007	
61407	DESCOTES	Jacques	10/04/2007	RE-DE	PFIZER	Toxicologie / Maraviroc	Rémunération personnelle	01/2006	12/2006
61407	DESCOTES	Jacques	10/04/2007	RE-DE	JOHNSON & JOHNSON	Toxicologie - Doripenem	rémunération personnelle	01/2007	
61407	DESCOTES	Jacques	10/04/2007	RE-DE	ORPHAN EUROPE	Pharmacovigilance / Vedrop	rémunération personnelle	01/2007	
61407	DESCOTES	Jacques	10/04/2007	LD-AR	TEVA	Expert Toxicologue	rémunération personnelle	01/2000	
61407	DESCOTES	Jacques	10/04/2007	LD-AR	STALLERGENES	Expert Toxicologue	rémunération personnelle	01/2003	
61407	DESCOTES	Jacques	10/04/2007	LD-AR	CENTELION	Expert Toxicologue	rémunération personnelle	01/2005	12/2005
61407	DESCOTES	Jacques	10/04/2007	LD-AR	BAYER-SCHERING	Expert Toxicologue	rémunération personnelle	01/2001	
61407	DESCOTES	Jacques	10/04/2007	EC-CO	SERONO	Raptiva	Comité Scientifique	01/2006	12/2006
61407	DESCOTES	Jacques	10/04/2007	RE-DE	MERCK GENERIQUES	Dossier clinique - Epipen	rémunération personnelle	01/2006	12/2006
61407	DESCOTES	Jacques	10/04/2007	RE-DE	PIERRE FABRE MED	Pharmacovigilance - Ribomunyl	rémunération personnelle	01/2001	
61407	DESCOTES	Jacques	10/04/2007	RE-DE	BRACCO	Toxicologie - Sonovue	rémunération personnelle	01/2005	12/2006
61407	DESCOTES	Jacques	10/04/2007	RE-AUT	ASTRA ZENECA	Toxicologie - Ximelagatran	rémunération personnelle	01/2005	12/2005
61407	DESCOTES	Jacques	10/04/2007	RE-AUT	BEZINS	Toxicologie - Ethers de glycol	rémunération personnelle	01/2005	12/2006
61407	DESCOTES	Jacques	10/04/2007	RE-AUT	BIOPROJET	Toxicologie - BP3.2000	rémunération personnelle	01/2007	
61407	DESCOTES	Jacques	10/04/2007	RE-AUT	FRESENIUS KABI	Toxicologie - Plasmion	rémunération personnelle	01/2003	12/2003
61407	DESCOTES	Jacques	10/04/2007	RE-AUT	GE HEALTHCARE	Toxicologie - Omnipaque	rémunération personnelle	01/2007	
61407	DESCOTES	Jacques	10/04/2007	IP-AC	COMBINATURE PHARMA	Immuno Toxicologie - Produits en développement < Phase 1	rémunération personnelle	01/2006	12/2006
61407	DESCOTES	Jacques	10/04/2007	IP-AC	MERCK SANTE	Immuno Toxicologie - Produits en développement < Phase 1	rémunération personnelle	01/2005	
61407	DESCOTES	Jacques	10/04/2007	IP-AC	MILLENIUM	Immuno Toxicologie - Produits en développement < Phase 1	rémunération personnelle	01/2007	
61407	DESCOTES	Jacques	10/04/2007	IP-AC	SERONO	Immuno Toxicologie - Produits en développement < Phase 1	rémunération personnelle	01/2006	12/2006
61407	DESCOTES	Jacques	10/04/2007	IP-AC	VOISIN CONSULTING	Immuno Toxicologie - Produits en développement < Phase 1	rémunération personnelle	01/2006	
61407	DESCOTES	Jacques	10/04/2007	IP-AC	PFIZER	Immuno Toxocologie - Produits en développement < Phase 1	rémunération personnelle	01/2007	
61407	DESCOTES	Jacques	25/01/2006	LD-AR	CENTELION	consultation tous produits	rémunération personnelle	01/2005	
61407	DESCOTES	Jacques	25/01/2006	LD-AR	STALLERGENES	Consultation tous produits	rémunération personnelle	01/2003	
61407	DESCOTES	Jacques	25/01/2006	LD-AR	TEVA	consultation tous produits	Rémunération personnelle	01/2000	
61407	DESCOTES	Jacques	25/01/2006	EC-CO	SERONO	Raptiva	Comité scientifique	01/2006	12/2006
61407	DESCOTES	Jacques	25/01/2006	RE-DE	AMYLIN	Pramlintide	Rémunération personnelle	01/2001	12/2002
61407	DESCOTES	Jacques	25/01/2006	RE-DE	BRACCO	SonoVue	rémunération personnelle	01/2004	12/2005
61407	DESCOTES	Jacques	25/01/2006	RE-DE	URIACH	Rupatadine	Rémunération personnelle	09/2000	12/2000
61407	DESCOTES	Jacques	25/01/2006	RE-DE	MERCK SANTE	Epifen	rémunération personnelle	01/2006	
61407	DESCOTES	Jacques	25/01/2006	RE-DE	PIERRE FABRE	Ribomunyl	Rémunération personnelle	01/2000	10/2005
61407	DESCOTES	Jacques	25/01/2006	RE-DE	PFIZER	Voriconazole	Rémunération personnelle	04/2002	12/2002
61407	DESCOTES	Jacques	25/01/2006	IP-AC	ASTRA ZENECCA	Conseil toxico - Ximelagatran	Rémunération personnelle	10/2005	12/2005
61407	DESCOTES	Jacques	25/01/2006	IP-AC	BRISTOL MEYERS	Conseil toxico - BMS 97610	Rémunération personnelle	09/2002	12/2002
61407	DESCOTES	Jacques	25/01/2006	IP-AC	BRISTOL MEYERS	Conseil toxico - Omapatrilat	Rémunération personnelle	01/2001	02/2002
61407	DESCOTES	Jacques	25/01/2006	IP-AC	FRESENIUS KABI	Conseil toxico - Plasmion	Rémunération personnelle	10/2002	03/2003
61407	DESCOTES	Jacques	25/01/2006	IP-AC	PFIZER	Conseil toxico - UK 390957/369003/	Rémunération personnelle	01/2001	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
31407	DESCOTES	Jacques	25/01/2006	IP-AC	SANOFI SYNTHELABO	Conseil toxico - SSR 125329C/126517	Rémunération personnelle	01/2002	12/2002
31407	DESCOTES	Jacques	25/01/2006	IP-AC	BEZINS	Conseil toxico - Ethers de glycol	Rémunération personnelle	06/2005	
31407	DESCOTES	Jacques	16/09/2005	IP-EC	BESINS INTERNATIONAL	revue de littérature			
31407	DESCOTES	Jacques	16/09/2005	IP-AC	BRACCO, CENTELION, COMBINATURE BIOPHARM, PFIZER, PIERRE FABRE, SANDOZ , SCHERING, STALLERGENES, TEVA	Conseil sur l'évaluation préclinique de la toxicité / immunotoxicité			
31407	DESCOTES	Jacques	16/09/2005	IP-AC	BRACCO, CENTELION, COMBINATURE BIOPHARM, PFIZER, PIERRE FABRE, SANDOZ,SCHERING, STALLERGENES, TEVA	Conseil sur l'évaluation préclinique de la toxicité / immunotoxicité			
31407	DESCOTES	Jacques	16/09/2005	IP-EC	BESINS INTERNATIONAL	revue de littérature			
31407	DESCOTES	Jacques	13/02/2003	IP-EC	PIERRE FABRE MEDICAMENTS	Essais cliniques Vaccins, Immunostim			
31407	DESCOTES	Jacques	13/02/2003	IP-EC	MERCK SANTE	Essais cliniques			
31407	DESCOTES	Jacques	13/02/2003	IP-RE	PFIZER, CHIRON, SCHERING	Expertises immunotoxicologiques			
31407	DESCOTES	Jacques	13/02/2003	IP-RE	TEVA, PHARMACIA, STALLERGENES	Expertises immunotoxicologiques			
31407	DESCOTES	Jacques	13/02/2003	IP-RE	PIERRE FABRE MEDICAMENTS	Expertises immunotoxicologiques			
31407	DESCOTES	Jacques	13/02/2003	IP-RE	BRISTOL MYERS SQUIBB	Expertises immunotoxicologiques			
31407	DESCOTES	Jacques	13/02/2003	IP-RE	OCTAPHARMA, OMRIX	Expertises immunotoxicologiques			
31407	DESCOTES	Jacques	13/02/2003	IP-AC	OM PHARMA	Conseil immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-AC	IPSEN-BEAUFOUR	Conseil immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-AC	GENODYSSEE- MERISTEM	Conseil Immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-AC	SANOFI-SYNTHELABO	Conseil immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-AC	TRANSGENE	Conseil immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-CF	EUROTOX	Immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-CF	DIA-SOT	Immunotoxicologie			
31407	DESCOTES	Jacques	13/02/2003	IP-CF	SFT	Immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	LD	TEVA Pharmaceuticals (Israel)	Contrat de consultant			
31407	DESCOTES	Jacques	30/01/2002	LD	SCHERING (Allemagne)	Contrat de consultant			
31407	DESCOTES	Jacques	30/01/2002	LD	STALLERGENES	Contrat de consultant			
31407	DESCOTES	Jacques	30/01/2002	IP-EC	PIERRE FABRE Médicaments	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-RE	ALIZYME (GB)	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-RE	AMYLIN (US)	Expertise toxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-AC	GENMAB (DK)	Conseil, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-AC	TRANSGENE	Conseil, toxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-EC	MERCK LIPHA	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-RE	BMS (US)	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-RE	CHIRON (US/F)	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-RE	PHARMACIA	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-AC	NOVO NORDISK (NK)	Expertise, immunotoxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-AC	GENODYSSEE	Expertise, toxicologie			
31407	DESCOTES	Jacques	30/01/2002	IP-AC	PFIZER (US/F)	Expertise, immunotoxicologie			
64177	DESSI	Fréderic	10/05/2006	LD-AR	SERVIER	veille bibliographique sur les troubles cognitifs	rémunération personnelle	01/2000	03/2006
60954	DESTEE	Alain	13/10/2002	IP-EC	ROCHE, NOVARTIS, AVENTIS, TEVA, SERVIER, LILLY, PHARMACIA, UPJOHN, GSK, SCHWARTZ, NEWRON	Investigateur de la quasi-totalité des essais Parkinson, coordonnateur de nombreux essais			
60954	DESTEE	Alain	13/10/2002	IP-RE	HEALTH EXPERTS				
60954	DESTEE	Alain	13/10/2002	IP-AC	LILLY, GSK				
60954	DESTEE	Alain	13/10/2002	IP-CF		Idem			
60954	DESTEE	Alain	10/04/2000	IP-EC	NOVARTIS/ ROCHE	Essai clinique			
60954	DESTEE	Alain	10/04/2000	IP-EC	SB/RPR/THERVAL	Essai clinique			
60954	DESTEE	Alain	10/04/2000	IP-EC	SUMITOMO				
60954	DESTEE	Alain	10/04/2000	IP-EC	SOLVAY				
60954	DESTEE	Alain	10/04/2000	IP-RE	ROCHE				
60954	DESTEE	Alain	10/04/2000	IP-AC	PHARMACIA UPJOHN				
60954	DESTEE	Alain	10/04/2000	IP-AC	LILLY				
60954	DESTEE	Alain	10/04/2000	IP-AC	SB				
60954	DESTEE	Alain	10/04/2000	IP-AC	NOVARTIS				
60954	DESTEE	Alain	10/04/2000	IP-AC	TEVA				
60954	DESTEE	Alain	10/04/2000	IP-CF	SB/ROCHE				
10139	DETILLEUX	Michel	29/06/2010	LD-AR	SOCIéTé ADIR (GROUPE SERVIER)	Contrat de consultant	Rémunération personnelle		09/2011
10139	DETILLEUX	Michel	19/06/2009	LD-AR	ADIR (GROUPE SERVIER)	Activité de consultant pour la conception et le déroulement des études cliniques, Veille scientifique.	Rémunération personnelle	05/2009	04/2010
10139	DETILLEUX	Michel	19/06/2009	EC-INV	AP-HP	baclofène	Investigateur principal	04/2009	12/2012
10139	DETILLEUX	Michel	14/06/2006	LD-AR	ADIR (GROUPE SERVIER)	Consultant	Rémunération partagée personnelle / institution au profit de l'APREMI	01/2006	04/2010
10139	DETILLEUX	Michel	14/06/2006	VB	ROUSSEL DIAMANT				
10139	DETILLEUX	Michel	30/07/2004	LD	ADIR (Société du Groupe SERVIER)	Contrat de consultant			
10139	DETILLEUX	Michel	02/06/1999	LD	Société ADIR (Groupe SERVIER)	Contrat de consultant			
10139	DETILLEUX	Michel	02/06/1999	IP-EC	IRIS (Groupe SERVIER)	Comité scientifique - Essais de phase III du Zanélate			
10139	DETILLEUX	Michel	01/01/1999	LD	ADIR (Groupe SERVIER)	Contrat de consultant			
10139	DETILLEUX	Michel	01/01/1999	IP-EC	Institut de recherches international SERVIER : IRIS				
10139	DETILLEUX	Michel	01/01/1999	IP-CF	ROCHE PRODUITS	Actions de formation continue en partenariat (organisées à l'initiative d'associations de FMC)			
10139	DETILLEUX	Michel	01/01/1999	VB	DIAMANT	Collaboration à une réunion scientifique - versement à l'Association pour la recherche en médecine interne	APREMI, hôpital Cochin		
10139	DETILLEUX	Michel	01/01/1998	LD	(Groupe Servier) Société ADIR	Contrat de consultant.			
10139	DETILLEUX	Michel	01/01/1998	VB	Innothera		au profit de l'APREMI		
10139	DETILLEUX	Michel	01/01/1998	VB	Roussel Diamant		au profit de l'APREMI		
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	STALLERGèNES	AAAAIDDEAACI			
60399	DEVILLIER	Philippe	01/10/2009	CF-INT	STALLERGèNES	EAACI Varsovie 2009DDCAAACI - Washington 2009	Aucune rémunération		
60399	DEVILLIER	Philippe	01/10/2009	PAR	BOEHRINGER INGELHEIM	déléguée médicale (en cours)	conjoint		
60399	DEVILLIER	Philippe	01/10/2009	VB	SERVIER	Pharmacologie pré-clinique de sécurité	UPRES EA 220	01/2007	12/2009
60399	DEVILLIER	Philippe	01/10/2009	VB	SANOFI AVENTIS	Recherche pré-clinique	UPRES EA 220	01/2003	
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	BOEHRINGER INGELHEIM	P2T Pharmacologie France (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	CHIESI , SCHERING PLOUGH	JPA & CNAA - Paris (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	SCHERING PLOUGH	JPD - Paris (tous les ans depuis 5 ans)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	SCHERING PLOUGH	EAACI 2008 (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	GLAXOSMITHKLINE, BOEHRINGER INGELHEIM	ERS Europe (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	01/10/2009	CF-AUD	GLAXOSMITHKLINE, MSD	ATS - USA (Tous es ans depuis 5 ans)			
60399	DEVILLIER	Philippe	01/10/2009	CF-INT	BOEHRINGER INGELHEIM	P2T Pharmacologie France			
60399	DEVILLIER	Philippe	01/10/2009	CF-INT	SCHERING PLOUGH	JPD - Paris			
60399	DEVILLIER	Philippe	01/10/2009	CF-INT	CHIESI, SCHERING PLOUGH	JPA & CNAA - Paris			
60399	DEVILLIER	Philippe	01/10/2009	CF-INT	SCHERING PLOUGH	AAACI 2005 - USA			
60399	DEVILLIER	Philippe	01/10/2009	CF-INT	BOEHRINGER INGELHEIM, GLAXOSMITHKLINE, CHIESI, ASTRA ZENECA	CPLF France			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	SANOFI AVENTIS	Comité d'expert "safety" développement clinique (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	STALLERGENES	Groupe experts statistiques - méthodologie développement (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	CHIESI SA	Groupe d'experts (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	BIOPROJET PHARMA	Expertise scientifique et médicale - préclinique et clinique (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	BOEHRINGER-INGELHEIM	Groupe d'experts BPCO (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	ASTRAZENECA	Groupe d'experts ASTHME - BPCO (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	IP-AC	GLAXOSMITHKLINE	Expertise scientifique et médicale - pré-clinique et clinique (en cours)			
60399	DEVILLIER	Philippe	01/10/2009	EC-CO	GLAXOSMITHKLINE	Observatoire (en cours)	collaborateur (expertise scientifique et statistique)		
60399	DEVILLIER	Philippe	01/10/2009	EC-CO	SERVIER	Etude pré-clinique / pharmacologie pré-clinique de sécurité : ligands récepteurs histamine (en cours)	expérimentateur		12/2009
60399	DEVILLIER	Philippe	01/10/2009	EC-CO	SCHERING PLOUGH	Observatoire Scoring rhinite	investigateur		
60399	DEVILLIER	Philippe	30/09/2008	EC-INV	SCHERING PLOUGH	Essai pharmacodynamie cutanée Desloratadine	coordonateur	01/2007	04/2007
60399	DEVILLIER	Philippe	30/09/2008	EC-CO	SCHERING PLOUGH	DESLORATADINE - études cliniques□□Etude AERONEFF : RAS□□Etude DEPART : RAP	collaborateur (expertise scientifique et statistique)		04/2007
60399	DEVILLIER	Philippe	30/09/2008	EC-CO	SCHERING PLOUGH	Observatoire Scoring rhinite	investigateur		
60399	DEVILLIER	Philippe	30/09/2008	EC-CO	SERVIER	Etude pré-clinique / pharmacologie pré-clinique de sécurité : ligands récepteurs histamine (en cours)	expérimentateur		
60399	DEVILLIER	Philippe	30/09/2008	EC-CO	GLAXOSMITHKLINE	Observatoire (en cours)	collaborateur (expertise scientifique et statistique)		
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	GLAXOSMITHKLINE	Expertise scientifique et médicale - pré-clinique et clinique (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	ASTRAZENECA	Groupe d'experts ASTHME - BPCO (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	BOEHRINGER-INGELHEIM	Groupe d'experts BPCO (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	BIOPROJET PHARMA	Expertise scientifique et médicale - préclinique et clinique (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	CHIESI SA	Groupe d'experts (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	STALLERGENES	Groupe experts statistiques - méthodologie développement (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	IP-AC	SANOFI AVENTIS	Comité d'expert "safety" développement clinique (en cours)			
60399	DEVILLIER	Philippe	30/09/2008	CF-INT	BOEHRINGER INGELHEIM, GLAXOSMITHKLINE, CHIESI, ASTRA ZENECA	CPLF France			
60399	DEVILLIER	Philippe	30/09/2008	CF-AUD	GLAXOSMITHKLINE, MSD	ATS - USA (Tous es ans depuis 5 ans)			
60399	DEVILLIER	Philippe	30/09/2008	VB	ALTANA PHARMA	Etude pré-clinique	UPRES EA 220	01/2006	12/2008
60399	DEVILLIER	Philippe	30/09/2008	VB	SANOFI AVENTIS	Recherche pré-clinique	UPRES EA 220	01/2003	
60399	DEVILLIER	Philippe	30/09/2008	VB	SERVIER	Pharmacologie pré-clinique de sécurité	UPRES EA 220	01/2007	12/2009
60399	DEVILLIER	Philippe	30/09/2008	PAR	BOEHRINGER INGELHEIM	déléguée médicale (en cours)	conjoint		
60399	DEVILLIER	Philippe	30/09/2008	CF-INT	SCHERING PLOUGH	AAACI 2005 - USA			
60399	DEVILLIER	Philippe	30/09/2008	CF-INT	CHIESI, SCHERING PLOUGH	JPA & CNAA - Paris			
60399	DEVILLIER	Philippe	30/09/2008	CF-INT	SCHERING PLOUGH	JPD - Paris			
60399	DEVILLIER	Philippe	30/09/2008	CF-INT	BOEHRINGER INGELHEIM	P2T Pharmacologie France			
60399	DEVILLIER	Philippe	30/09/2008	CF-AUD	GLAXOSMITHKLINE, BOEHRINGER INGELHEIM	ERS Europe (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	30/09/2008	CF-AUD	SCHERING PLOUGH	EAACI 2008 (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	30/09/2008	CF-AUD	CHIESI, SCHERING PLOUGH	JPA & CNAA - Paris (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	30/09/2008	CF-AUD	SCHERING PLOUGH	JPD - Paris (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	30/09/2008	CF-AUD	BOEHRINGER INGELHEIM	P2T Pharmacologie France (tous les ans depuis 5 ans)			
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	ALTANA PHARMA	Conseils en développement / communication	rémunération partagée personnelle / institution	01/2004	12/2006
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	ASTRA ZENECA	Conseils en développement / communication	rémunération partagée personnelle / institution	01/2002	
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	GLAXO SMITH KLINE	Conseils en développement / communication	rémunération partagée personnelle / institution	01/2002	
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	BIOPROJET PHARMA	Conseils en développement / communication	rémunération partagée personnelle / institution	01/2000	
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	SCHERING PLOUGH	Conseils en développement / communication	Rémunération partagée personnelle / institution	01/2003	
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	CHIESI	Conseils en développement / communication	Rémunération partagée personnell / institution	01/2006	
60399	DEVILLIER	Philippe	08/06/2006	LD-AR	BOEHRINGER INGELHEIM	Conseils en développement / communication	Rémunération partagée perosnnelle / institution	01/2004	
60399	DEVILLIER	Philippe	08/06/2006	EC-INV	SCHERING PLOUGH	Essai clinique	coordonnateur	01/2005	12/2006
60399	DEVILLIER	Philippe	08/06/2006	EC-INV	ALTANA PHARMA	Recherche en pharmacologie fondamentale (Roflumilast)	expérimentateur principal	01/2005	12/2006
60399	DEVILLIER	Philippe	08/06/2006	EC-INV	BOEHRINGER INGELHEIM	Recherche en pharmacologie fondamentale (Tiotropium)	expérimentateur principal	01/2005	12/2006
60399	DEVILLIER	Philippe	08/06/2006	EC-INV	SANOFI AVENTIS	Essai clinique Nasacort	coordonnateur	01/2005	12/2006
60399	DEVILLIER	Philippe	08/06/2006	EC-CO	SANOFI AVENTIS	Recherche en pharmacologie sur produits recherche Sanofi	experimentateur non principal	01/2005	
60399	DEVILLIER	Philippe	08/06/2006	RE-DE	MSD	Rapports d'expertise	rémunération personnelle	01/2004	12/2004
60399	DEVILLIER	Philippe	08/06/2006	IP-AC	MSD	Conseils en développement	rémunération personnelle	01/2000	
60399	DEVILLIER	Philippe	08/06/2006	IP-AC	STALLERGENES	Conseils en développement	Rémunération personnelle	01/2004	
60399	DEVILLIER	Philippe	08/06/2006	CF-INT	ASTRA ZENECA	Congrès multiples nationaux / régionaux (physiopathologie - pharmacologie) - depuis plus de 10 ana	rémunération personnelle		
60399	DEVILLIER	Philippe	08/06/2006	CF-INT	GSK	Congrès multiples nationaux / régionaux - depuis plus de 10 ans	rémunération personnelle		
60399	DEVILLIER	Philippe	08/06/2006	CF-INT	SCHERING PLOUGH	Congrès multiples nationaux / régionaux + 1 congrès international - depuis plus de 10 ans	rémunération personnelle		
60399	DEVILLIER	Philippe	08/06/2006	CF-INT	BOEHRINGER INGELHEIM	Congrès multiples nationaux / régionaux - depuis + de 5 ans	rémunération personnelle		
60399	DEVILLIER	Philippe	08/06/2006	CF-INT	MSD	Congrès multiples nationaux / régionaux (SINGULAIR / physiopathologie/ phanmacologie) depuis + de 5 ans	rémunération personnelle		
60399	DEVILLIER	Philippe	08/06/2006	CF-INT	STALLERGENES	Congrès nationaux d'allergologie - depuis 2 ans	rémunération personnelle		
60399	DEVILLIER	Philippe	08/06/2006	VB	ALTANA PHARMA	Recherche en pharmacologie expérimentale	UPRES EA 220	01/2005	12/2008
60399	DEVILLIER	Philippe	08/06/2006	VB	SANOFI AVENTIS	Recherche en pharmacologie expérimentale	UPRES EA 220	01/2000	
60399	DEVILLIER	Philippe	08/06/2006	VB	ASTRA ZENECA	Recherche en pharmacologie expérimentale	UPRES EA 220	01/2003	
60399	DEVILLIER	Philippe	08/06/2006	VB	BOEHRINGER INGELHEIM	Recherche en pharmacologie expérimentale	UPRES EA 220	01/2004	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60399	DEVILLIER	Philippe	13/02/2005	LD-AR	SCHERING PLOUGH	ORL, consultant régulier			
60399	DEVILLIER	Philippe	13/02/2005	LD-AR	BIOPROJET	Tous produits, consultant régulier			
60399	DEVILLIER	Philippe	13/02/2005	LD-AR	GLAXO SMITH KLINE	Pneumo, consultant régulier			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	ASTRA ZENECA	Membre du comité scientifique pneumologie			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	MERCK SHARP & DOHME	Singulair			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	ZAMBON	Budésonide			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	THERABEL	Canal 55, anti-histaminiques : mizolastine			
60399	DEVILLIER	Philippe	13/02/2005	IP-RE	MERCK	Rapport d'expert pour la transparence - Singulair			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	BOEHRINGER INGELHEIM	Symposium, BPCO, une fois anti-cholinergique, ipratropium, tiotropium			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	GSK	Asthme, BPCO, parfois sérévent, flixotide, sérétide			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	SCHERING PLOUGH	Tests cutanés, asmanex, aérius			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	MSD	Prise en charge asthme ou rhinite, leucotriènes, singulair			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	ASTRA ZENECA	Stratégie traitement asthme ou rhinite, symbicort, rhinocort			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	AVENTIS	Tolérance AINS, IPP, telfast, lanzor, nouveaux traitements			
60399	DEVILLIER	Philippe	13/02/2005	CF-INT	SCHWARTZ PHARMA	Nexxair			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	ASTRA ZENECA	Groupe de réflexion, stratégie dans asthme, Symbicort			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	ALTANA PHARMA	Groupe de travail BPCO + / Daxas			
60399	DEVILLIER	Philippe	13/02/2005	IP-AC	SFORL	En partenariat avec Schering Plough (groupe de travail rhinites inflammatoires, pas de produit spécifique)			
60399	DEVILLIER	Philippe	13/02/2005	CF-AUD	BOEHRINGER INGELHEIM	CPLF 2005			
60399	DEVILLIER	Philippe	13/02/2005	CF-AUD	GSK	ATS 2002 & 2001, ERS 2004, CPLF 2002, SF pharmacologie 2004, SFAIC 2000			
60399	DEVILLIER	Philippe	13/02/2005	CF-AUD	SCHERING PLOUGH	JPA 2003 & 2004, SPAIC 2002-2003 & 2004, AAACI 2005			
60399	DEVILLIER	Philippe	13/02/2005	CF-AUD	MSD	CPLF 2002 & 2004, ERS 2001 & 2003, Interasthma 2003			
60399	DEVILLIER	Philippe	13/02/2005	CF-AUD	ASTRA ZENECA	ATS 2004, Rhinoforum 2003, SWAN 2002 & 2003, Workshop pneumo, SA3P, pédiatrie pratique			
60399	DEVILLIER	Philippe	13/02/2005	VB	ASTRA ZENECA	Laboratoire de Pharmacologie UFR Médecine, ADEBIOPHARM, recherche fondamentale sans relation avec produit			
60399	DEVILLIER	Philippe	13/02/2005	(Autre)	ALTANA PHARMA	Subvention Laboratoire de Pharmacologie respiratoire Paris-Ouest, recherche fondamentale, phosphodiestérase			
60399	DEVILLIER	Philippe	13/02/2005	(Autre)	STALLERGENES	Activité ponctuelle de consultant en développement clinique pour immunothérapie spécifique			
60399	DEVILLIER	Philippe	13/02/2005	(Autre)	GSK	FMC, réunions loco-régionales, invitation comme orateur			
60399	DEVILLIER	Philippe	13/02/2005	IP-AUT	MSD	FMC, réunions loco-régionales, invitation comme orateur			
60399	DEVILLIER	Philippe	13/02/2005	IP-AUT	ASTRA ZENECA	FMC, réunions loco-régionales, invitation comme orateur			
60399	DEVILLIER	Philippe	13/02/2005	IP-AUT	SCHERING	FMC, réunions loco-régionales, invitation comme orateur			
60399	DEVILLIER	Philippe	13/02/2005	IP-AUT	BOEHRINGER INGELHEIM	FMC, réunions loco-régionales, invitation comme orateur			
60399	DEVILLIER	Philippe	16/09/2003	IP-EC	BIOPROJET PHARMA	Développement clinique et préclinique			
60399	DEVILLIER	Philippe	16/09/2003	IP-EC	SCHERING-PLOUGH	Conseil en développement			
60399	DEVILLIER	Philippe	16/09/2003	IP-AC	ASTRA ZENECA	Essais cliniques - Analyse littérature			
60399	DEVILLIER	Philippe	16/09/2003	IP-AC	ZAMBON	Essais cliniques - Analyse littérature			
60399	DEVILLIER	Philippe	16/09/2003	IP-AC	LAB CONSEIL	Communication			
60399	DEVILLIER	Philippe	16/09/2003	IP-AC	MSD-CHIBRET	Analyse littérature - Pharmacologie			
60399	DEVILLIER	Philippe	16/09/2003	IP-AC	GLAXO SMITHKLINE	Analyse littérature - Essai clinique			
60399	DEVILLIER	Philippe	16/09/2003	IP-AC	ALTANA PHARMA	Analyse littérature - Pharmacologie			
60399	DEVILLIER	Philippe	16/09/2003	IP-CF	AVENTIS	Symposium IPP			
60399	DEVILLIER	Philippe	16/09/2003	IP-CF	SCHERING-PLOUGH	Symposium sur allergie, anti-hg			
60399	DEVILLIER	Philippe	16/09/2003	IP-CF	GLAXO SMITHKLINE	Symposium sur asthme/BPCO			
60399	DEVILLIER	Philippe	16/09/2003	IP-CF	ASTRA ZENECA	Symposium sur asthme			
60399	DEVILLIER	Philippe	16/09/2003	IP-CF	MSD CHIBRET	Symposium sur asthme/allergie/leucotriène			
60399	DEVILLIER	Philippe	16/09/2003	IP-AUT	GLAXO SMITHKLINE	Invitation congrès/workshop			
60399	DEVILLIER	Philippe	16/09/2003	IP-AUT	MSD CHIBRET	Invitation congrès/workshop			
60399	DEVILLIER	Philippe	16/09/2003	IP-AUT	ASTRA ZENECA	Invitation congrès/workshop			
60399	DEVILLIER	Philippe	16/09/2003	CF-AUD	SCHERING-PLOUGH	Invitation congrès/workshop			
60399	DEVILLIER	Philippe	10/07/2000	LD	BIOPROJET, GLAXO WELLCOME	Analyse littérature, actualisation des connaissances sur la physiopathologie et le mode d'action des médicaments dans l'asthme. Analyse des paramètres pharmacocliniques de			
60399	DEVILLIER	Philippe	10/07/2000	IP-AC	ASTRA, BOEHRINGER INGELHEIM	Conseil en développement clinique et en analyse données littérature			
60399	DEVILLIER	Philippe	10/07/2000	IP-AC	MERCK SHARP DOHME, SANOFI SYNTHELABO	Plan expérimental de protocole d'essai clinique			
60399	DEVILLIER	Philippe	10/07/2000	IP-AC	SCHERING PLOUGH	Pharmacologie fondamentale et clinique			
60399	DEVILLIER	Philippe	10/07/2000	IP-CF	GLAXO WELLCOME	B2-longue action, corticoïdes : pharmacologie			
60399	DEVILLIER	Philippe	10/07/2000	IP-CF	BOEHRINGER INGELHEIM	Pharmacologie			
60399	DEVILLIER	Philippe	10/07/2000	IP-CF	NOVARTIS	B2-longue action, nouveaux traitements : pharmacologie			
60399	DEVILLIER	Philippe	10/07/2000	IP-CF	MERCK SHARP DOHME	Pharmacologie			
60399	DEVILLIER	Philippe	10/07/2000	IP-CF	SCHERING PLOUGH	Corticoïdes : pharmacologie			
60399	DEVILLIER	Philippe	10/07/2000	IP-CF	AVENTIS	Anti-histaminiques : pharmacologie			
60399	DEVILLIER	Philippe	10/07/2000	IP-AUT	AVENTIS	Analyse littérature et rédaction de chapitres sur la pharmacologie de l'inflammation de la sphère ORL pour établissement de recommandations			
60138	DEVISSAGUET	Jean-Philippe	10/07/2000	IP-RE	SERVIER	Pharmacocinétique : "Aerodiol"			
60138	DEVISSAGUET	Jean-Philippe	10/07/2000	IP-AC	SERVIER	Pharmacocinétique et métabolisme			
60138	DEVISSAGUET	Jean-Philippe	10/07/2000	PAR	Institut de Recherche International SERVIER (IRIS)	Conjoint			
60119	DIERAS	Véronique	25/09/2003	IP-EC	AVENTIS	Investigateur - Etude de phase II du RPR 109881 - 01/04/2001-30/09/2003	(Liste détaillée des essais jointe à la DPI)		
60119	DIERAS	Véronique	25/09/2003	IP-EC	PFIZER	Investigateur - Etude de phase II de l'agent CI-1033 - 21/03/2003-31/12/2004			
60119	DIERAS	Véronique	25/09/2003	IP-EC	MGI PHARMA	Investigateur - Etude de phase II de l'huiven - 01/05/2001-06/05/2003			
60119	DIERAS	Véronique	25/09/2003	IP-EC	BAYER PHARMA	Investigateur - Etude de phase I de BAY 59-8862 - 07/03/2002-30/04/2004			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CYCLACEL Ltd	Investigateur - Etude clinique de phase I et de pharmacocinétique du CYC202 - 01/06/2001-01/05/2004			
60119	DIERAS	Véronique	25/09/2003	IP-EC	ASTRA ZENECA	Investigateur - Etude de phase II de l'association ZD1839 (Iressa TM)/Docétaxel versus placebo/Docétaxel - 26/07/2002-31/12/2004			
60119	DIERAS	Véronique	25/09/2003	IP-EC	SANOFI	Investigateur - Etude de phase II de l'Oxaliplatine seul ou associé avec le 5 Fluorouracile - 19/07/2002-31/12/2004			
60119	DIERAS	Véronique	25/09/2003	IP-EC	INSTITUT CURIE	Coinvestigateur - Taxotère sujets âgés - Phase I (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	BAYER PHARMA	Coinvestigateur - Taxane TWIST - Phase I (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CAC	Coinvestigateur - CYC 202 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CENTRE LEON BERRARD	En qualité de chef de service délégué recherche clinique - Temodal HD (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	BAYER PHARMA	Coinvestigateur - Taxane TWIST - extension pahse I (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	EORTC	En qualité de chef de service délégué recherche clinique - EORTC 16023 Tax. Hercepline FTI (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	GLAXO	En qualité de chef de service délégué recherche clinique - HER 2 15-002 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	EUREKA	Coinvestigateur - Eureka 01 (Taxotère) (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	INSTITUT CURIE	En qualité de chef de service délégué recherche clinique - Néo-adjuvant - S14 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	FNCLCC	En qualité de chef de service délégué recherche clinique - Adjuvant - PACS 04 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	FNCLCC	En qualité de chef de service délégué recherche clinique - Adjuvant - PEGASE 06			
60119	DIERAS	Véronique	25/09/2003	IP-EC	FNCLCC	En qualité de chef de service délégué recherche clinique - Inflammatoire - PEGASE 07 (en cours)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60119	DIERAS	Véronique	25/09/2003	IP-EC	ASTRA ZENECA	Coinvestigateur - Métastatique - Taxotère +/- Iressa (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	WYETH	En qualité de chef de service délégué recherche clinique - Métastatique - CCI 779/Letrozole (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	AVENTIS	Coinvestigateur - Taxoide V204 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	PFIZER	Coinvestigateur - CI 1033 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	FNLCC/EORTC	En qualité de chef de service délégué recherche clinique - Euro-Ewing99 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	I.G.R	En qualité de chef de service délégué recherche clinique - SARG/GYN1 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	FNLCC	En qualité de chef de service délégué recherche clinique - Sarcome 04 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	ASTRA ZENECA	En qualité de chef de service délégué recherche clinique - Iressa Col (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	TRANSGENE S.A	En qualité de chef de service délégué recherche clinique - TG 4001 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	SANOFI	Coinvestigateur - EFC 7496 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	INSTITUT CURIE	En qualité de chef de service délégué recherche clinique - VP 16-IFO (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	SAINT-LOUIS	En qualité de chef de service délégué recherche clinique - IFCT 0002 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	PIERRE FABRE	En qualité de chef de service délégué recherche clinique - PM 0259 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	I.C.	En qualité de chef de service délégué recherche clinique - CP9904 et CP9903 - IFM 99-06 et TAM Myelo (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	MEDIGENE	En qualité de chef de service délégué recherche clinique - CT 1002 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CHU Poitiers	En qualité de chef de service délégué recherche clinique - AFR04-GLIVEC (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	SFGM	En qualité de chef de service délégué recherche clinique - AUTO-LLC 1865 et LNH 2ème ligne (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	AP-HP	En qualité de chef de service délégué recherche clinique - LMC 97 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	EORTC	En qualité de chef de service délégué recherche clinique - EORTC 20981 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	GELA	En qualité de chef de service délégué recherche clinique - GELA H3-4 et LNH 98 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CHU Nancy	En qualité de chef de service délégué recherche clinique - IFM 01-01 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	LAPHAL	En qualité de chef de service délégué recherche clinique - IFM 01-02 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CHU Toulouse	En qualité de chef de service délégué recherche clinique - IFM 99-01 et 99-02 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-EC	CHU Nantes	En qualité de chef de service délégué recherche clinique - IFM 99-04 (en cours)			
60119	DIERAS	Véronique	25/09/2003	IP-AC	AVENTIS	Advisory Boards			
60119	DIERAS	Véronique	25/09/2003	IP-AC	ASTRA ZENECA	Advisory Boards			
60119	DIERAS	Véronique	25/09/2003	IP-AC	LILLY	Advisory Boards			
60119	DIERAS	Véronique	25/09/2003	IP-AC	WYETH	Advisory Boards			
60119	DIERAS	Véronique	25/09/2003	IP-AC	GLAXO	Advisory Boards			
60119	DIERAS	Véronique	25/09/2003	IP-CF	ASTRA ZENECA	Séminaire Méthodologie essais cliniques			
60119	DIERAS	Véronique	25/09/2003	IP-CF	ROCHE	Conférences			
60119	DIERAS	Véronique	25/09/2003	IP-CF	AVENTIS	Advisory Boards			
60119	DIERAS	Véronique	25/09/2003	IP-AC	LILLY	Conférences			
60119	DIERAS	Véronique	25/09/2003	IP-CF	ELAU	Conférence			
60119	DIERAS	Véronique	25/09/2003	VB		Honoraires, observations, essais,cliniques versés directement à l'Institut Curie			
60119	DIERAS	Véronique	25/09/2003	PAR	SERVIER	Soeur			
60119	DIERAS	Véronique	25/09/2003	(Autre)	AVENTIS, PHARMACIA, ROCHE, ASTRA ZENECA, BAYER	Invitations à congrès			
60119	DIERAS	Véronique	07/10/2000	IP-AC	ASTRA ZENECA	Advisory board			
60119	DIERAS	Véronique	07/10/2000	IP-AC	NOVARTIS	Advisory board			
60119	DIERAS	Véronique	07/10/2000	IP-CF	AVENTIS	Symposium			
60119	DIERAS	Véronique	07/10/2000	IP-CF	ROCHE	Symposium			
60119	DIERAS	Véronique	07/10/2000	IP-CF	ASTRA ZENECA	Formation			
60119	DIERAS	Véronique	07/10/2000	VB		Essais cliniques - Institut Curie			
60119	DIERAS	Véronique	07/10/2000	(Autre)	SERVIER	Soeur			
64768	DOAT	Marc	11/09/2007	CF-AUD	ALCON	Alsace - Présentation de l'usine de fabrication de collyre unidose		12/2006	12/2006
64768	DOAT	Marc	11/09/2007	PAR	SERVIER	Chef de projet pharmacien	Conjoint	01/2002	
63965	DORE	Jean-François	08/02/2010	LD-AR	CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER (OMS-LYON)	scientific secretary, projets européens : CD-EUROCAN + PLUS (faisabilité de la coordination de la recherch	rémunération personnelle	01/2005	12/2009
63965	DORE	Jean-François	08/02/2010	CF-INT	SOCIETE INTERNATIONALE DES ANTIOXYDANTS	mailo antioxydants conférence / le soleil ami ou ennemi de la peau:	aucune rémunération	10/2009	
63965	DORE	Jean-François	08/02/2010	CF-INT	SOCIETE FRANCAISE DES ANTIOXYDANTS	conférence SFA / soleil et cancers cutanés	aucune rémunération	12/2007	
63965	DORE	Jean-François	08/02/2010	(Autre)	ASSOCIATION SECURITE SOLAIRE	membre du conseil scientifique			
63965	DORE	Jean-François	08/02/2010	(Autre)	EURO SKIN (EUROPEAN SOCIETY FOR SKIN CANCER PREVENTION-SOCIETE ALLEMANDE)	president		01/2010	12/2011
63965	DORE	Jean-François	08/02/2010	(Autre)	AFSSET	président, CES agents physiques. Président, groupe de travail : UV (2005), RFID (2008), radiofrequences (2009). Rapporteur : cancers et env		01/2006	
63965	DORE	Jean-François	08/02/2010	(Autre)	INSTITUT DE VEILLE SANITAIRE	cohorte ELFE	mesure de l'exposition UV des enfants	01/2007	
63965	DORE	Jean-François	11/01/2008	LD-AR	INTERNATIONAL AGENCY FOR RESEARCH ON CANCER - LYON	Visiting scientist		01/2005	
63965	DORE	Jean-François	11/01/2008	LD-AR	INSTITUT EUROPEEN D'ONCOLOGIE - MILAN	Consultant		01/2001	12/2003
63965	DORE	Jean-François	11/01/2008	IP-RE	COMMISSION EUROPEENNE - DG RECHERCHE	Evaluation de projets FP5 - FP6 - FP7		01/2000	
63965	DORE	Jean-François	11/01/2008	IP-RE	AFSSAPS	Expert groupe de travail produits de protection solaire		01/2005	
63965	DORE	Jean-François	11/01/2008	IP-RE	AFSSET	Président CESagents physiques DDPrésident groupe de travail Ultraviolets		01/2005	
63965	DORE	Jean-François	11/01/2008	IP-AC	MAXIM PHARMACEUTICAL SAN DIAGO - CA USA	Calcul de prévalence du mélanomeen europe		01/2003	01/2004
63965	DORE	Jean-François	11/01/2008	IP-CF	NIVEA	Conférencce de presse - Paris : protection solaire "le bon usage du soleil"		01/2005	01/2005
63965	DORE	Jean-François	11/01/2008	IP-CF	OCIETE FRANCAISE DES ANTIOXYDANTS	conférences ingrédients solaires et vieillissement		05/2005	05/2005
63965	DORE	Jean-François	11/01/2008	IP-CF	OCIETE FRANCAISE DES ANTIOXYDANTS	conférences ingrédients solaires et vieillissement		12/2007	12/2007
63965	DORE	Jean-François	11/01/2008	(Autre)	ASSOCAITION SECURITE SOLAIRE	MEMEBRE DU CONSEIL SCIENTIFIQUE		01/1997	
63965	DORE	Jean-François	13/01/2006	LD-AR	INSTITUT EUROPEEN D'ONCOLOGIE	Consultant Milan, Italie	Rémunération personnelle	01/2001	12/2003
63965	DORE	Jean-François	13/01/2006	LD-AR	CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER	Consultant, OMS	Rémunération personnelle	01/2006	01/2006
63965	DORE	Jean-François	13/01/2006	RE-AUT	COMMISSION EUROPEENNE DG RECHERCHE	Evaluation de projets FP5 ET FP6 - Bruxelles	Rémunération personnelle	01/2000	12/2003
63965	DORE	Jean-François	13/01/2006	IP-AC	MAXIM PHARMACEUTICALS	Evaluation de la prévalence du mélanome en Europe - San Diego, CA, USA	Rémunération personnelle	01/2003	01/2004
63965	DORE	Jean-François	13/01/2006	IP-CF	NIVEA	Conférence de Presse, Protection solaire : le bon usage du soleil	Rémunération personnelle	01/2005	01/2005
63965	DORE	Jean-François	13/01/2006	CF-INT	SOCIETE FRANCAISE DES ANTI-OXYDANTS	Paris, conférence SFA ingrédients solaires et Vieillissement cutané / Soleil, Ultraviolets et peau	Aucune rémunération	05/2005	05/2005
63965	DORE	Jean-François	13/01/2006	VB	SERVIER	Traitement du gliome par irradiation fractionnée et fotémustine pour l'INSERM		01/2003	12/2003
63965	DORE	Jean-François	13/01/2006	(Autre)	ASS. SECURITE SOLAIRE	Membre du Conseil Scientifique		01/1997	
63965	DORE	Jean-François	11/08/2005	LD	INSTITUT EUROPEEN D'ONCOLOGIE	Consultant, Milan, Italie	Rémunération personnelle	01/2001	12/2003
63965	DORE	Jean-François	11/08/2005	LD	COMMISSION EUROPEENNE DGF SAMCO	Member Scientific Committee Cosmetics, Bruxelles		01/1997	12/2000
63965	DORE	Jean-François	11/08/2005	IP-RE	COMMISSION EUROPEENNE DG RECHERCHE	Evaluation de projets FP5 ET FP6 - Bruxelles	Rémunération personnelle	01/2000	12/2003
63965	DORE	Jean-François	11/08/2005	IP-AC	MAXIM PHARMACEUTICALS	Evaluation de la prévalence du mélanome en Europe - San Diego, CA, USA	Rémunération personnelle	01/2003	01/2004
63965	DORE	Jean-François	11/08/2005	IP-CF	NIVEA	Conférence de Presse, Protection solaire : le bon usage du soleil	Rémunération personnelle	01/2005	01/2005

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
53965	DORE	Jean-François	11/08/2005	(Autre)	ASS. SECURITE SOLAIRE	Membre du Conseil Scientifique		01/1997	12/1997
50956	DOSQUET	Christine	02/09/2009	EC-CO	GENEVRIER	DERMAGEN - participation à la mise au point coordination scientifique de l'essai clinique (en cours)	Expérimentateur	10/2002	
50956	DOSQUET	Christine	06/06/2000	VB	IRIS/SERVIER	Association Claude Bernard			
60088	DOUCET	Jean	07/12/2010	IP-AUT	NOVO-NORDISK	Réalisation d'un livret d'information sur l'insulinothérapie chez les patients agés diabétiques.		11/2010	12/2010
60088	DOUCET	Jean	07/12/2010	IP-AUT	BECTON-DICKINSON	Réalisation d'un livret d'éducation thérapeutique destiné aux patients agés diabétiques.		09/2010	11/2010
60088	DOUCET	Jean	13/10/2010	CF-AUD	NOVO-NORDISK	Congrès de l'EASD, Stockholm		09/2010	09/2010
60088	DOUCET	Jean	13/10/2010	CF-AUD	BMS	Congrès de la Société Francophone du Diabète, Lille		03/2010	03/2010
60088	DOUCET	Jean	13/10/2010	CF-INT	NOVO-NORDISK	Séminaire Perspectives 2020	Aucune rémunération	05/2010	05/2010
60088	DOUCET	Jean	01/02/2010	IP-AC	BMS - ASTRA ZENECA	Conseils pour la rédaction d'un article sur des résultats d'essais avec la Saxagliptine	Aucune rémunération	07/2009	10/2010
60088	DOUCET	Jean	01/02/2010	CF-AUD	NOVO-NORDISK	45° congrès de l'European Association for the Study of Diabetes, Vienne (Autriche)		09/2009	10/2009
60088	DOUCET	Jean	01/02/2010	CF-AUD	NOVO-NORDISK	60° congrès de la Société Nationale Française de Médecine Interne, Toulouse		12/2009	12/2009
60088	DOUCET	Jean	01/02/2010	CF-INT	NOVO-NORDISK	Pratiques et perspectives en Diabétologie	Rémunération institution	12/2009	12/2009
60088	DOUCET	Jean	26/05/2009	VB	NOVO-NORDISK	Subvention pour une étude épidémiologique prospective sur les patients diabétiques âgés (sans intervention	Association GERODIAB (loi 1901)	12/2008	
60088	DOUCET	Jean	26/05/2009	VB	MERCK-SERONO	Subvention pour une étude épidémiologique prospective sur les patients diabétiques âgés (sans intervention	Association GERODIAB (loi 1901)	12/2008	
60088	DOUCET	Jean	26/05/2009	CF-AUD	NOVO-NORDISK	Réunion Perspectives 2020, Paris		04/2009	04/2009
60088	DOUCET	Jean	26/05/2009	CF-AUD	SERVIER	Congrès de l'ALFEDIAM, Strasbourg		03/2009	03/2009
60088	DOUCET	Jean	10/11/2008	CF-AUD	SERVIER	Congrès européen de l'EASD, Rome		09/2008	09/2008
60088	DOUCET	Jean	10/11/2008	CF-INT	NOVO-NORDISK	Séminaire Perspectives 2020,Oxford. Présentation d'un projet de suivi de cohorte de diabétiques âgés.	Aucune rémunération	10/2008	10/2008
60088	DOUCET	Jean	10/11/2008	CF-INT	THERVAL MEDICAL	Enseignement post-universitaire: Avances thérapeutiques sur le diabète et l'HTA, Mt St Michel	Aucune rémunération	10/2008	10/2008
60088	DOUCET	Jean	05/06/2008	CF-AUD	SERVIER MEDICAL	Congrès francophone de l'ALFEDIAM, Bruxelles		12/2007	12/2007
60088	DOUCET	Jean	05/06/2008	CF-INT	GSK	Saint Gatien (14). Diabétologie et Pneumologie du sujet âgé.□□"Spécificités de la prise en charge des diabé	Rémunération institution	11/2007	11/2007
60088	DOUCET	Jean	28/09/2007	CF-AUD	NOVO-NORDISK	Congrès de l'European Association for the Study of Diabetes, Amsterdam		09/2007	09/2007
60088	DOUCET	Jean	18/06/2007	CF-INT	NOVO-NORDISK	Symposium sur le diabète, congrès national de la SNFMI, Narbonne, 7 juin 2007. Intervention sur le passage	Rémunération institution	06/2007	06/2007
60088	DOUCET	Jean	23/04/2007	CF-AUD	TAKEDA	Congrès de l'ALFEDIAM, Marseille		03/2007	03/2007
60088	DOUCET	Jean	29/01/2007	IP-AUT	EDITIONS DE LA BLOUSE BLANCHE, EN COLLABORATION AVEC NOVO-NORDISK	Rédaction d'une plaquette d'information scientifique sur "prise en charge du diabète de type 2: les enjeux lié		07/2006	07/2006
60088	DOUCET	Jean	29/01/2007	CF-INT	NOVO-NORDISK	"Perspectives 2020", Salzburg (Autriche) sur la prise en charge du diabète à l'horizon 2020	Aucune rémunération	10/2006	10/2006
60088	DOUCET	Jean	10/10/2006	CF-AUD	THERVAL	6° rencontres franco-italiennes d'HTA, Rome (Italie)		09/2006	10/2006
60088	DOUCET	Jean	10/10/2006	CF-AUD	NOVO-NORDISK	Congrès européen de l'EASD, Copenhague (Danemark)		09/2006	09/2006
60088	DOUCET	Jean	30/06/2006	EC-INV	NOVO-NORDISK	Etude comparative de l'action de l'insuline Detemir vs NPH chez les diabétiques de plus de 75 ans	Coordonateur- consultant	06/2006	
60088	DOUCET	Jean	12/04/2006	VB	ABBOTT, THERVAL, HOMEPERF, LUNDBECK, NOVARTIS, PFIZER, NUTRITIA, SERVIER, TAKEDA, MERCK-LIPHA, BIOCODEX, SANOFI-AVENTIS, HARTMANN, NORGINE, BMS, ASTRA-ZENECA, NOVO-NORDISK, GENEVRIER, EUTHERAPIE, ROCHE DIAGNOSTICS, GSK, MSD	Deux EPU annuels de Gériatrie facultaires (180 médecins et 200 soignants) (budget 12500 €)	Association "Recherche en Gérontologie"	04/2006	05/2006
60088	DOUCET	Jean	12/04/2006	CF-AUD	NOVO-NORDISK	Congrès de l'ALFEDIAM, Paris		03/2006	03/2006
60088	DOUCET	Jean	12/04/2006	CF-INT	ALTANA	Symposium aux Journées francophones de pathologie digestive, Paris. Conférence sur les risques évitables	Rémunération institution	03/2006	03/2006
60088	DOUCET	Jean	17/01/2006	EC-INV	JANSSEN-CILAG	Epidémiologie des complications du reflux gastro-oesophagien chez les patients agés consultant en gastro-e	Coordonnateur	03/2006	
60088	DOUCET	Jean	19/12/2005	EC-CO	THERVAL MEDICAL	Etude Optimax sur l'efficacité de l'association Périndopril-Indapamide à petite dose sur l'HTA avec ou sans s	Co-investigateur	09/2005	03/2006
60088	DOUCET	Jean	19/12/2005	EC-CO	NOVO	Etude Predictive sur la tolérance de l'insuline Levemir à 3, 6 ou 12 mois		10/2005	12/2006
60088	DOUCET	Jean	19/12/2005	EC-CO	THERVAL MEDICAL	Etude Perfuse sur le taux de normalisation artérielle sous association Périndopril-Indapamil à petite dose		12/2005	12/2006
60088	DOUCET	Jean	19/12/2005	IP-AC	GROUPE SANTE EN ACTION	Elaboration de documents pédagogiques sur la prévention de la iatrogénèse en pédiatrie	Aucune rémunération	09/2003	
60088	DOUCET	Jean	19/12/2005	IP-AC	LUNDBECK	Corrections d'un document "Questions/Réponses" sur l'Ebixa		07/2005	07/2005
60088	DOUCET	Jean	19/12/2005	CF-INT	IFIS	Evaluation des antidiabétiques en gériatrie	Sans rémunération	06/2005	06/2005
60088	DOUCET	Jean	19/12/2005	CF-INT	THERVAL MEDICAL	Réunion sur l'hypertension artérielle et ses complications (Mont Saint-Michel)		04/2005	04/2005
60088	DOUCET	Jean	19/12/2005	CF-INT	SANOFI-AVENTIS	1ère Rencontre de Gériatrie (Deauville). Iatrogénèse gériatrique		10/2005	10/2005
60088	DOUCET	Jean	19/12/2005	CF-INT	SANOFI-AVENTIS	Rendez-vous Santé de Normandie. Iatrogénèse gériatrique		12/2005	12/2005
60088	DOUCET	Jean	19/12/2005	CF-AUD	NOVO	Congrès de l'EASD, Munich		09/2004	09/2004
60088	DOUCET	Jean	19/12/2005	CF-AUD	NOVO	Congrès de l'EASD (Athènes)		09/2005	09/2005
60088	DOUCET	Jean	19/12/2005	CF-AUD	NOVO	Congrès ALFEDIAM		03/2005	03/2005
60088	DOUCET	Jean	19/12/2005	CF-AUD	THERVAL	Journées franco-italiennes d'Hypertension artérielle (Bologne)		10/2003	10/2003
60088	DOUCET	Jean	19/12/2005	VB	Abbott, Astra-Zeneca, Biocodex, Euthérapie, GSK, Genevrier, Janssen-Cilag, Johnson and Johnson, Hartmann, MSD, Merck-Lipha, Novartis, Novo, Nutritia, Sanofi-Aventis, Servier, Therval Médical, Ypsomed	Financement de 2 réunions d'EPU pour un budget total de 13 050 euros		04/2005	05/2005
60088	DOUCET	Jean	19/12/2005	EC-CO	LEO	Etude sur la tolérance de l'innohep chez le sujet agé avec fonction rénale altérée et thrombo-phlébite profon		12/2005	
60088	DOUCET	Jean	02/06/2004	EC-CO	SERVIER	Etude Paradis - Actuellement terminée (inclusion)	Rémunération personnelle	01/2004	12/2004
60088	DOUCET	Jean	02/06/2004	EC-CO	ARDIX	Etudes Hyvet - Etude arrêtée par le service	Rémunération institution	01/2003	12/2003
60088	DOUCET	Jean	02/06/2004	EC-CO	AVENTIS	Etude Exclaim - Etude arrêtée par le service	Rémunération institution	01/2004	12/2004
60088	DOUCET	Jean	02/06/2004	EC-CO	ASTRA	Etude Sportif III - Actuellement terminée (inclusion)	Rémunération institution	01/2003	12/2003
60088	DOUCET	Jean	02/06/2004	CF-INT	ASTRA	Comparaison IEC et sartans			06/2003
60088	DOUCET	Jean	02/06/2004	CF-INT	BRISTOL MYERS SQUIBB	Tolérance des statines		04/2004	04/2004
60088	DOUCET	Jean	02/06/2004	CF-INT	LEO	Critères de décision des Héparines			02/2004
60088	DOUCET	Jean	02/06/2004	CF-INT	ARDIX	Essais thérapeutiques et HTA		05/2004	05/2004
60088	DOUCET	Jean	02/06/2004	CF-AUD	THERVAL	Journées franco-italiennes d'Hypertension artérielle (Rome)		12/2004	10/2004
60088	DOUCET	Jean	02/06/2004	VB	ABBOTT, ARDIX, ASTRA, AVENTIS, BIOCODEX, CHIESI, EISAI, GLAXO SMITHKLINE, HARDIX MEDICAL, KCI, JANSSEN, LUNDBECK, MEDIX, NOVARTIS, SANOFI, SERVIER, TAKEDA	Financement de 2 réunions d'EPU pour un budget total de 6000 Euros environ / association Recherche en gérontologie (2ème journée le 20		04/2004	04/2004
60088	DOUCET	Jean	02/06/2004	IP-AC	SERVIER	Participation à un groupe de travail (1 seule réunion) sur le rôle de l'Indapamide dans l'HTA		12/2003	12/2003
60088	DOUCET	Jean	17/04/2003	IP-EC	SERVIER	Etude Paradis			
60088	DOUCET	Jean	17/04/2003	IP-EC	ARDIX	Etude Hyvet			
60088	DOUCET	Jean	17/04/2003	IP-EC	AVENTIS	Etude Exclaim			
60088	DOUCET	Jean	17/04/2003	IP-CF	ARDIX THERVAL	HTA et personne âgée (2002-2003)			
60088	DOUCET	Jean	17/04/2003	IP-CF	ASTRA ZENECA	IEC et sartans/personne agée (juin 2002)			
60088	DOUCET	Jean	17/04/2003	IP-CF	LUNDBECK	Pharmacologie de la mémantine (mars 2003)			
60088	DOUCET	Jean	17/04/2003	VB	ARDIX, EISAI, AVENTIS, NOVO, LIFESCAN, SERVIER, THERVAL, MUNDIPHARMA, JANSSEN, SANOFI, MERCK SHARP & DOHME, SOLVAY	"Recherches gérontologie" pour 1 EPU annuel (budget total # 5 000 €)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
50088	DOUCET	Jean	14/06/2000	IP-EC	ARDIX	Essai Pretherax			
50088	DOUCET	Jean	14/06/2000	IP-EC	ASTRA ZENECA	Essai Sportif III			
50088	DOUCET	Jean	14/06/2000	IP-CF	NOVARTIS	12 mai 2000			
61357	DRICI	Milou-Daniel	12/04/2010	CF-INT	NOVARTIS	Mougins 08/Réunion de cardiologues/ hypertension artérielle et trithérapie/ Exforge HCT®	Rémunération personnelle	04/2010	04/2010
61357	DRICI	Milou-Daniel	12/04/2010	CF-INT	MEDA	Paris/Ateliers de Rythmologie/Pharmacogénétique des anticoagulants/aucun produit	Rémunération personnelle	03/2010	03/2010
61357	DRICI	Milou-Daniel	20/01/2010	LD-AR	DAICHII-SANKYO	Board OLMESARTAN	Rémunération personnelle	01/2009	
61357	DRICI	Milou-Daniel	20/01/2010	LD-AR	MEDA-PHARMA	Board des 24 heures de rythmologie	Rémunération personnelle	01/2009	
61357	DRICI	Milou-Daniel	20/01/2010	LD-AR	NEGMA-LERADS	Board NEBIVOLOL	Rémunération personnelle	01/2009	
61357	DRICI	Milou-Daniel	20/01/2010	CF-AUD	BOEHRINGER	European Society of Cardiology□□Munich-Allemagne		08/2009	08/2009
61357	DRICI	Milou-Daniel	20/01/2010	CF-AUD	BOEHRINGER	American Heart Association□□Orlando-USA		11/2009	11/2009
61357	DRICI	Milou-Daniel	20/01/2010	CF-AUD	NEGMA	Présentations des interactions médicamenteuses chez le sujet agé au CNCF	rémunération personnelle	04/2009	04/2009
61357	DRICI	Milou-Daniel	20/01/2010	CF-AUD	ABBOTT	Présentation aux Journées d'HTA des associations IEC-antagonistes calciques	rémunération personnelle	12/2009	12/2009
61357	DRICI	Milou-Daniel	20/01/2010	CF-AUD	THEA	Présentation aux ophtalmologistes libéraux des béta-bloquants en cardiologie	rémunération personnelle	07/2009	07/2009
61357	DRICI	Milou-Daniel	20/01/2010	CF-AUD	DAICHII-SANKYO	Présentation à la Société Croate et Française de cardio en relation avec l'association olmesartan-amlodipine	rémunération personnelle	11/2009	11/2009
61357	DRICI	Milou-Daniel	20/01/2010	CF-INT	DAICHII-SANKYO	Présentation aux Journées Européennes de la Société Française de cardio en relation avec l'association olm	Rémunération personnelle	01/2010	01/2010
61357	DRICI	Milou-Daniel	20/01/2010	CF-INT	DAICHII-SANKYO	Présentation au CNCF en relation avec l'association olmesartan-amlodipine	Rémunération personnelle	10/2009	01/2010
61357	DRICI	Milou-Daniel	20/01/2010	CF-INT	DAICHII-SANKYO	Présentation au Printemps de la cardio en relation avec l'association olmesartan-amlodipine	Rémunération personnelle	06/2009	06/2009
61357	DRICI	Milou-Daniel	20/01/2010	LD-AR	BOEHRINGER	Activité de conseil□□telmisartan	Rémunération personnelle	06/2009	09/2009
61357	DRICI	Milou-Daniel	18/03/2009	IP-AC	LUNDBECK SA	Conseils en développement du sertindole	Rémunération personnelle/institution	11/2008	05/2009
61357	DRICI	Milou-Daniel	18/03/2009	CF-INT	SERVIER	Formation médicale continue: présentation de l'étude Advance	Rémunération personnelle/institution	12/2008	12/2008
61357	DRICI	Milou-Daniel	18/03/2009	CF-INT	SERVIER	Formation médicale continue: présentation de l'étude Advance	Rémunération personnelle/institution	12/2007	12/2007
61357	DRICI	Milou-Daniel	18/03/2009	LD-AR	LUNDBECK SA	Sertindole	Rémunération personnelle/institution	01/2008	01/2009
61357	DRICI	Milou-Daniel	18/03/2009	LD-AR	MEDA PHARMA	Activité de Conseil	Rémunération personnelle/institution	01/2008	
61357	DRICI	Milou-Daniel	18/03/2009	LD-AR	DAICHI-SANKYO	Membre Comité de Conseil SEVIKAR	Rémunération personnelle/institution	10/2008	
61357	DRICI	Milou-Daniel	18/03/2009	CF-INT	BOEHRINGER INGELHEIM	Formation médicale continue de délégués médicaux	rémunération personnelle	03/2009	03/2009
61357	DRICI	Milou-Daniel	11/09/2008	CF-AUD	SERVIER MEDICAL	Société Européenne d'Hypertension		06/2008	09/2008
61357	DRICI	Milou-Daniel	11/09/2008	CF-AUD	BOERHINGER INGELHEIM	American Heart Association		11/2007	11/2007
61357	DRICI	Milou-Daniel	11/09/2008	CF-AUD	BOEHRINGER INGELHEIM	Société Européenne de Cardiologie		09/2008	09/2008
61357	DRICI	Milou-Daniel	11/09/2008	LD-AR	MEDA PHARMA	Activité de Conseil	Rémunération personnelle/institution	01/2008	
61357	DRICI	Milou-Daniel	11/09/2008	LD-AR	DAICHI-SANKYO	Membre Comité de Conseil SEVIKAR	Rémunération personnelle/institution	10/2008	
61357	DRICI	Milou-Daniel	25/09/2007	CF-AUD	SERVIER MEDICAL	Invitation à l'European Society of Cardiology- Vienne (AUT) du 31/8 au 4/9 2007		08/2007	09/2007
61357	DRICI	Milou-Daniel	25/09/2007	CF-INT	NOVARTIS	Defraiement de participation au CNCF à Marseille le 12/10/2007	Aucune rémunération	10/2007	10/2007
61357	DRICI	Milou-Daniel	25/09/2007	CF-INT	SERVIER MEDICAL	Présentation d'étude multicentrique et de son rationnel à Nice le 7/12/2007	Rémunération institution		
61357	DRICI	Milou-Daniel	16/07/2007	LD-AR	NEGMA LERADS	Membre Comité de Conseil Nébivolol	Rémunération institution	05/2003	
61357	DRICI	Milou-Daniel	16/07/2007	LD-AR	LUNDBECK-SA	Membre de l'International DSMB sertindole/risperidone	Rémunération institution	01/2003	
61357	DRICI	Milou-Daniel	16/07/2007	CF-AUD	SERVIER	International CardioVascular Research à Bologne (IT)		06/2007	06/2007
61357	DRICI	Milou-Daniel	16/07/2007	CF-INT	MERCK-LIPHA	Defraiement de participation aux deux séminaires annuels des DES de cardiologie (sans rapport avec les pr	Aucune rémunération	01/2006	12/2007
61357	DRICI	Milou-Daniel	27/06/2006	IP-RE	AMGEN	Evaluation scientifique d'un dossier préclinique	Association Loi 1901	02/2006	04/2006
61357	DRICI	Milou-Daniel	27/06/2006	CF-INT	BOEHRINGER	Telmisartan - Canada, MacMaster University, séminaire syndrome métabolique		09/2005	09/2005
61357	DRICI	Milou-Daniel	27/06/2006	CF-AUD	BAYER	Telmisartan - Marrakech, Congrès syndrome métabolique		05/2006	05/2006
61357	DRICI	Milou-Daniel	27/06/2006	CF-INT	BAYER	Telmisartan - Séminaire de formation, Congrès syndrome métabolique - Milan		05/2006	05/2006
61357	DRICI	Milou-Daniel	27/06/2006	IP-AC	SANKYO-MERCK LIPHA	Groupe d'experts Olmesartan - 1 ou 2 réunions par an	Association Loi 1901		06/2006
61357	DRICI	Milou-Daniel	27/06/2006	IP-AC	NEGMA	Groupe d'experts "Nebivolol"	Association Loi 1901	01/2005	
61357	DRICI	Milou-Daniel	08/06/2006	LD-AR	LUNDBECK S.A	Membre du management - Committee du DSMB international. SERTINDOLE / RISPERIDONE	rémunération versée à une institution	01/2003	06/2006
61357	DRICI	Milou-Daniel	08/06/2006	LD-AR	SANKYO-MERCK LIPHA	Membre Groupe expert OLMETEC ®	rémunération versée à une institution	01/2004	06/2006
61357	DRICI	Milou-Daniel	08/06/2006	LD-AR	NEGMA-LERADS	Membre Groupe expert NEBILOX ®	rémunération versée à une institution	01/2005	
61357	DRICI	Milou-Daniel	08/06/2006	CF-INT	BAYER	Milan - TRT de l'HTA / TELMISARTAN PRITOR ®	aucune versée à une institution	06/2006	06/2006
61357	DRICI	Milou-Daniel	08/06/2006	CF-INT	NEGMA-LERADS	Marseille - les B-bloquants / NEBILOX ®	aucune versée à une institution	06/2004	06/2004
61357	DRICI	Milou-Daniel	08/06/2006	CF-AUD	SERVIER	Milan - co-prêterax ®		09/2005	09/2005
61357	DRICI	Milou-Daniel	16/03/2005	(Autre)	MERCK	"Merck Fellow in clinical pharmacology" aux USA de 1995 à 1997	<5000 € ou <5% du capital		12/2004
61357	DRICI	Milou-Daniel	10/01/2005	IF	AVENTIS	38 actions (04/2002 - 12/2004) cédées en décembre 2004	Versement au budget d'une association loi 1901	01/2005	
61357	DRICI	Milou-Daniel	10/01/2005	IP-AC	NEGMA	Groupe d'experts "NEBIVOLOL" à partir du 01/01/2005			
61357	DRICI	Milou-Daniel	10/01/2005	RE-DE	LUNDBECK SA	"Management Committee Sertindole" depuis 2002 - Association Loi 1901			10/2003
61357	DRICI	Milou-Daniel	10/01/2005	RE-DE	NOVARTIS	Safety Commitee "Valsartan" - 2003	Association Loi 1901		
61357	DRICI	Milou-Daniel	10/01/2005	IP-AC	SANKYO-MERCK LIPHA	Groupe d'experts Olmesartan - 1 ou 2 réunions par an - Conférencier en 2004			
61357	DRICI	Milou-Daniel	10/01/2005	VB	NEGMA	Conférencier en 2004			
61357	DRICI	Milou-Daniel	10/01/2005	(Autre)	MERCK-LIPHA (2002), ASTRA ZENECA (2003), PFIZER (2004)	Invitation au Congrès de l'American Heart Association			
61357	DRICI	Milou-Daniel	10/01/2005	(Autre)	SERVIER	Invitation au Congrès de l'European Society of Cardiology (2004)			
61357	DRICI	Milou-Daniel	10/01/2005	IP-AC	SOCIETE BIOTRIAL	Activité de conseil	Sans rémunération		
61357	DRICI	Milou-Daniel	10/01/2005	CF-INT	NEGMA	Conférencier	Association loi 1901	02/2004	02/2004
61357	DRICI	Milou-Daniel	10/01/2005	(Autre)		Invitation au congrès de l'American Heart Association, 2002 Merck Lipha, 2003 Astra Zeneca, 2004 Pfizer, i			
61357	DRICI	Milou-Daniel	18/12/2000	IP-RE	SCHERING-PLOUGH	Evaluation ECG en insu. Evaluation de dossiers			
61357	DRICI	Milou-Daniel	18/12/2000	VB	LUNDBECK SA	Lecture ECG : ANDER (Association loi 1901) - Faculté de Médecine de Nice			
60224	DROUET	Ludovic	08/03/2010	LD-AR	INSTITUT DE L'ATHEROTHROMSE	Soutenu par Sanofi-Aventis et BMS - Membre du conseil scientifique	Rémunération personnelle/institution	01/2004	12/2009
60224	DROUET	Ludovic	08/03/2010	LD-AR	ETATS GENERAUX DE LA THROMBOSE	Soutenu par Sanofi-Aventis - Membre du conseil scientifique	Rémunération personnelle	01/2003	12/2009

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60224	DROUET	Ludovic	08/03/2010	LD-AR	KEOCYT	Membre du conseil scientifique Estramustine	Rémunération personnelle/institution	01/2008	
60224	DROUET	Ludovic	08/03/2010	EC-INV	SANOFI AVENTIS	Stackenox (Etude pharmacocinétique dynamique de l'association HNF + Lovenox)	Investigateur principal	01/2007	12/2008
60224	DROUET	Ludovic	08/03/2010	EC-INV	ENDOTIS PHARMA	Single-center, open-label study to assess the in vitro anticoagulant properties of EP42675 in human blood of	Investigateur principal	01/2008	12/2009
60224	DROUET	Ludovic	08/03/2010	EC-CO	ELI LILLY	A randomized, Double-blind, cross-over study comparing the parmacodynamic response in subjects with acu	Collaborateur à l'étude	01/2007	12/2008
60224	DROUET	Ludovic	08/03/2010	EC-CO	SANOFI AVENTIS	POP 450 (CLOPI_C_02827) "Pharmacodynamic effects of repeated and escalading oral doses	Collaborateur à l'étude	01/2008	12/2010
60224	DROUET	Ludovic	08/03/2010	EC-CO	ENDOTIS PHARMA	Single-center, open-label, in vitro study to assess the anticoagulant properties of EP217609 in preventig car	Collaborateur à l'étude	01/2010	12/2011
60224	DROUET	Ludovic	08/03/2010	IP-AC	ASTRA ZENECA	Board national ticagrelor	Rémunération personnelle	01/2009	
60224	DROUET	Ludovic	08/03/2010	IP-AC	ASTRA ZENECA	Board international (pharmacodynamie) Ticagrelor	Rémunération personnelle	01/2010	
60224	DROUET	Ludovic	08/03/2010	IP-AC	BOEHRINGER INGELHEIM	Board national Dabigatran	Rémunération institution	01/2009	
60224	DROUET	Ludovic	08/03/2010	CF-INT	BOEHRINGER INGELHEIM	Conférencier pour congrès, conférences, colloques - 2 à 3 par an	Rémunération personnelle	01/2008	
60224	DROUET	Ludovic	08/03/2010	CF-INT	ASTRA ZENECA	Conférencier pour congrès, conférences, colloques - 1 à 2 par an	Rémunération personnelle	01/2010	
60224	DROUET	Ludovic	08/03/2010	CF-INT	SANOFI AVENTIS	Conférencier pour congrès, conférences, colloques - 2 à 3 par an	Rémunération personnelle	01/2007	
60224	DROUET	Ludovic	08/03/2010	CF-INT	OCTAPHARMA	Conférencier pour congrès, conférences, colloques - 1 au moins par an	Rémunération personnelle	01/2007	12/2009
60224	DROUET	Ludovic	08/03/2010	CF-INT	LFB	Conférencier pour congrès, conférences, colloques - 1 au moins par an	Rémunération personnelle	01/2008	
60224	DROUET	Ludovic	08/03/2010	CF-INT	MEDICINE COMPANY	Conférencier pour congrès, conférences, colloques - 2 à 3 par an	Rémunération personnelle	01/2008	
60224	DROUET	Ludovic	08/03/2010	CF-INT	BMS	Conférencier congrès, conférences, colloques - 1 à 2 par an	Rémunération personnelle	01/2007	
60224	DROUET	Ludovic	08/03/2010	CF-AUD	LFB	Boston (USA) XXII congrès de l'ISTH (internation society of thrombosis and haemostasis)		07/2009	07/2009
60224	DROUET	Ludovic	08/03/2010	CF-AUD	BOEHRINGER INGELHEIM	New Orleans (USA) 52ème congrès de l'ASF (american society of hematology)		12/2009	12/2009
60224	DROUET	Ludovic	08/03/2010	VB	INSTITUT ATHEROTHROMBOSE	Soutien au développement d'un modèle de porcs athérothrombotiques	Bénéficiaire - IVS	01/2004	12/2009
60224	DROUET	Ludovic	14/04/2008	Néant					
60224	DROUET	Ludovic	15/11/2007	CF-INT	OCTAPHARMA	GEHT / Lille / Octaplex	Rémunération personnelle	10/2007	10/2007
60224	DROUET	Ludovic	15/11/2007	EC-CO	BAXTER	evaluation preclinique chez le porc willebrand d'un facteur willebrand recombinant	experimentation animale	01/2007	12/2007
60224	DROUET	Ludovic	15/11/2007	EC-CO	SANOFI-AVENTIS	partie biologique de l'etude phase 1 sur l'association Lovenox -HNF	laboratoire chargé des examens specialisés	01/2007	12/2008
60224	DROUET	Ludovic	15/11/2007	EC-CO	ELI-LILLY	partie biologique de l'etude / Acapulco / Prasugrel	laboratoire central en charge des tests biologiques	01/2006	12/2007
60224	DROUET	Ludovic	15/11/2007	RE-AUT	NEGMA	etude préclinique Tookad	Rémunération personnelle/institution	01/2003	12/2006
60224	DROUET	Ludovic	15/11/2007	CF-INT	SANOFI-AVENTIS	congrès de la societé américaine d'hématologie ASH / Atlanta données post hoc de l'étude PREVAIL (Lover	Aucune rémunération	12/2007	12/2007
60224	DROUET	Ludovic	15/11/2007	IP-AC	NEGMA	comprehension des effets secondaires de Tookad	Rémunération personnelle/institution	01/2003	
60224	DROUET	Ludovic	15/11/2007	RE-AUT	NEGMA	etude preclinique LC45	Rémunération personnelle/institution	01/2006	12/2007
60224	DROUET	Ludovic	15/11/2007	EC-CO	SANOFI-AVENTIS	partie biologique de l'etude POP 8010 ' Plavix	laboratoire central en charge des tests biologiques	01/2005	
60224	DROUET	Ludovic	15/11/2007	EC-CO	SANOFI-AVENTIS	partie biologique de l'etude albion / dose de charge SCA / Plavix	laboratoire central en charge des tests biologiques	01/2005	12/2006
60224	DROUET	Ludovic	15/11/2007	CF-AUD	GSK	Congrès international Geneve - ISTH		07/2007	07/2007
60224	DROUET	Ludovic	24/05/2006	LD-AR	INSTITUT DE L'ATHEROTHROMBOSE (SOUTENU PAR SANOFI-AVENTIS ET BMS)	Membre du conseil scientifique	rémunération personnelle / institution	01/2004	
60224	DROUET	Ludovic	24/05/2006	LD-AR	CLUB JET (soutenu par ASTRA-ZENECA)	Président	rémunération personnelle	01/2002	12/2003
60224	DROUET	Ludovic	24/05/2006	LD-AR	ETATS GéNéRAUX DE LA THROMBOSE (SOUTENU PAR AVENTIS PUIS SANOFI AVENTIS)	Membre du conseil scientifique	rémunération personnelle	01/2003	
60224	DROUET	Ludovic	24/05/2006	EC-INV	NEGMA	Corrélation de l'effet in vivo du Tookad ® sur la circulation de l'oreille a son effet systémique sur la coagulati	expérimentateur principal	01/2005	12/2006
60224	DROUET	Ludovic	24/05/2006	EC-CO	SANOFI	Platelet activity Extinction in non-Q myocardial infarction with Aspirin, Clopidogrel and Eptifibatide (PEACE)	Co-investigateur	01/2001	12/2002
60224	DROUET	Ludovic	24/05/2006	EC-CO	SANOFI	Clopidogrel + Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (Caress)	Collaborateur à l'étude	01/2001	12/2003
60224	DROUET	Ludovic	24/05/2006	EC-CO	THERAPLIX	Etude de l'effet de l'Introduction de Paracétamol sur l'effet Anticoagulant de la Warfarine (Inpawa)	Collaborateur à l'étude	01/2002	12/2003
60224	DROUET	Ludovic	24/05/2006	EC-CO	LEO	Anti-Xa activity of 2 LMWH (Tinzaparin,Enoxaparin) given at prophylactic dose over 8 days. A pharmacodyn	Co-investigateur	01/2002	12/2005
60224	DROUET	Ludovic	24/05/2006	EC-CO	SANOFI	Assessment of the best Loading dose of clopidogrel to Blunt platelet activation, Inflammation and Ongoing N	Co-investigateur	01/2004	12/2004
60224	DROUET	Ludovic	24/05/2006	EC-CO	SANOFI	Effets pharmacodynamiques de doses orales répétées de clopidogrel 75 mg administrées une fois par jour c	Collaborateur à l'étude	01/2005	12/2006
60224	DROUET	Ludovic	24/05/2006	IP-AC	ROCHE	Réunions de conseil pour le développements de nouveaux antithrombotiques (une à deux par an)	rémunération personnelle	01/2004	
60224	DROUET	Ludovic	24/05/2006	IP-AC	ASTRA ZENECA	Réunion de conseil sur le monitoring des antithrombines directes (une réunion)	rémunération personnelle	01/2004	
60224	DROUET	Ludovic	24/05/2006	IP-AC	PROCTER GAMBLE	Réunions de conseil de développement Previscan (une à deux par an)	rémunération institution	01/2004	
60224	DROUET	Ludovic	24/05/2006	IP-AC	NOVO NORDISK	Réunion de conseil pour le développement des antihémorragiques (une réunion)	rémunération personnelle	01/2005	
60224	DROUET	Ludovic	24/05/2006	IP-AC	SANOFI-AVENTIS	Réunions sur le développement du clopidogrel (une à deux réunions par an)	rémunération personnelle / institution	01/2002	
60224	DROUET	Ludovic	24/05/2006	CF-INT	ELI LILLY	Conférencier pour congrès, conférence colloques 0 à 1 par an	rémunération personnelle	01/2003	12/2005
60224	DROUET	Ludovic	24/05/2006	CF-INT	ASTRA ZENECA	Conférencier pour congrès, conférence colloques 1 à 2 par an	rémunération personnelle	01/2003	12/2005
60224	DROUET	Ludovic	24/05/2006	CF-INT	SANOFI AVENTIS	Conférencier pour congrès, conférence colloques 3 à 4 par an (<2003)	rémunération personnelle		
60224	DROUET	Ludovic	24/05/2006	CF-INT	BMS	Conférencier pour congrès, conférence colloques 2 à 3 par an (<2003)	rémunération personnelle		
60224	DROUET	Ludovic	24/05/2006	CF-AUD	SANOFI AVENTIS	Congrès international - Birmingham - ISTH		07/2003	07/2003
60224	DROUET	Ludovic	24/05/2006	CF-AUD	GSK	Congrès international - Sydney - ISTH		08/2005	08/2005
60224	DROUET	Ludovic	24/05/2006	VB	INSTITUT ATHEROTHROMBOSE	Soutien au développement d'un modèle de porcs athérothrombotiques	IVS	01/2004	12/2006
60224	DROUET	Ludovic	24/05/2006	(Autre)	AVENTIS	Prix Hoptria	Aide au développement d'une clinique d'anticoagulation	01/2005	12/2006
60224	DROUET	Ludovic	10/01/2006	LD-AR	INSTITUT DE L'ATHEROTHROMBOSE (SOUTENU PAR SANOFI-AVENTIS ET BMS)	membre du conseil scientifique	rémunération personnelle / institution	01/2004	
60224	DROUET	Ludovic	10/01/2006	LD-AR	CLUB JET (Soutenu par ASTRA-ZENECA)	président	rémunération personnelle	01/2002	12/2003
60224	DROUET	Ludovic	10/01/2006	LD-AR	ETATS GéNéRAUX DE LA THROMBOSE (SOUTENU PAR AVENTIS PUIS SANOFI AVENTIS)	membre du conseil scientifique	rémunération personnelle	01/2003	
60224	DROUET	Ludovic	10/01/2006	EC-INV	NEGMA	Corrélation de l'effet in vivo du tookad sur la circulation de l'oreille à son effet systémique sur la coagulation	expérimentateur principal	01/2005	12/2006
60224	DROUET	Ludovic	10/01/2006	EC-CO	SANOFI	Platelet activity Extinction in non-Q myocardial infarction with Aspirin Clopidogrel and Eptifibatide (PEACE)	co-investigateur	01/2001	12/2002
60224	DROUET	Ludovic	10/01/2006	EC-CO	SANOFI	Clopidogrel + Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (caress)	collaborateur à l'étude	01/2001	12/2003
60224	DROUET	Ludovic	10/01/2006	EC-CO	THERAPLIX	Etude de l'effet de l'introduction de Paracétamol sur l'effet Anticoagulant de la Warfarine (Inpawa)	collaborateur à l'étude	01/2002	12/2003
60224	DROUET	Ludovic	10/01/2006	EC-CO	LEO	Anti-Xa activity of 2 LMWH (Tinzaparin Enoxaparin) given at prophylactic dose over 8 days. A pharmacodyn	co-investigateur	01/2002	12/2005
60224	DROUET	Ludovic	10/01/2006	EC-CO	SANOFI	Assessment of the best Loading dose of clopidogrel to Blunt platelet activation inflammation and Ongoing N	co-investigateur	01/2004	12/2004
60224	DROUET	Ludovic	10/01/2006	EC-CO	SANOFI	Effets pharmacodynamiques de doses orales répétées de clopidogrel 75 mg administrées une fois par jour c	collaborateur à l'étude	01/2005	12/2006
60224	DROUET	Ludovic	10/01/2006	IP-AC	ROCHE	Réunions de conseil pour le développements de nouveaux antithrombotiques (une à deux par an)	rémunération personnelle	01/2004	
60224	DROUET	Ludovic	10/01/2006	IP-AC	ASTRA ZENECA	Réunion de conseil sur le monitoring des antithrombines directes (une réunion)	rémunération personnelle	01/2004	
60224	DROUET	Ludovic	10/01/2006	IP-AC	PROCTER GAMBLE	Réunion de conseil de développement Previscan (une à deux par an)	rémunération institution	01/2004	
60224	DROUET	Ludovic	10/01/2006	IP-AC	NOVO NORDISK	Réunion de conseil pour le développement des antihémorragiques (une réunion)	rémunération personnelle	01/2005	

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60224	DROUET	Ludovic	10/01/2006	IP-AC	SANOFI-AVENTIS	Réunion sur le développement du clopidogrel (une à deux réunions par an)	rémunération personnelle / institution	01/2002	
60224	DROUET	Ludovic	10/01/2006	CF-INT	ELI LILLY	conférencier pour congrès, conférence colloques 0 à 1 par an	rémunération personnelle	01/2003	12/2005
60224	DROUET	Ludovic	10/01/2006	CF-INT	ASTRA ZENECA	conférencier pour congrès, conférences colloques 1 à 2 par an	rémunération personnelle	01/2003	12/2005
60224	DROUET	Ludovic	10/01/2006	CF-INT	SANOFI AVENTIS	conférencier pour congrès, conférence colloques 3 à 4 par an (<2003)	rémunération personnelle		
60224	DROUET	Ludovic	10/01/2006	CF-INT	BMS	conférencier pour congrès, conférence colloques 2 à 3 par an (< 2003)	rémunération personnelle		
60224	DROUET	Ludovic	10/01/2006	CF-AUD	SANOFI AVENTIS	congrès international Birmingham - ISTH		07/2003	
60224	DROUET	Ludovic	10/01/2006	CF-AUD	GSK	congrès international Sydney - ISTH		08/2005	
60224	DROUET	Ludovic	10/01/2006	VB	INSTITUT ATHEROTHROMBOSE	Soutien au développement d'un modèle de porcs athérothrombotiques	IVS	01/2004	12/2006
60224	DROUET	Ludovic	10/01/2006	(Autre)	AVENTIS	Prix Hoplria		01/2005	12/2006
60224	DROUET	Ludovic	12/09/2003	IP-AC	SANOFI SYNTHELABO	Groupe expert Arixtra			
60224	DROUET	Ludovic	12/09/2003	IP-AC	WHY	Evaluation préclinique d'un nouvel antithrombotique			
60224	DROUET	Ludovic	12/09/2003	IP-AC	AMGEN	EPO et insuffisance cardiaque			
60224	DROUET	Ludovic	12/09/2003	IP-CF	SANOFI SYNTHELABO	Séminaires intensifs de thrombose			
60224	DROUET	Ludovic	12/09/2003	IP-CF	ASTRA ZENECA	Présidence groupe Jet			
60224	DROUET	Ludovic	12/09/2003	IP-CF	LABORATOIRE FRANCAIS DU FRACTIONNEMENT ET DES BIOTECHNOLOGIES	CD-Rom CIVD			
60224	DROUET	Ludovic	12/09/2003	IP-CF	AVENTIS	Groupes urgence-thrombose et zoom-thrombose			
60224	DROUET	Ludovic	12/09/2003	IP-CF	BRISTOL MYERS SQUIBB, SANOFI-SYNTHELABO	EPU			
60224	DROUET	Ludovic	12/09/2003	IP-AUT	BRISTOL MYERS SQUIBB, SANOFI-SYNTHELABO	Conseil scientifique des universités de l'athérothrombose			
60224	DROUET	Ludovic	12/09/2003	VB	SANOFI-SYNTHELABO, LEO	Evaluation expérimentale sur modèles animaux d'antithrombotique et de produits de substitution			
60224	DROUET	Ludovic	12/09/2003	VB	SERVIER, NOVO NORDISK	Etudes pharmacocinétiques, pharmcodynamiques sur volontaires sains et sur patients			
60224	DROUET	Ludovic	12/09/2003	VB	LABORATOIRE FRANCAIS DU FRACTIONNEMENT ET DES BIOTECHNOLOGIES, ASTRA ZENECA	Evaluation anti-coagulation en France			
60224	DROUET	Ludovic	12/09/2003	VB	BRISTOL MYERS SQUIBB, SANOFI-SYNTHELABO	Conseil scientifique de l'institut de l'athérothrombose			
60224	DROUET	Ludovic	12/09/2003	(Autre)	ISTH, ESC, AHA, ASH	Prise en charge par les entreprises sus-nommées aux congrès de la spécialité (ISTH, ESC, AHA, ASH)			
60304	DRUGEON	Henri	19/07/2006	PAR	DRUG R&D	RESPONSABLE	CONJOINT	01/1995	
60304	DRUGEON	Henri	19/07/2006	CF-AUD	CHIRON	eccmid		01/2006	
60304	DRUGEON	Henri	19/07/2006	LD-AR	SERVIER	Consultant	Rémunération personnelle	01/2004	12/2005
60304	DRUGEON	Henri	19/07/2006	EC-CO	ABBOTT	clanthromycine EABC	Collaborateur	01/2003	12/2006
60304	DRUGEON	Henri	19/07/2006	RE-DE	SERVIER	fusafungine	Rémunération personnelle	01/2004	12/2005
60304	DRUGEON	Henri	19/07/2006	IP-AC	ABBOTT	groupe de travail sur macrolides et infections de surface	Rémunération personnelle	01/2005	
60304	DRUGEON	Henri	19/07/2006	IP-AC	BAYER-PHARMA	groupe de reflexion AGIR	Rémunération personnelle	01/2004	
60304	DRUGEON	Henri	19/07/2006	CF-INT	ABBOTT	Macrolides et inflammation : modérateur	Aucune rémunération	06/2006	06/2006
60304	DRUGEON	Henri	19/07/2006	CF-INT	BAYER-PHARMA	Agir: modérateur	Aucune rémunération	11/2005	11/2005
60304	DRUGEON	Henri	19/07/2006	CF-AUD	ABBOTT	ICAAC		01/2004	
60304	DRUGEON	Henri	19/07/2006	CF-AUD	BAYER-PHARMA	ICAAC		01/2005	
60304	DRUGEON	Henri	19/07/2006	CF-AUD	BAYER- PHARMA	ICAAC		01/2005	
60304	DRUGEON	Henri	19/07/2006	IP-AC	SANOFI-AVENTIS	groupe de reflexion écologie bactérienne	Rémunération personnelle	01/2004	
60304	DRUGEON	Henri	19/07/2006	EC-CO	SANOFI-AVENTIS	Telithromycine EABC	Collaborateur	01/2004	
60304	DRUGEON	Henri	19/07/2006	LD-AR	BAYER-PHARMA	Consultant	Rémunération personnelle	01/2003	
60304	DRUGEON	Henri	19/07/2006	LD-AR	SANOFI-AVENTIS	Consultant	Rémunération personnelle	01/2003	
60304	DRUGEON	Henri	11/06/2006	LD-AR	SANOFI-AVENTIS	consultant		01/2003	
60304	DRUGEON	Henri	11/06/2006	LD-AR	BAYER PHARMA	consultant		01/2003	
60304	DRUGEON	Henri	11/06/2006	EC-CO	ABBOTT	Essai clinique clarithromycine	collobarateur	01/2003	12/2005
60304	DRUGEON	Henri	11/06/2006	EC-CO	SANOFI-AVENTIS	Télithromycine	collaborateur	01/2004	12/2006
60304	DRUGEON	Henri	11/06/2006	RE-DE	SERVIER	Fusafungine	rémunération personnelle	01/2004	12/2005
60304	DRUGEON	Henri	11/06/2006	IP-AC	SANOFI AVENTIS	groupe de réflexion écologie bactérienne (en cours)	rémunération personnelle	01/2004	
60304	DRUGEON	Henri	11/06/2006	CF-INT	ABBOTT	Macrolides et inflammation : modérateur	rémunération personnelle	01/2006	01/2006
60304	DRUGEON	Henri	11/06/2006	CF-INT	BAYER	réunions AGIR	rémunération personnelle	01/2004	01/2004
60304	DRUGEON	Henri	11/06/2006	CF-INT	BAYER	réunions AGIR	rémunération personnelle	01/2005	01/2005
60304	DRUGEON	Henri	11/06/2006	PAR	DRUG R&D STE DE RECHERCHE SOUS CONTRAT	Responsable	conjoint	01/1995	
62922	DUBOC	Denis	06/09/2003	LD	Département de Biologie du CEA	Conseiller scientifique			
62922	DUBOC	Denis	06/09/2003	IP-EC	SERVIER	Périndopril et dysfonction vg dans la myopathie de Duchesne (phase III)			
62922	DUBOC	Denis	06/09/2003	IP-RE	FOURNIER	Cardiac Safety report du LF 15-0195 (phase II)			
62922	DUBOC	Denis	06/09/2003	IP-AC	WYETH-AYERST	Comité de surveillance d'études sur rPSGL-Ig (phase III)			
62922	DUBOC	Denis	06/09/2003	IP-CF	AVENTIS	EPU Insuffisance cardiaque			
62922	DUBOC	Denis	06/09/2003	IP-CF	MERCK SHARP & DOHME	EPU Coronaropathie			
62922	DUBOC	Denis	06/09/2003	IP-CF	TAKEDA	EPU Insuffisance cardiaque			
62922	DUBOC	Denis	06/09/2003	IP-CF	PFIZER	EPU Athérome			
60959	DUBOIS	Bruno	25/08/2003	IP-EC	EISAI				
60959	DUBOIS	Bruno	25/08/2003	IP-EC	NOVARTIS				
60959	DUBOIS	Bruno	25/08/2003	IP-EC	JANSSEN CILAG				
60959	DUBOIS	Bruno	25/08/2003	IP-EC	SERVIER				
60959	DUBOIS	Bruno	25/08/2003	IP-EC	GLAXO SMITHKLINE				
60959	DUBOIS	Bruno	25/08/2003	IP-CF		Participation à des conférences et colloques : Maladie de Parkinson, maladie d'Alzheimer, mémoire, démence			
60959	DUBOIS	Bruno	14/10/2002	IP-EC	ETSAI				
60959	DUBOIS	Bruno	14/10/2002	IP-CF	JANSSEN-CILAG, ETSAI, NOVARTIS				
60959	DUBOIS	Bruno	14/10/2002	IP-EC	NOVARTIS				
60959	DUBOIS	Bruno	14/10/2002	IP-EC	SERVIER				
60959	DUBOIS	Bruno	25/02/2000	IP-EC	NOVARTIS	Etude INDREX - Coordonnateur National			
60959	DUBOIS	Bruno	25/02/2000	IP-EC	RPR	Etude RILUZOLE dans la maladie de Huntington - Coordonnateur National			
60959	DUBOIS	Bruno	25/02/2000	IP-EC	SERVIER	Etude Sulbutiamine - Coordonnateur National			
60959	DUBOIS	Bruno	25/02/2000	IP-EC	SB	Validation des SMOTS - Coordonnateur National			
60959	DUBOIS	Bruno	25/02/2000	IP-AC	SERVIER				
60959	DUBOIS	Bruno	25/02/2000	IP-AC	ESAI				
60959	DUBOIS	Bruno	25/02/2000	IP-AC	NOVARTIS				
60959	DUBOIS	Bruno	25/02/2000	IP-CF	ESAI				
60959	DUBOIS	Bruno	25/02/2000	IP-CF	NOVARTIS				
60959	DUBOIS	Bruno	25/02/2000	VB	NOVARTIS et SB	Subvention à l'Association Claude Bernard pour l'aménagement du Centre de Neuropsychologie			
60392	DULY-BOUHANICK	Béatrice	28/09/2010	CF-AUD	NOVARTIS	congrès de l EADS Stockhlom		09/2010	09/2010
60392	DULY-BOUHANICK	Béatrice	28/09/2010	CF-AUD	BMS	congrès de la SFD Lille		03/2010	03/2010

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60392	DULY-BOUHANICK	Béatrice	28/09/2010	CF-AUD	SERVIER	journee post IDF: rapport de congrès□□Paris		01/2010	01/2010
60392	DULY-BOUHANICK	Béatrice	28/09/2010	IP-AC	LILLY	consultant ponctuel	Rémunération personnelle	05/2010	05/2010
60392	DULY-BOUHANICK	Beatrice	28/09/2010	EC-CO	DANISCO	ESSAI MONOCENTRIQUE chez le volontaire sain avec probiotiques sur la flore intestinale	co-investigateur toulouse	04/2010	
60392	DULY-BOUHANICK	Béatrice	09/10/2009	IP-AUT	SERVIER	DIU d'HTA (Tours)	Remboursement de frais de déplacement	05/2009	05/2009
60392	DULY-BOUHANICK	Béatrice	09/10/2009	CF-AUD	SERVIER	ALFEDIAM strasbourg		03/2009	03/2009
60392	DULY-BOUHANICK	Béatrice	09/10/2009	CF-AUD	NOVARTIS	reunion coeur et diabete Paris		02/2009	02/2009
60392	DULY-BOUHANICK	Béatrice	09/10/2009	IP-AC	LILLY	exenatide: plan de développement	Rémunération personnelle	06/2009	06/2009
60392	DULY-BOUHANICK	Béatrice	09/10/2009	EC-CO	BMS	essai multicentrique MB 102 029□□dapagliflozine	investigateur local toulouse	11/2008	
60392	DULY-BOUHANICK	Béatrice	09/10/2008	CF-AUD	TAKEDA	easd	rome	09/2008	09/2008
60392	DULY-BOUHANICK	Béatrice	09/10/2008	CF-AUD	BOERHINGER	acc	chicago	03/2008	04/2008
60392	DULY-BOUHANICK	Béatrice	09/10/2008	IP-AC	LILLY	consultant ponctuel sur développement des incrétinomimetiques	Rémunération personnelle	08/2020	
60392	DULY-BOUHANICK	Béatrice	09/10/2008	CF-AUD	NOVARTIS	alfediam	Marseille	03/2007	03/2007
60392	DULY-BOUHANICK	Béatrice	09/10/2008	CF-AUD	SERVIER	journees d'HTA	Paris	12/2007	12/2007
60392	DULY-BOUHANICK	Béatrice	09/10/2008	CF-AUD	MSD	EASD congrès de diabétologie		09/2007	10/2007
60392	DULY-BOUHANICK	Béatrice	09/10/2008	EC-CO	SANOFI	essai multicentrique Rimonabant. CRESCENDO vs placebo	investigateur local toulouse	01/2006	12/2009
60392	DULY-BOUHANICK	Béatrice	09/10/2008	(Autre)	TAKEDA	rédaction d'une brochure sur l'HTA		06/2007	07/2007
60392	DULY-BOUHANICK	Béatrice	02/10/2007	(Autre)	TAKEDA	redaction d'une brochure sur l'HTA		06/2007	
60392	DULY-BOUHANICK	Béatrice	02/10/2007	CF-INT	MSD	incretines physiopathologie CHU Rangueil Toulouse	Rémunération personnelle	06/2007	06/2007
60392	DULY-BOUHANICK	Béatrice	02/10/2007	CF-AUD	SERVIER	journees d'HTA	Paris	12/2007	
60392	DULY-BOUHANICK	Béatrice	02/10/2007	CF-AUD	NOVARTIS	alfediam	Marseille	03/2007	
60392	DULY-BOUHANICK	Béatrice	02/10/2007	CF-INT	MSD	CHU Rangueil mecanisme d'action des incrétines	Rémunération personnelle	06/2007	06/2007
60392	DULY-BOUHANICK	Béatrice	02/10/2007	CF-AUD	SERVIER	journées d'HTA	PARIS	12/2006	12/2006
60392	DULY-BOUHANICK	Béatrice	02/10/2007	CF-AUD	NOVARTIS	congrès de l'ALFEDIAM	Marseille	03/2007	03/2007
60392	DULY-BOUHANICK	Béatrice	13/07/2007	CF-AUD	MSD	EASD congrès de diabétologie		09/2007	
60392	DULY-BOUHANICK	Béatrice	13/07/2007	CF-AUD	NOVARTIS CARDIO	ALFEDIAM congres		03/2007	03/2007
60392	DULY-BOUHANICK	Béatrice	13/07/2007	EC-CO	SANOFI	essai multicentrique Rimonabant. CRESCENDO vs placebo	investigateur local toulouse	01/2006	
60392	DULY-BOUHANICK	Béatrice	13/07/2007	IP-AC	LILLY	expert dans le développement d'exenatide Byetta	Rémunération personnelle	01/2004	12/2007
60392	DULY-BOUHANICK	Béatrice	21/04/2006	EC-INV	NOVO NORDISK	essais cliniques Levemir	investigateur coordonnateur	01/2000	12/2003
60392	DULY-BOUHANICK	Béatrice	21/04/2006	EC-INV	TAKEDA	étude proactive sur essai clinique - Proglitazone vs placebo - Angers	investigateur coordonnateur	01/2001	12/2003
60392	DULY-BOUHANICK	Béatrice	21/04/2006	EC-INV	SANOFI	essai clinique Rimonabant	investigateur coordonnateur	01/2006	
60392	DULY-BOUHANICK	Béatrice	21/04/2006	IP-AC	LILLY	consultant dans le développement du dossier GLP-1	rémunération personnelle	01/2004	12/2006
60392	DULY-BOUHANICK	Béatrice	21/04/2006	IP-AC	NOVO NORDISK	intervention ponctuelle pour formation du personnel de l'entreprise sur la diabète /1 fois	rémunération personnelle	01/2005	12/2005
60392	DULY-BOUHANICK	Béatrice	21/04/2006	CF-INT	CONGRES ALFEDIAM 2006	PARIS Mars 2006 - néphropathie diabétique - soutien logistique de Novartis	aucune rémunération	03/2006	03/2006
60392	DULY-BOUHANICK	Béatrice	21/04/2006	CF-INT	JOURNEES D'HTA	PARIS décembre 2005 - intervenant - soutien logistique PFIZER	aucune rémunération	12/2005	12/2005
60392	DULY-BOUHANICK	Béatrice	21/04/2006	IP-AUT	GSK	invitée au CHU de Nantes pour colloque sur le thème HTA et diabète - soutien logistique	aucune rémunération	01/2005	01/2005
60392	DULY-BOUHANICK	Béatrice	06/04/2006	EC-INV	NOVO-NORDISK	Essais cliniques Levemir - Angers	Investigateur principal	01/2000	12/2003
60392	DULY-BOUHANICK	Béatrice	06/04/2006	EC-INV	TAKEDA	Etude Proactive sur essai clinique - Proglitazone vs placebo - Angers	Investigateur principal	01/2001	12/2003
60392	DULY-BOUHANICK	Béatrice	06/04/2006	EC-INV	SANOFI-AVENTIS	Etude crescendo Rimonabant - Toulouse	Investigateur principal	01/2006	
60392	DULY-BOUHANICK	Béatrice	06/04/2006	RE-DE	LILLY	Expert dossier GLP-1□□Byetta aux USA	Rémunération personnelle	01/2004	12/2006
60392	DULY-BOUHANICK	Béatrice	06/04/2006	RE-AUT	NOVO NORDISK	Intervention pour formation du personnel de l'entreprise (1 fois)	Rémunération personnelle	01/2005	12/2005
60392	DULY-BOUHANICK	Béatrice	06/04/2006	CF-INT	NOVARTIS	Alfediam 2006, soutien logistique (Paris)	Aucune rémunération	03/2006	03/2006
60392	DULY-BOUHANICK	Béatrice	06/04/2006	CF-INT	PFIZER	Journées d'HTA, soutien logistique (Paris)	Aucune rémunération	12/2005	12/2005
60392	DULY-BOUHANICK	Béatrice	06/04/2006	CF-AUD	GSK	Intervention sur invitation au CHU de Nantes sur "HTA et diabète" / soutien logistique	Aucune rémunération	01/2005	12/2005
60392	DULY-BOUHANICK	Béatrice	01/03/2005	EC-CO	AVENTIS	Glargine		01/2002	12/2003
60392	DULY-BOUHANICK	Béatrice	01/03/2005	EC-CO	NOVO	Detemir		01/2002	12/2002
60392	DULY-BOUHANICK	Béatrice	01/03/2005	EC-CO	GSK	Pioglitazone		01/2003	12/2003
60392	DULY-BOUHANICK	Béatrice	01/03/2005	EC-CO	PFIZER	insuline inhalée		01/2003	12/2003
60392	DULY-BOUHANICK	Béatrice	01/03/2005	EC-CO	LILLY			01/2000	12/2000
60392	DULY-BOUHANICK	Béatrice	01/03/2005	CF-INT	SFC (Société Française de Cardiologie)	Communication orale		01/2004	12/2004
60392	DULY-BOUHANICK	Béatrice	01/03/2005	IP-CF	MERCK, NOVO, NOVARTIS, GSK (etc..)	Prise en charge de congrès		01/2005	12/2005
60392	DULY-BOUHANICK	Béatrice	01/03/2005	(Autre)	ALFEDIAM	Membre			
60392	DULY-BOUHANICK	Béatrice	01/03/2005	(Autre)	SFHTA, SNFMI, APNET, SFP	Sociétés savantes			
60392	DULY-BOUHANICK	Béatrice	16/09/2004	IP-EC	AVENTIS	Investigateur en 2002 par la Glargine			
60392	DULY-BOUHANICK	Béatrice	16/09/2004	IP-EC	NOVO	Investigateur en 2002 pour la Detemir			
60392	DULY-BOUHANICK	Béatrice	16/09/2004	IP-EC	GSK	Investigateur en 2003 pour la Proglitozone			
60392	DULY-BOUHANICK	Béatrice	16/09/2004	IP-EC	PFIZER	Investigateur en 2003 pour l'insuline nasale			
60392	DULY-BOUHANICK	Béatrice	16/09/2004	IP-EC	AVENTIS	Investigateur en 2003 pour le gl mépuidide			
60392	DULY-BOUHANICK	Béatrice	29/12/2003	IP-EC	TAKEDA	Investigateur pioglitazone 2002			
60392	DULY-BOUHANICK	Béatrice	29/12/2003	IP-EC	AVENTIS	Investigateur Lantius 2002			
60392	DULY-BOUHANICK	Béatrice	29/12/2003	IP-EC	PFIZER	Investigateur Insuline Inhalée 2002			
60392	DULY-BOUHANICK	Béatrice	29/12/2003	IP-EC	AVENTIS	Investigateur 2002			
60392	DULY-BOUHANICK	Béatrice	29/06/2000	IP-EC	NOVO NORDISK	Etudes phase 3 Detemir			
60392	DULY-BOUHANICK	Béatrice	29/06/2000	IP-EC	HOESCHT MARION ROUSSEL	Phase 3 Insuline inhalée			
60392	DULY-BOUHANICK	Béatrice	29/06/2000	IP-EC	AVENTIS	Phase 3 Analogue lent			
65424	DURAND	Eric	19/06/2009	LD-AR	MEDICINE COMPANY	Coordinateur d'un registre monocentrique rétrospectif et prospectif sur la prise en charge des syndromes cor	rémunération personnelle	06/2009	06/2010
65424	DURAND	Eric	19/06/2009	EC-INV	ARTERIAL REMODELING TECHNOLOGIES (ART)	Stent biorésorbale	Expérimenteur dans un modèle expérimental (lapin)	01/2005	
65424	DURAND	Eric	19/06/2009	EC-CO	ROCHE	Etude multicentrique Dual-out come (dalcetrapib)	Co-investigateur	01/2009	
65424	DURAND	Eric	19/06/2009	EC-CO	PHRC	Etude EPOMI (EPD au cours de l'IDM)	Co-investigateur	01/2008	
65424	DURAND	Eric	19/06/2009	CF-INT	TUC 2009	Optimisation de prise en charge de la douleur thoracique	rémunération personnelle	03/2009	03/2009
65424	DURAND	Eric	19/06/2009	CF-AUD	TERUMO	Euro-PCR 2009		05/2009	05/2009
65424	DURAND	Eric	19/06/2009	CF-AUD	SERVIER	ESC 2008		09/2008	09/2008
10159	DURAND-ZALESKI	Isabelle	20/10/2002	IP-EC	Tous				
10159	DURAND-ZALESKI	Isabelle	20/10/2002	IP-RE	Tous				
10159	DURAND-ZALESKI	Isabelle	20/10/2002	IP-AC	Tous				
10159	DURAND-ZALESKI	Isabelle	20/10/2002	IP-CF	Tous				
10159	DURAND-ZALESKI	Isabelle	06/11/2000	IP-EC	COOK ; GUIDANT ; LPI ; EDWARDS ; LIFE SCIENCE SULZER ; BOSTON SCIENTIFIC ; MEDTRONIC	Essai ACE			
10159	DURAND-ZALESKI	Isabelle	06/11/2000	IP-EC	GUIDANT	Essai PACHAM			
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	MSD				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	ROCHE				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	MERCK AG				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	DUPONT				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	SCHERING AG				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	SCHERING PLOUGH				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	VISIBLE GENETICS				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-EC	GLAXO WELLCOME				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-CF	ROCHE				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-CF	SKB				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	IP-CF	GLAXO WELLCOME				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	VB	GLAXO WELLCOME				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	VB	SERVIER				
10159	DURAND-ZALESKI	Isabelle	14/05/2000	VB	SNIP				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-EC	Amgen				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-EC	Parke-Davis				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-RE	Sanofi				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-RE	Schering				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-AC	Zeneca				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-CF	Roche				
10159	DURAND-ZALESKI	Isabelle	01/01/1999	IP-CF	MSD				
10159	DURAND-ZALESKI	Isabelle	01/01/1998	IP-AUT	AMGEN				
10159	DURAND-ZALESKI	Isabelle	01/01/1998	IP-AUT	Servier				
10159	DURAND-ZALESKI	Isabelle	01/01/1998	IP-AUT	Sanofi				
10159	DURAND-ZALESKI	Isabelle	01/01/1998	IP-AUT	Zeneca				
10159	DURAND-ZALESKI	Isabelle	01/01/1998	IP-AUT	Lilly				
10159	DURAND-ZALESKI	Isabelle	01/01/1998	IP-AUT	MSD				
10160	DURIEUX	Pierre	01/01/1999	IP-AC	THERAPLIX				
10160	DURIEUX	Pierre	01/01/1999	IP-AC	Groupe de recherche SERVIER				
10160	DURIEUX	Pierre	01/01/1999	IP-CF	BOEHRINGER INGELHEIM France				
10160	DURIEUX	Pierre	01/01/1998	IP-AUT	Théraplix				
10160	DURIEUX	Pierre	01/01/1998	IP-AUT	Roche				
55649	DURON	François	01/01/1999	IP-EC	MERCK	En cours : protocoles			
55649	DURON	François	01/01/1999	IP-EC	PARKE-DAVIS	En cours : protocoles			
55649	DURON	François	01/01/1999	IP-EC	SERVIER	En cours : protocoles			
55649	DURON	François	01/01/1999	IP-CF	EPU				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	3M				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Bayer				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Bellon				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Bioprojet				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Bristol Myers				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	E. Merk				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Eulhérapie				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	FDM Pharma				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Ferring				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Fujisawa SARL				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Hoechst				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Houdé				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	I.B.S.				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Inserm				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Ipson				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Iris				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Item				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Janssen-Cilag				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Kabi Pharmacia				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Lilly				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Lipha				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Logeais				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Lundbeck				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Merck Clevenot				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Merz & Co				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Pharmaco LSR				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Pharmakoplus				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Pharmascience				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Riom/cerm				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Sanofi				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Schering-Plough				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Servier				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Smithkline				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Synthélabo Recherche				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Takéda				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Téva Pharma				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Upjhon				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Upsa				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Wyeth				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Yamanouchi				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	IP-EC	Zéneca				
10163	EFTHYMIOU	Marie-Louise	01/01/1999	VB	Association Naturalia Biologia				
10163	EFTHYMIOU	Marie-Louise	01/01/1998	VB	participation indirecte à des essais cliniques				
62789	ELIAS	Riad	01/12/2010	RE-DE	ARKOPHARMA FERRIER	Abbé Chaupitre N°6 et	Rémunération personnelle	01/2007	07/2010
62789	ELIAS	Riad	01/12/2010	VB	BOIRON	Mise au point analytique	Université de la méditerranée (Protisvalor)	01/2002	
62789	ELIAS	Riad	01/12/2010	VB	BOIRON	Mise au point analytique	Université de la Méditerrannée (Protisvalor)	01/2002	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62789	ELIAS	Riad	01/12/2010	EC-INV	BOIRON	Mise au point analytique	Coordonnateur	05/2002	
62789	ELIAS	Riad	01/12/2010	EC-INV	BOIRON	Mise au point analytique	coordonnateur	05/2002	
62789	ELIAS	Riad	12/03/2009	EC-INV	BOIRON	Mise au point analytique	Coordonnateur	05/2002	
62789	ELIAS	Riad	12/03/2009	EC-INV	ARKOPHARMA	Mise au point analytique et réduction des procédures	Coordonnateur	02/2007	02/2008
62789	ELIAS	Riad	12/03/2009	IP-RE	ETHYPHARM DBF	Fucus Bayer, vigne rouge Bayer, marron d'inde Bayer, pissenlit Bayer	Rémunération institution	01/2002	12/2004
62789	ELIAS	Riad	12/03/2009	IP-RE	ARKOPHARM FERRIER	Veinosium phytoSOYA	Rémunération personnelle	01/2004	12/2006
62789	ELIAS	Riad	12/03/2009	IP-RE	ARKOPHARM FERRIER	Souches : Silicea, Rhustox, Calcarea	Rémunération personnelle	01/2007	12/2007
62789	ELIAS	Riad	12/03/2009	RE-DE	ARKOPHARMA	Abbé champitre no 6 et 7 (en cours)	Rémunération personnelle	01/2007	07/2010
62789	ELIAS	Riad	12/03/2009	VB	BOIRON	Mise au point analytique	Université de la méditerranée (Protisvalor)	01/2002	
62789	ELIAS	Riad	12/03/2009	VB	ARKAPHARM	Mise au point analytique et réduction des procédures	Université de la méditerranée (Prostisvalor)	02/2007	02/2008
62789	ELIAS	Riad	10/02/2009	EC-INV	BOIRON	Mise au point analytique	coordonnateur	05/2002	
62789	ELIAS	Riad	10/02/2009	RE-DE	ARKOPHARMA-FERRIER	Abbé Chaupitre n°6 et 7	rémunération personnelle	01/2007	07/2010
62789	ELIAS	Riad	10/02/2009	VB	BOIRON	Mise au point analytique	Université de la Méditerrannée (Protisvalor)	01/2002	
62789	ELIAS	Riad	10/02/2009	EC-INV	ARKOPHARMA	Mise au point analytique et rédaction des procédures	coordonnateur	02/2007	02/2008
62789	ELIAS	Riad	10/02/2009	RE-DE	ETHYPHARM DBF	Fucus Bayer - vigne rouge Bayer, marron d'inde Bayer, pissenlit Bayer	rémunération institution	01/2002	12/2004
62789	ELIAS	Riad	27/10/2008	EC-INV	BOIRON	Mise au point analytique	coordonateur	05/2002	
62789	ELIAS	Riad	27/10/2008	EC-INV	ARKOPHARMA	Mise au point analytique, et rédaction des procédures	coordonateur	02/2007	02/2008
62789	ELIAS	Riad	27/10/2008	RE-DE	ETHYPHARM DBF	Fucus Bayer, Vigne rouge Bayer, marron d'Inde Bayer, pissenlit Bayer	rémunération institution	01/2002	12/2004
62789	ELIAS	Riad	27/10/2008	RE-DE	ARKOPHARMA-FERRIER	Veinosium, PhytoSoya	rémunération personnelle	01/2004	12/2006
62789	ELIAS	Riad	27/10/2008	RE-DE	ARKOPHARMA-FERRIER	souches : calcarea carbonica, rhustox, silicea	rémunération personnelle	01/2007	12/2007
62789	ELIAS	Riad	27/10/2008	RE-DE	ARKOPHARMA-FERRIER	Abbé Chaupitre n°6 et 7	rémunération personnelle	01/2007	
62789	ELIAS	Riad	27/10/2008	VB	BOIRON	Mise au point analytique	Université de la Méditerrannée (Protisvalor)	01/2002	
62789	ELIAS	Riad	27/10/2008	VB	ARKOPHARMA	Mise au point analytique et rédaction des procédures	Université de la Méditerrannée (Protisvalor)	02/2007	02/2008
62789	ELIAS	Riad	23/05/2006	EC-INV	BOIRON	Mise au point analytiques	travaux réalisés dans le laboratoire (rôle de coordonateur)	01/2002	
62789	ELIAS	Riad	23/05/2006	RE-DE	ARKOPHARMA	PhytoSoya	rémunération personnelle	01/2004	12/2006
62789	ELIAS	Riad	23/05/2006	RE-DE	ARKOPHARMA	VeinoStim	rémunération personnelle	01/2004	12/2006
62789	ELIAS	Riad	23/05/2006	RE-DE	ETHYPHARM DBF	Fucus, vigne rouge, marron d'inde, pissenlit (Bayer) gélules de microgranules	rémunération versée à une institution	01/2002	12/2004
62789	ELIAS	Riad	23/05/2006	IP-AC	ARKOPHARMA	Consultant ponctuel (1 fois)	rémunération personnelle	01/2004	12/2004
62789	ELIAS	Riad	23/05/2006	VB	BOIRON	Mise au point analytiques	Université de la Méditerranée	01/2002	
62789	ELIAS	Riad	23/05/2006	VB	ARKOPHARMA, ASTRA ZENECA, BAYER PHARMA, BOIRON, BROTHIER, DEB ARMA, DOLISOS, FERRIER, HAUTES SYNERGIE, ICC, IFORA, PFIZER, PHARMACIE DU ROCHER, PIERRE FABRE, SANOFI SYNTHELABO	Taxe d'apprentissage		01/2005	12/2005
62789	ELIAS	Riad	23/02/2005	IP-AC	ARKOPHARMA	2004			
62789	ELIAS	Riad	23/02/2005	IP-RE	ETHYPHARM DBF	2002			
62789	ELIAS	Riad	23/02/2005	IP-RE	ETHYPHARM DBF	2003			
62789	ELIAS	Riad	23/02/2005	IP-RE	ETHYPHARM DBF	2004			
62789	ELIAS	Riad	23/02/2005	VB	BOIRON	Financements > 15% du budget (ou équivalent) du service, 2002			
62789	ELIAS	Riad	23/02/2005	VB	BOIRON	Financements > 15% du budget (ou équivalent) du service, 2003			
62789	ELIAS	Riad	23/02/2005	VB	BOIRON	Financements > 15% du budget (ou équivalent) du service, 2004			
62789	ELIAS	Riad	23/02/2005	VB	BOIRON	Financements > 15% du budget (ou équivalent) du service, 2005			
62789	ELIAS	Riad	23/02/2005	IP-CF	ARKOPHARMA	Financements < 15% du budget du service, travaux de recherche ponctuels, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	ASTRA ZENECA	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	BAYER PHARMA	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	BOIRON	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	BROTHIER	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	DEB ARMA	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	DOLISOS	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	FERRIER	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	HAUTES SYNERGIE	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	ICC	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	IFORA	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	PFIZER SAS	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	PHARMACIE DU ROCHER	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	PIERRE FABRE	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	SANOFI SYNTHELABO	Financements < 15% du budget du service, taxes d'apprentissage, 2004			
62789	ELIAS	Riad	23/02/2005	IP-CF	BOIRON	Financements < 15% du budget du service, participation au congrès			
62789	ELIAS	Riad	23/02/2005	IP-CF	DOLISOS	Financements < 15% du budget du service, participation au congrès			
62789	ELIAS	Riad	23/02/2005	IP-CF	WELEDA	Financements < 15% du budget du service, participation au congrès			
62789	ELIAS	Riad	23/02/2005	IP-CF	FERRIER	Financements < 15% du budget du service, participation au congrès			
62789	ELIAS	Riad	23/02/2005	IP-CF	LEHNING	Financements < 15% du budget du service, participation au congrès			
62789	ELIAS	Riad	23/02/2005	IP-AUT	SFE	Aucun intérêt			
62789	ELIAS	Riad	23/02/2005	IP-AUT	AFERP	Aucun intérêt			
62789	ELIAS	Riad	10/06/2004	IP-EC	BOIRON				
62789	ELIAS	Riad	10/06/2004	IP-RE	BOIRON				
62789	ELIAS	Riad	10/06/2004	IP-AC	ARKOPHARMA				
62789	ELIAS	Riad	10/06/2004	IP-AUT	SANOFI	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	PFIZER	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	PIERRE FABRE	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	BOIRON	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	SERVIER	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	ASTRA	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	ARKOPHARMA	Taxes			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62789	ELIAS	Riad	10/06/2004	IP-AUT	FRESENIUS	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	TISANE PROVENCALE	Taxes			
62789	ELIAS	Riad	10/06/2004	IP-AUT	SCRAS				
62789	ELIAS	Riad	10/06/2004	VB	BOIRON				
62789	ELIAS	Riad	16/09/2003	IP-EC	BOIRON				
62789	ELIAS	Riad	16/09/2003	IP-EC	DBF ETYPHARM				
62789	ELIAS	Riad	16/09/2003	IP-EC	TISANE PROVENCALE				
62789	ELIAS	Riad	16/09/2003	IP-RE	DBF ETHYPHARM				
62789	ELIAS	Riad	16/09/2003	VB	BOIRON				
62789	ELIAS	Riad	16/09/2003	LD	SERVIER	Groupe recherche - Salarié			
10166	EOLE	Christian	21/09/2005	LD	SERVIER	Groupe recherche - Salarié			
10166	EOLE	Christian	28/04/2003	LD	SCIENCE UNION ET CIE	Salarié			
10166	EOLE	Christian	21/06/2000	LD	UNION DES ANNONCEURS				
10166	EOLE	Christian	21/06/2000	(Autre)	Salarié du groupe de Recherche Servier				
10166	EOLE	Christian	01/01/1999	LD	Sciences Po Formation				
10166	EOLE	Christian	01/01/1999	IP-CF	Servier		expérimentateur principal	03/2010	05/2010
10166	EOLE	Christian	01/01/1998	LD	SERVIER	Essai pré-clinique	Rémunération personnelle	03/2008	03/2010
60966	ESCHALIER	Alain	17/04/2010	EC-INV	WYETH PHARMACEUTICALS	Membre du groupe de travail opioide	Rémunération personnelle	05/2009	
60966	ESCHALIER	Alain	17/04/2010	IP-AC	SANOFI	Membre du groupe de travail Antalgie	rémunération personnelle	01/2003	12/2009
60966	ESCHALIER	Alain	17/04/2010	IP-AC	SANOFI	Groupe d'expert antalgie adulte	Rémunération personnelle	09/2009	09/2009
60966	ESCHALIER	Alain	17/04/2010	LD	PFIZER	Nice, université d'été, Approches translationnelles dans les douleurs neuropathiques	Rémunération personnelle	03/2008	
60965	ESCHALIER	Alain	06/10/2009	CF-INT	WYETH PHARMACEUTICALS	Membre du groupe de travail opioide	Rémunération personnelle	01/2009	01/2009
60966	ESCHALIER	Alain	06/10/2009	IP-AC	WYETH PHARMACEUTICALS	Paris, Aux frontières de la Gastroentérologie	Rémunération personnelle	03/2009	03/2009
60966	ESCHALIER	Alain	06/10/2009	CF-INT	WEYTH PHARMACEUTICALS	Paris, 8è Congrès National des Professionnels de la Gériatrie/ Constipation et Opioides Chez la personn	Rémunération personnelle	06/2009	06/2009
60966	ESCHALIER	Alain	06/10/2009	CF-INT	WEYTH PHARMACEUTICALS	Paris, Innovation thérapeutique dansla prise en charge de la constipationinduite par les opioides/Nouvelles a	Rémunération personnelle	05/2009	
60966	ESCHALIER	Alain	06/10/2009	CF-INT	WEYTH PHARMACEUTICALS	Membre du groupe de travail Antalgie	rémunération personnelle	01/2003	
60966	ESCHALIER	Alain	06/10/2009	IP-AC	SANOFI	Groupe d'expert antalgie adulte	expérimentateur principal	06/2008	10/2008
60965	ESCHALIER	Alain	06/10/2009	LD	SANOFI	protocole d'étude préclinique anti-angineux	rémunération personnelle	01/2007	09/2008
60965	ESCHALIER	Alain	06/10/2009	EC-INV	SERVIER	Membre du groupe de travail douleur neuropathique	rémunération personnelle	01/2006	
60965	ESCHALIER	Alain	09/09/2008	IP-AC	PFIZER	Membre du groupe de travail douleur adulte	rémunération personnelle	06/2007	
60966	ESCHALIER	Alain	09/09/2008	IP-AC	SANOFI	membre du groupe de travail opioide (en cours)	rémunération personnelle	01/2003	
60966	ESCHALIER	Alain	09/09/2008	IP-AC	WEYTH LEDERLE	groupe expert antalgie adulte	rémunération personnelle / institution	01/2003	
60966	ESCHALIER	Alain	09/09/2008	LD-AR	SANOFI		rémunération personnelle / institution	01/2003	
60966	ESCHALIER	Alain	30/04/2007	LD-AR	PFIZER	groupe expert douleur Neuropathique	rémunération personnelle	01/2003	
60966	ESCHALIER	Alain	26/09/2006	LD-AR	PFIZER	groupe expert douleur Neuropathique	investigateur principal	01/2005	03/2006
60966	ESCHALIER	Alain	26/09/2006	LD-AR	SANOFI	groupe expert antalgie adulte	rémunération personnelle	03/2007	03/2007
60966	ESCHALIER	Alain	26/09/2006	EC-INV	GRUNENTHAL	étude préclinique sur l'association Tramadol + Paracétamol	rémunération personnelle	03/2007	03/2007
60966	ESCHALIER	Alain	26/09/2006	CF-INT	GRUNENTHAL	Symposium douleur - Paris - Sujet : " co-antalgiques "			
60966	ESCHALIER	Alain	26/09/2006	CF-INT	MEDTRONIC	Lille : Société Francophone de neurochirurgie Pharmacologie des morphiniques			
60966	ESCHALIER	Alain	29/03/2005	IP-AC	SANOFI	Activité de conseil sur les antalgiques			
60966	ESCHALIER	Alain	29/03/2005	IP-AC	AVENTIS	Activité de conseil sur les antalgiques			
60966	ESCHALIER	Alain	29/03/2005	IP-CF	SANOFI	1 EPU sur Télithromycine			
60966	ESCHALIER	Alain	29/03/2005	IP-CF	AVENTIS	1 EPU sur Télithromycine			
60966	ESCHALIER	Alain	30/08/2004	IP-AC	AVENTIS	Conseil pour le développement de produits antalgiques			
60966	ESCHALIER	Alain	30/08/2004	VB	UCB Belgique	Travaux scientifiques : INSERM (ex Equipe E9904 dont j'assume la responsabilité)			
60966	ESCHALIER	Alain	30/08/2004	VB	FOURNIER	Travaux scientifiques : Université d'Auvergne (Equipe de recherche dont j'assume la responsabilité)			
60966	ESCHALIER	Alain	30/08/2004	VB	PFIZER	Activités de conseil (sur les douleurs neuropathiques) : Association pour le soutien de la pharmacologie en région Auvergne			
60966	ESCHALIER	Alain	26/10/1999	IP-RE	UPSA	Efferalgan 500 mg , efferalgan tablet(1998)			
60966	ESCHALIER	Alain	26/10/1999	IP-RE	BMS	Excedrin central eastein europe (1999)			
60966	ESCHALIER	Alain	26/10/1999	VB	GRUNENTHAL (conférence)	Université			
60966	ESCHALIER	Alain	26/10/1999	VB	HOUDE(conseil)	association			
60966	ESCHALIER	Alain	26/10/1999	VB	SMITHKLINE BEECHAM(conseil)	Association			
60966	ESCHALIER	Alain	26/10/1999	VB	PARKE DAVIS	Université			
60966	ESCHALIER	Alain	26/10/1999	IP-AC	BAYER PHARMA	Conseil scientifique risque cv absolu			
10167	ESCHWEGE	Evelyne	19/05/1999	IP-AC	ROCHE	Conseil scientifique développement Orlestat			
10167	ESCHWEGE	Evelyne	19/05/1999	IP-AC	BEECHAM	Conseil scientifique développement Rosigletarane			
10167	ESCHWEGE	Evelyne	19/05/1999	IP-AC	PARKE DAVIS	Conseil scientifique essais "Target" (Atorvastatine)			
10167	ESCHWEGE	Evelyne	19/05/1999	IP-CF	SANOFI	Conférence de presse Diastabol			
10167	ESCHWEGE	Evelyne	19/05/1999	VB	SERVIER	Inserm			
10167	ESCHWEGE	Evelyne	19/05/1999	VB	LIPHA	Inserm			
10167	ESCHWEGE	Evelyne	19/05/1999	VB	ROCHE	Inserm			
10167	ESCHWEGE	Evelyne	19/05/1999	VB	NOVARTIS	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	IP-AC	BAYER				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-AC	SANDOZ-NOVARTIS				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-AC	ROCHE				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-AC	BEECHAM				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-CF	BAYER				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-CF	FOURNIER				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-CF	SANDOZ-NOVARTIS				
10167	ESCHWEGE	Evelyne	01/01/1999	IP-AUT	FABRE	Audit, à la demande du MRES			
10167	ESCHWEGE	Evelyne	01/01/1999	IP-AC	LIPHA				
10167	ESCHWEGE	Evelyne	01/01/1999	VB	CASSENNE	Contrats avec Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	INNOTHERA	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	SYNTHELABO	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	SERVIER	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	LIPHA	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	ROCHE	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	JOUVEINAL	Inserm			
10167	ESCHWEGE	Evelyne	01/01/1999	VB	SMITHKLINE BEECHAM				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Bayer				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Lipha				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Sandoz				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Negma				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Roche				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Fournier				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Beecham				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	BMS				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Servier				
10167	ESCHWEGE	Evelyne	01/01/1998	IP-AUT	Fabre		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Lipha		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Synthelabo		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	MSD		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Houdé		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Hoescht		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Besin Iscovesco		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Organon		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Fisons		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Servier		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Cassenne		contrats avec INSERM		
10167	ESCHWEGE	Evelyne	01/01/1998	VB	Innothéra		vous	08/2005	
10167	ESCHWEGE	Evelyne	01/01/1998	VB	SANOFI-AVENTIS	Conseil à propos d'une étude de pharmacoépidémiologie dans la schizophrénie	Vous	10/2004	
60700	FALISSARD	Bruno	17/10/2005	EC-CO	LA-SER	Etude de pharmacoépidémiologie dans la schizophrénie (Risperdal constat)	Vous	10/2005	
60700	FALISSARD	Bruno	17/10/2005	EC-CO	SERVIER	Méthodologie de mesure de la subjectivité dans les études cliniques	Vous	10/2001	
60700	FALISSARD	Bruno	17/10/2005	IP-AC	LILLY	Etude épidémiologique européenne Adore	Vous	10/2003	06/2005
60700	FALISSARD	Bruno	19/08/2003	EC-CO	PFIZER	Etude épidémiologique dans la dépression au long cours	Vous	10/2001	
60700	FALISSARD	Bruno	19/08/2003	IP-EC	DGS-CEMKAIEVA	Etude santé mentale en prison	Vous	06/2001	06/2001
60700	FALISSARD	Bruno	19/08/2003	IP-EC	LILLY	Efficacité d'Olenzapine dans la schizophrénie	Vous	06/2001	06/2001
60700	FALISSARD	Bruno	19/08/2003	RE-DE	LILLY	Expertise ADV	Vous	10/2002	10/2002
60700	FALISSARD	Bruno	19/08/2003	IP-RE	LILLY	Etude qualitative de l'effet d'antidépresseur	Vous	01/2005	01/2005
60700	FALISSARD	Bruno	19/08/2003	IP-AC	CHIESI	Méthodologie de recherche clinique	Vous	06/2005	06/2005
60700	FALISSARD	Bruno	19/08/2003	IP-CF	SERVIER	Méthodologie de recherche clinique			
60700	FALISSARD	Bruno	19/08/2003	IP-CF	GLAXO SMITHKLINE	Etude épidémiologique chez enfant			
60700	FALISSARD	Bruno	11/06/2002	IP-EC	LILLY	Etude épidémiologique sur la prescription au long cours des anti-dépresseurs			
60700	FALISSARD	Bruno	11/06/2002	IP-EC	PFIZER	Analyse de données sur essai thérapeutique			
60700	FALISSARD	Bruno	11/06/2002	IP-EC	SERVIER	Publication concernant Zyprexa			
60700	FALISSARD	Bruno	11/06/2002	IP-RE	LILLY	Mise en route observatoire Thales			
60700	FALISSARD	Bruno	11/06/2002	IP-AC	LILLY	Conseil de méthodologie de mesure de la subjectivigé en santé			
60700	FALISSARD	Bruno	11/06/2002	IP-AC	PIG Pharmaceuticals, MERCK	Méthodologie de la recherche en psychatrie			
60700	FALISSARD	Bruno	11/06/2002	IP-CF	SERVIER				
60700	FALISSARD	Bruno	11/06/2002	VB	DGS / Inserm	Participation au capital social à hauteur de 15% (après accord de la Commission Nationale de Déontologie)			
63307	FANTINO	Marc	09/06/2004	IF	ALPHAMAP SARL	Conseiller scientifique avec l'autorisation des Ministères de tutelle après avis favorable de la Commission Nationale de Déontologie			
63307	FANTINO	Marc	09/06/2004	LD	ALPHAMAP SARL				
63307	FANTINO	Marc	09/06/2004	IP-RE	ALPHAMAP SARL	Activité de conseil occasionnel, validation de rapports scientifiques ou membre de jury scientifique ou participation à des conseils scientiques pour des sociétés telles que			
63307	FANTINO	Marc	09/06/2004	IP-AC	Société EQUITABLE	Id.			
63307	FANTINO	Marc	09/06/2004	IP-AC	Société SPRIMBOX	id.			
63307	FANTINO	Marc	09/06/2004	IP-AC	Société ALIGENCE	Jury scientifique			
63307	FANTINO	Marc	09/06/2004	IP-AC	DANONE	Conseil scientifique			
63307	FANTINO	Marc	09/06/2004	IP-AC	ALPHAMAP	Conseil scientifique			
63307	FANTINO	Marc	09/06/2004	IP-AC	NESTLE France				
63307	FANTINO	Marc	09/06/2004	IP-CF	EQUITABLE, SPRIMBOX, ALIGENCE, DANONE, ALPHAMAP, NESTLE	Conférences, colloques, actions de formation, conférences de presse, validation de documents bibliographiques			
63307	FANTINO	Marc	09/06/2004	IP-CF	EUROFORUM Paris, Société PAIN VIN ET COMPANY (Paris)	Id.			
63307	FANTINO	Marc	09/06/2004	IP-CF	ITI (Rueil Malmaison)	id.			
63307	FANTINO	Marc	09/06/2004	IP-CF	Sociétés COMPLIANCE ET LESIEUR	Conférences ou participation à des Colloques			
63307	FANTINO	Marc	09/06/2004	IP-CF	SOGERES (Paris)	Validation de documents pédagogiques, participation à des colloques			
63307	FANTINO	Marc	09/06/2004	IP-CF	NESTLE France	Validation de documents, participation à des colloques			
63307	FANTINO	Marc	09/06/2004	IP-CF	BOOT II PHARMA (Paris)	Participation à des colloques			
63307	FANTINO	Marc	09/06/2004	IP-CF	KNOLL BASF (Levallois-Perret)	Participation à des colloques			
63307	FANTINO	Marc	09/06/2004	IP-CF	ABBOTT (Rungis)	Participation à des colloques			
63307	FANTINO	Marc	09/06/2004	IP-AUT	SYNDICAT NATIONAL DES BOISSONS RAFRAICHISSANTES	Invitation à un repas de travail			
63307	FANTINO	Marc	09/06/2004	IP-AUT	DANONE	Invitation à un repas de travail			
63307	FANTINO	Marc	09/06/2004	VB	FOURNIER (Dijon, Daix)	Réalisation de travaux scientifiques et d'essais sur volontaires sains en collaboration avec ou sous contrat entre ces entreprises et essentiellement l'Université de Bourgogne, l			
63307	FANTINO	Marc	09/06/2004	VB	DANONE Groupe et notamment Société DES EAUX D'EVIAN (Rungis)	Réalisation de travaux scientifiques et d'essais sur volontaires sains en collaboration avec ou sous contrat entre ces entreprises et essentiellement l'Université de Bourgogne, l			
63307	FANTINO	Marc	09/06/2004	VB	BECKTON-DIKINSON (Grenoble et USA)	Réalisation de travaux scientifiques et d'essais sur volontaires sains en collaboration avec ou sous contrat entre ces entreprises et essentiellement l'Université de Bourgogne, l			
63307	FANTINO	Marc	09/06/2004	VB	MASTER FOOD (Strasbourg)	Réalisation de travaux scientifiques et d'essais sur volontaires sains en collaboration avec ou sous contrat entre ces entreprises et essentiellement l'Université de Bourgogne, l			
63307	FANTINO	Marc	09/06/2004	VB	LACTEL - LACTALIS (Laval et Paris)	Réalisation de travaux scientifiques et d'essais sur volontaires sains en collaboration avec ou sous contrat entre ces entreprises et essentiellement l'Université de Bourgogne, l			
63307	FANTINO	Marc	09/06/2004	VB	OENOBIOL (Paris)	Réalisation de travaux scientifiques et d'essais sur volontaires sains en collaboration avec ou sous contrat entre ces entreprises et essentiellement l'Université de Bourgogne, l			
63307	FANTINO	Marc	09/06/2004	PAR	INSTITUT DE RECHERCHE EN MARKETING DE L'ALIMENTATION SANTE - IREMAS	Participation au conseil scientifique			
63307	FANTINO	Marc	09/06/2004	PAR	NUTRIMATE (Marly Le Roi)	Discussions scientifiques sans rémunération, ni versement financier à un organisme bénéficiaire			
63307	FANTINO	Marc	09/06/2004	PAR	ROCHE NICHOLAS SA: Consumer Helth / Division Serdex (Saint Ouen)	Discussions scientifiques sans rémunération, ni versement financier à un organisme bénéficiaire			
63307	FANTINO	Marc	09/06/2004	PAR	ABBOTT France	Discussions scientifiques sans rémunération, ni versement financier à un organisme bénéficiaire			
63307	FANTINO	Marc	09/06/2004	PAR	NUTRASWWET/MONSANTO (Paris)	Relations antérieures (datant de plus de trois ans)			
63307	FANTINO	Marc	09/06/2004	PAR	LAFON, BOOT PHARMA, SERVIER	Relations antérieures (datant de plus de cinq ans)			
62501	FARINOTTI	Robert	30/09/2009	CF-INT	FRESENIUS	Paris : symposium perfusion (pas de nom de produit)	rémunération personnelle-institution		
62501	FARINOTTI	Robert	30/09/2009	CF-INT	VIFOR	Paris : symposium fer-venofer	rémunération personnelle-institution		
62501	FARINOTTI	Robert	30/09/2009	CF-INT	NOVO NORDISK	Reims : symposium - incrétines (pas de nom de produit)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62501	FARINOTTI	Robert	15/05/2008	CF-AUD	SERVIER	Congres SNPHPU St Malo		02/2008	02/2008
62501	FARINOTTI	Robert	06/02/2007	LD-AR	JANSEN-CILAG	Conseil / EPO / FENTANYL (groupe conseil)	rémunération personnelle	01/2005	03/2007
62501	FARINOTTI	Robert	06/02/2007	EC-INV	BMS	Thèse - Bourse CIFRE (EFAVIRENZ)	expérimentation	10/2003	12/2006
62501	FARINOTTI	Robert	06/02/2007	EC-INV	SERVIER	Thèse - Bourse CIFRE (Module Cellulaire)	expérimentation	05/2005	12/2008
62501	FARINOTTI	Robert	06/02/2007	CF-INT	ASTRA-ZENECA	Evian / recherche en Cancérologie	aucune rémunération	01/2007	
62501	FARINOTTI	Robert	06/02/2007	VB	QUASIMENT TOUS LES GRANDS LABORATOIRES PHARMACEUTIQUES	Taxe d'Apprentissage	faculté de pharmacie Paris XI		
62501	FARINOTTI	Robert	14/03/2004	IP-EC	UCB, BRISTOL MYERS SQUIBB, ABBOTT				
62501	FARINOTTI	Robert	14/03/2004	IP-CF	LILLY, FRESENIUS	Enfant salarié			
62501	FARINOTTI	Robert	14/03/2004	PAR	ABBOTT				
62501	FARINOTTI	Robert	07/11/2002	IP-CF	LILLY, ASTRA ZENECA, GLAXO SMITHKLINE	Pharmacocinétique			
62501	FARINOTTI	Robert	03/07/2002	IP-EC	GLAXO SMITHKLINE	Pharmacocinétique			
62501	FARINOTTI	Robert	03/07/2002	IP-EC	ASTRA ZENECA	Pharmacocinétique			
62501	FARINOTTI	Robert	03/07/2002	IP-EC	ROCHE	Sujets : pharmacocinétique	Rémunération personnelle	07/2009	07/2009
62501	FARINOTTI	Robert	03/07/2002	IP-CF	Divers laboratoires pharmaceutiques	Conseil sur les formes ophtalmiques	Rémunération institution	09/2009	
62939	FATTAL	Elias	21/06/2010	IP-AC	SOLVAY FRANCE	Responsable programme scientifique	Rémunération institution	09/2009	
62939	FATTAL	Elias	21/06/2010	LD-AR	GUERBET	Responsable programme scientifique	Rémunération personnelle	01/2010	
62939	FATTAL	Elias	21/06/2010	LD-AR	SERVIER	Consultant	Rémunération personnelle	06/2010	06/2010
62939	FATTAL	Elias	21/06/2010	LD-AR	ZCUBE	Conférence sur les nanotechnologies	Rémunération personnelle	01/2010	
62939	FATTAL	Elias	21/06/2010	CF-INT	FLAMEL TECHNOLOGIES	Editeur adjoint	Rémunération personnelle	01/2010	
62939	FATTAL	Elias	21/06/2010	LD-AR	EDITIONS DE SANTÉ	Consultant	Rémunération personnelle	01/2010	
62939	FATTAL	Elias	21/06/2010	LD-AR	O'BOTICARIO	Consultant	Rémunération personnelle	03/2007	03/2007
62939	FATTAL	Elias	21/06/2010	LD-AR	NOVAGALLI	Conférence sur les nanotechnologies	Rémunération personnelle	10/2007	10/2007
62939	FATTAL	Elias	21/06/2010	CF-INT	GSK	Workshop sur les nanotechnologies	Rémunération personnelle	03/2007	
62939	FATTAL	Elias	21/06/2010	CF-INT	LEK SLOVENIE	Conférence sur les nanotechnologies	Rémunération personnelle	10/2007	
62939	FATTAL	Elias	02/12/2007	CF-INT	GSK	Workshop sur les nanotechnologies	Rémunération personnelle	10/2007	10/2007
62939	FATTAL	Elias	02/12/2007	CF-INT	LEK SLOVENIE	Conseil sur la stabilité de nanoparticules	Rémunération personnelle	01/2006	12/2007
62939	FATTAL	Elias	02/12/2007	IP-AC	NANOBIOTIX	Conseil pour la formulation d'émulsion cosmétique	Rémunération personnelle	01/2007	12/2007
62939	FATTAL	Elias	02/12/2007	LD-AR	O'BOTICARIO BRÉSIL	Conseil pour la délivrance colique	Co-investigateur	01/2005	
62939	FATTAL	Elias	02/12/2007	LD-AR	DA VOLTERRA FRANCE	Participation à des essais thérapeutiques ou à des enquêtes à valeur épidémiologiques	Rémunération personnelle	01/2008	12/2009
63919	FAUTREL	Bruno	18/03/2009	EC-CO	WYETH, ABBOTT, BMS, SCHERING PLOUGH, ROCHE		Rémunération personnelle/institution	01/2005	
63919	FAUTREL	Bruno	18/03/2009	RE-DE	UCB, ROCHE	Travaux d'expertise scientifique□□Participation à des board d'experts nationaux ou internationaux	Rémunération personnelle	01/2008	12/2009
63919	FAUTREL	Bruno	18/03/2009	IP-AC	WYETH, ABBOTT, BMS, SCHERING PLOUGH, ROCHE, SANOFI AVENTIS	Symposium lors de congès ou de réunion de lancement		01/2006	
63919	FAUTREL	Bruno	18/03/2009	CF-INT	WYETH, ABBOTT, BMS, SCHERING PLOUGH, ROCHE	Etude SMART (rituximab) + étude LITHE (tocilizumab) (collaborateur de l'étude)		01/2008	
63919	FAUTREL	Bruno	13/02/2008	EC-CO	ROCHE	Etude Abatacept SC (collaborateur de l'étude)		01/2007	
63919	FAUTREL	Bruno	13/02/2008	EC-CO	BMS	Conseil pour des études scientifiques (études en cours) :□□- enquête PRISME (anti-TNF)□□- BOARD modélisation médicoéconomique□□-		01/2007	
63919	FAUTREL	Bruno	13/02/2008	IP-AC	WYETH	Conseil pour ds études scientifiques (études en cours) :□□- étude OPERA (rituximab)□□- board tocilizumab□□compte rendu de congrès		10/2007	12/2007
63919	FAUTREL	Bruno	13/02/2008	IP-AC	ROCHE	Lancement ORENCIA		02/2008	02/2008
63919	FAUTREL	Bruno	13/02/2008	IP-AC	BMS	Board international golimuimab		03/2007	03/2007
63919	FAUTREL	Bruno	13/02/2008	IP-AC	SCHERIG PLOUGH - CENTOCOR	résentation séminaire adalimumab	rémunération personnelle	02/2006	12/2007
63919	FAUTREL	Bruno	13/02/2008	IP-AC	ABBOTT	Rituximab - projet médico-éco□□programme éducation patient	rémunération personnelle	01/2006	12/2007
63919	FAUTREL	Bruno	12/06/2006	LD-AR	ROCHE	ENBREL - programme FMC - projet médico-éco	membre du comité de pilotage - projet médico-éco	01/2006	12/2010
63919	FAUTREL	Bruno	12/06/2006	LD-AR	WYETH		rémunération personnelle		
63919	FAUTREL	Bruno	12/06/2006	EC-CO	WYETH	Cohorte SPA	rémunération personnelle		
63919	FAUTREL	Bruno	12/06/2006	IP-AC	WYETH	ENBREL - Formation Médicale Continue	rémunération personnelle	01/2006	
63919	FAUTREL	Bruno	12/06/2006	IP-AC	ROCHE	RITUXIMAB - Formation Médicale Continue	Rémunération personnelle	01/2002	07/2005
63919	FAUTREL	Bruno	12/06/2006	CF-INT	WYETH	Programme Prisme	Rémunération personnelle	09/2005	12/2005
63919	FAUTREL	Bruno	09/11/2005	LD-AR	PFIZER FANCE	Consulting/Conseil Celerex	Rémunération personnelle	01/2004	08/2005
63919	FAUTREL	Bruno	09/11/2005	LD-AR	SERVIER	Conseil sur Protelos	Rémunération personnelle	04/2005	
63919	FAUTREL	Bruno	09/11/2005	IP-AC	ABBOTT France	Rencontre d'experts en rhumatologie			
63919	FAUTREL	Bruno	09/11/2005	IP-AC	WYETH France	Programme de FMC Prisme			
63919	FAUTREL	Bruno	09/11/2005	CF-INT	WYETH France		concepteur	01/2010	
63919	FAUTREL	Bruno	09/11/2005	EC-CO	T.O. LYON	developpement implant PTH□□gamme XO	investigateur principal	04/2010	
62895	FERON	Jean-Marc	08/07/2010	EC-INV	SERVIER	etude phase III, Protelos	Rémunération personnelle	04/2010	05/2010
62895	FERON	Jean-Marc	08/07/2010	CF-INT	LEO PHARMA	Journées de FMC Franco-Marocaine en orthopédie	Rémunération personnelle	05/2010	
62895	FERON	Jean-Marc	08/07/2010	IP-AC	SERVIER	International protelos Advisory Committee	Rémunération personnelle	01/2010	12/2010
62895	FERON	Jean-Marc	08/07/2010	IP-AC	AMGEN	International Advisory Board	Rémunération personnelle		
62895	FERON	Jean-Marc	08/07/2010	CF-INT	SERVIER	Symposium satellite Congres de rhumato Paris 12/09	Investigateur	12/2009	
62895	FERON	Jean-Marc	04/01/2010	EC-CO	AMGEN	Etude phase 2 AMG 785	Investigateur	12/2009	
62895	FERON	Jean-Marc	30/11/2009	EC-CO	SERVIER	Etude Protelos >Pseudarthrose	Osteosynthesis and Trauma Care foundation France		
62895	FERON	Jean-Marc	30/11/2009	VB	STRYKER	Educational Grant 2009	Osteosynthesis and Trauma Care foundation France		
62895	FERON	Jean-Marc	30/11/2009	VB	LEO PHARMA	educational grant 2009	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	CF-INT	HERAUS	Palacademie Berlin□□Clment chirurgical	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	CF-INT	SERVIER	Actualité en biologie osseuse□□Conférencier Paris	Rémunération personnelle	07/2009	
62895	FERON	Jean-Marc	30/11/2009	IP-AC	NOVARTIS	conseil	Rémunération personnelle	06/2009	
62895	FERON	Jean-Marc	30/11/2009	IP-AC	AMGEN	advisory board	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	CF-INT	BIOMET	AAOS Las Vegas USA 2009	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	LD-AR	STRYKER	Brevet, contrat d'exploitation commerciale	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	CF-INT	STRYKER	JODFDF Martinique 03/08□□Workshop traumatologie	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	CF-INT	LEO PHARMA	Journée Franco européenne d'orthopédie□□Cork IRL Organisation scientifique	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	CF-INT	LEO PHARMA	JODFDF Martinique 03/08□□Symposium traumatologie	Rémunération personnelle		
62895	FERON	Jean-Marc	30/11/2009	LD-AR	ZIMMER	Brevet, contrat d'exploitation commerciale	hébergement transport		
62895	FERON	Jean-Marc	30/11/2009	CF-AUD	LEO PHARMA	EFORT congress Nice 06/08	hébergement transport		
62895	FERON	Jean-Marc	30/11/2009	CF-AUD	STRYKER	AAOS San Francisco USA 02/08	hébergement transport		
62895	FERON	Jean-Marc	30/11/2009	CF-AUD	STRYKER	JOFDF Martinique 03/08	hébergement transport		
62895	FERON	Jean-Marc	30/11/2009	CF-AUD	STRYKER	réunion OTC fondation Nice 06/08	hébergement transport		
62895	FERON	Jean-Marc	30/11/2009	CF-AUD	STRYKER	International Trauma Congress□□Barcelona Spain 04/08			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62895	FERON	Jean-Marc	30/11/2009	VB	SANOFI AVENTIS	Subvention 06/08	Assoc Chirurgie orthop et communication : Co&Co		
62895	FERON	Jean-Marc	22/12/2008	LD-AR	ZIMMER	Brevet ,contrat d'exploitation commerciale	Rémunération personnelle		
62895	FERON	Jean-Marc	22/12/2008	CF-AUD	STRYKER	International Trauma Congress□□Barcelona Spain 04/08	hebergement transport		
62895	FERON	Jean-Marc	22/12/2008	VB	SANOFI AVENTIS	Subvention 06/08	Assoc Chirurgie orthop et communication: Co&Co		
62895	FERON	Jean-Marc	22/12/2008	CF-AUD	STRYKER	reunion OTC fondation Nice 06/08	hebergement transport		
62895	FERON	Jean-Marc	22/12/2008	CF-AUD	STRYKER	Journée Nationale OTC France Marseille 10/08	hebergement transport	10/2008	10/2008
62895	FERON	Jean-Marc	22/12/2008	CF-INT	LEO PHARMA	Journée Franco européenne d'orthopédie□□Cork IRL Organisation scientifique	Rémunération personnelle		
62895	FERON	Jean-Marc	22/12/2008	CF-AUD	STRYKER	JOFDF Martinique 03/08	hebergement transport		
62895	FERON	Jean-Marc	22/12/2008	CF-AUD	STRYKER	AAOS San Francisco USA 02/08	hebergement transport		
62895	FERON	Jean-Marc	22/12/2008	CF-AUD	LEO PHARMA	EFORT congress Nice 06/08	hebergement transport		
62895	FERON	Jean-Marc	22/12/2008	CF-INT	STRYKER	JODFDF Martinique 03/08□□Workshop traumatologie	Rémunération personnelle		
62895	FERON	Jean-Marc	22/12/2008	CF-INT	LEO PHARMA	JODFDF Martinique 03/08□□Symposium traumatologie	Rémunération personnelle		
62895	FERON	Jean-Marc	08/12/2007	VB	WHYETH	Honoraires etude clinique	Association "chirurgie orthopédique et communication" loi 1901		06/2007
62895	FERON	Jean-Marc	17/11/2006	VB	ASTRA ZANECA	subvention	Assoc 1901□ Communication et chirurgie orthopédique (Co&Co)	06/2006	06/2006
62895	FERON	Jean-Marc	17/11/2006	VB	AVENTIS	subvention	Assoc 1901□ Communication et chirurgie orthopédique (Co&Co)	05/2006	05/2006
62895	FERON	Jean-Marc	17/11/2006	CF-AUD	STRYKER	SOFCOT Paris nov 06		11/2006	11/2006
62895	FERON	Jean-Marc	17/11/2006	CF-INT	STRYKER	AIOD intenational NICE	Aucune rémunération	06/2006	11/2006
62895	FERON	Jean-Marc	17/11/2006	CF-INT	STRYKER	AIOD francophone Biarritz	Aucune rémunération	10/2006	10/2006
62895	FERON	Jean-Marc	17/11/2006	CF-INT	ORTHOFIX	Internal fixation course□□elderly fractures□□Verona, Italie, 23/10/06	Aucune rémunération	10/2006	10/2006
62895	FERON	Jean-Marc	27/10/2005	VB	LEO PHARMA	Don	Association 1901	10/2001	
62895	FERON	Jean-Marc	27/10/2005	VB	MSD	Don	Association 1901	01/2005	
62895	FERON	Jean-Marc	27/10/2005	IP-AC	GSK	Int'l Orthopaedic surgeon advisory board on osteoporosis fractures	Aucune	09/2005	11/2005
62895	FERON	Jean-Marc	07/12/2004	LD-AR	STRYKER	Brevet, contrat d'exploitation commerciale	Royalties personnelles	09/2004	
62895	FERON	Jean-Marc	07/12/2004	LD-AR	ZIMMER	Brevet, groupe de recherche et développemnt (pas de rémunération)	aucune	09/2004	
62895	FERON	Jean-Marc	07/12/2004	EC-INV	WYETH	Co investigateur, étude multicentrique "RHBMP2" 2004/2005		10/2004	
62895	FERON	Jean-Marc	07/12/2004	IP-AC	BIOBANK	ML du conseil scientifique 2004	Aucune	06/2004	
62895	FERON	Jean-Marc	18/02/2004	LD-AR	STRYKER	Cession d'exploitation sur brevet tige fémorale DEDICACE (PTH aimantée)		09/2004	
62895	FERON	Jean-Marc	18/02/2004	PAR	ST ZIMMER	Recherche "Cotyle"	ERREUR/ SANS OBJET□ Voir 2.1	10/2005	10/2005
62895	FERON	Jean-Marc	20/12/2003	LD	STRYKER	Cession d'exploitation sur brevet tige fémorale DEDICACE (PTH			
62895	FERON	Jean-Marc	20/12/2003	(Autre)	ZIMMER	Groupe de recherche sur cotyle double mobilité anti luxation			
10174	FIESSINGER	Jean-Noël	22/02/2005	IP-AC	ASTRA ZENECA	Investigateur principal THRIVE (2000-2004)			
10174	FIESSINGER	Jean-Noël	22/02/2005	IP-AC	LEO	Innahep, conseil			
10174	FIESSINGER	Jean-Noël	22/02/2005	IP-EC	ASTRA ZENECA	Investigateur de l'étude Pivot			
10174	FIESSINGER	Jean-Noël	22/02/2005	IP-EC	EXANTA	Investigateur de l'étude Pivot			
10174	FIESSINGER	Jean-Noël	22/02/2005	VB	LEO	Innohep			
10174	FIESSINGER	Jean-Noël	04/09/2003	LD	ASTRA ZENECA	Steering Committee Melagatron			
10174	FIESSINGER	Jean-Noël	04/09/2003	IP-EC	ASTRA ZENECA	Thrive II et III			
10174	FIESSINGER	Jean-Noël	29/08/2003	LD	ASTRA ZENECA	President steering committee Thrive II			
10174	FIESSINGER	Jean-Noël	29/08/2003	IP-EC	ASTRA ZENECA	Thrive II et III			
10174	FIESSINGER	Jean-Noël	29/06/2000	LD	EXELGYN	Conseil			
10174	FIESSINGER	Jean-Noël	29/06/2000	IP-EC	ASTRA ZENECA	Thrive II et III			
10174	FIESSINGER	Jean-Noël	29/06/2000	IP-EC	SERVIER	Taipad			
10174	FIESSINGER	Jean-Noël	29/06/2000	IP-EC	KNOLL	Sacre			
10174	FIESSINGER	Jean-Noël	29/06/2000	VB	EXELGYN	Conseil Claude Bernard			
10174	FIESSINGER	Jean-Noël	19/06/2000	LD	EXELGYN	Conseil			
10174	FIESSINGER	Jean-Noël	19/06/2000	IP-EC	ASTRA ZENECA	Protocole Mélagatron			
10174	FIESSINGER	Jean-Noël	19/06/2000	IP-EC	SERVIER	Protocole antithrombotique			
10174	FIESSINGER	Jean-Noël	19/06/2000	IP-AC	SERVIER	Développement antithrombotiques			
10174	FIESSINGER	Jean-Noël	19/06/2000	VB	EXELGYN	Association Claude Bernard			
10174	FIESSINGER	Jean-Noël	19/06/2000	VB	SERVIER	Association Claude Bernard			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-EC	ASTRA	Protocole Mélagatron			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-EC	KNOLL	Protocole Chévanni			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-EC	SANOFI	Protocole Frosopavir			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-AC	EXELGYN	Conseil			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-CF	RHONE POULENC	Conférences			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-CF	LEO	Conférences			
10174	FIESSINGER	Jean-Noël	14/01/2000	IP-CF	SANOFI	Conférences			
10174	FIESSINGER	Jean-Noël	14/01/2000	VB	EXELGYN	Versement à l'Association Claude Bernard			
10174	FIESSINGER	Jean-Noël	01/01/1999	IP-EC	Sanofi				
10174	FIESSINGER	Jean-Noël	01/01/1999	IP-EC	Schering				
10174	FIESSINGER	Jean-Noël	01/01/1999	IP-EC	Pharmacia				
10174	FIESSINGER	Jean-Noël	01/01/1999	IP-AC	Knoll				
10174	FIESSINGER	Jean-Noël	01/01/1998	IP-AUT	Sanofi				
10174	FIESSINGER	Jean-Noël	01/01/1998	IP-AUT	Schering				
10174	FIESSINGER	Jean-Noël	01/01/1998	IP-AUT	Knoll				
10174	FIESSINGER	Jean-Noël	01/01/1998	IP-AUT	Léo				
10174	FIESSINGER	Jean-Noël	01/01/1998	VB	Conseil pour Knoll				
10178	FORETTE	Françoise	01/01/1999	IP-EC	NOVARTIS				
10178	FORETTE	Françoise	01/01/1999	IP-EC	MERCK				
10178	FORETTE	Françoise	01/01/1999	IP-EC	HOECHST				
10178	FORETTE	Françoise	01/01/1999	IP-RE	PARKE DAVIS				
10178	FORETTE	Françoise	01/01/1999	IP-AC	Institut LILLY	Conseil Scientifique			
10178	FORETTE	Françoise	01/01/1999	IP-CF	SERVIER				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10178	FORETTE	Françoise	01/01/1999	IP-CF	ESAI LIPHA				
10178	FORETTE	Françoise	01/01/1999	IP-CF	PARKE DAVIS				
10178	FORETTE	Françoise	01/01/1999	IP-EC	ROUSSEL-UCLAF				
10178	FORETTE	Françoise	01/01/1999	VB	SPECIA	Fondation Nationale de Gérontologie			
10178	FORETTE	Françoise	01/01/1999	VB	NOVARTIS	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	MERCK	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	LILLY	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	RHONE POULENC	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	SERVIER	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	SNIP	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	EISAI	ILC France			
10178	FORETTE	Françoise	01/01/1999	VB	PARKE DAVIS	ILC France			
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Roussel				
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Merz				
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Sandoz				
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Parke Davis				
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Lilly				
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Pfizer				
10178	FORETTE	Françoise	01/01/1998	IP-AUT	Hoechst				
10178	FORETTE	Françoise	01/01/1998	VB	RPR-Spécia		Subvention à la Fondation Nationale de gérontologie	06/2010	06/2010
61603	FRACHET	Bruno	15/06/2010	CF-AUD	NEURELEC	Stockholm (Suède) implants cochléaires Digisonic	Rémunération personnelle	06/2010	06/2010
61603	FRACHET	Bruno	15/06/2010	IP-AC	AUDIO 2000 - PROTHèSES AUDITIVES	Organisation d'une formation professionnelle		05/2009	05/2009
61603	FRACHET	Bruno	15/04/2009	CF-AUD	AUDIO 2000	Slovénie - Audition et Santé publique, les implants d'oreille moyenne en 2009 - distributeur de prothèses auc	investigateur principal	05/2009	12/2011
61603	FRACHET	Bruno	15/04/2009	EC-INV	NEUROSYSTEC	NST001, produit anti-glutamate injecté directement dans l'oreille interne - étude de phase 1	réseau IFIC	01/2008	12/2011
61603	FRACHET	Bruno	10/06/2008	VB	ARH	financement réseau	réseau IFIC	01/2008	12/2011
61603	FRACHET	Bruno	10/06/2008	VB	APHP	loyer	Aucune rémunération		
61603	FRACHET	Bruno	10/06/2008	CF-INT	MEDEL	congrès scientifiques-rapport d'études	Aucune rémunération		
61603	FRACHET	Bruno	10/06/2008	CF-INT	COCHLEAR	congrès scientifiques-rapport d'études	Aucune rémunération		
61603	FRACHET	Bruno	10/06/2008	CF-INT	MXM	congrès scientifiques-rapport d'études	Aucune rémunération		
61603	FRACHET	Bruno	10/06/2008	CF-INT	ABIONICS	congrès scientifiques-rapport d'études	co-investigateur		
61603	FRACHET	Bruno	10/06/2008	EC-CO	MXM	étude Tonnelec-traitement électrique des acouphènes	co-investigateur-étude européenne		
61603	FRACHET	Bruno	10/06/2008	EC-CO	COCHLEAR	étude hybrid L stimulation mixte électro-acoustique	co-investigateur		
61603	FRACHET	Bruno	10/06/2008	EC-CO	COCHLEAR	étude MP3000-implant cochléaire Freedom-codage MP3 de la parole			
61603	FRACHET	Bruno	10/06/2008	EC-CO	COCHLEAR	étude SOE-implant cochléaire Freedom- diffusion de l'excitation nerveuse			
61603	FRACHET	Bruno	10/06/2008	EC-CO	MEDEL	VSB-étude vibroplastie ossiculaire□□implant d'oreille moyenne	étude multicentrique européenne	04/2006	
61603	FRACHET	Bruno	10/06/2008	EC-CO	MEDEL	VSB-étude Vibroplastie - sur la fenêtre ronde□□implant d'oreille moyenne	étude multicentrique européenne	04/2006	09/2007
61603	FRACHET	Bruno	23/04/2007	LD-ODE	MISSION INFORMATIQUE EN ORL (MIORL)	Bénévole : structure émanant des tutelles de la discipline ORL (société savante, collège, syndicat)	président	01/2003	
61603	FRACHET	Bruno	23/04/2007	LD-AR	SOCIETE AMPLIFON	Distribution de prothèses auditives : au board du conseil scientifique	rémunération personnelle	01/2006	12/2007
61603	FRACHET	Bruno	23/04/2007	EC-INV	COCHLEAR	Implant COCHLEAIRE (étude MX 3000)	investigateur principal	01/2007	12/2007
61603	FRACHET	Bruno	23/04/2007	IP-EC	MEDEL	Implant d'oreille moyenne 1	Investigateur principal	01/2007	
61603	FRACHET	Bruno	23/04/2007	EC-CO	MXM	Implant COCHLEAIRE	Co-investigateur	01/2006	12/2007
61603	FRACHET	Bruno	23/04/2007	EC-CO	CLARION	Implant COCHLEAIRE	Co-investigateur	01/2006	12/2007
61603	FRACHET	Bruno	23/04/2007	EC-CO	MEDEL	Implant d'oreille moyenne 2	Co-investigateur	01/2006	12/2007
61603	FRACHET	Bruno	23/04/2007	IP-AC	SOCIETE FRANCAISE D'ORL	EPP	aucune rémunération	01/2007	12/2007
61603	FRACHET	Bruno	23/04/2007	IP-CF	MXM - CLARION - MEDEL - COCHLEAR	Présentations régulières : congrès médicaux : Paris - USA - France - Autriche	aucune rémunération	01/2004	12/2007
61603	FRACHET	Bruno	23/04/2007	CF-AUD	COCHLEAR	Australie : visite d'entreprise		01/2005	12/2005
61603	FRACHET	Bruno	23/04/2007	CF-AUD	CLARION	Californie : visite d'entreprise		01/2006	12/2006
61603	FRACHET	Bruno	23/04/2007	IP-AUT	MXM	Brevet datant de 1987 (inventeur) : electrode vibrante		01/1987	12/2007
61603	FRACHET	Bruno	23/04/2007	VB	Réseau d'implantation COCHLEAIRE "IFIC"	Fonctionnement (ARH)		01/2004	12/2007
61603	FRACHET	Bruno	23/04/2007	VB	IFIC	Loyer : APHP		01/2005	
61603	FRACHET	Bruno	23/04/2007			Contrats MREWX2			
61603	FRACHET	Bruno	17/03/2004	IP-EC		Etude clinique AP-HP			
61603	FRACHET	Bruno	17/03/2004	IP-EC					
61603	FRACHET	Bruno	17/03/2004	IP-RE	ANVAR	Régulièrement			
61603	FRACHET	Bruno	17/03/2004	IP-CF		Président - Soutien Implants codleaire			
61603	FRACHET	Bruno	17/03/2004	IP-AUT	IFIC (Association)	Participation Groupe d'Etude sur Prothèse Auditive (GIRA) - Soutenu par Industriel			
61603	FRACHET	Bruno	17/03/2004	IP-AUT	GIRA	Président Groupe de Promotion de l'informatisation en ORL - Type SAS - Financement par tutelles de la discipline (Société savante)			
61603	FRACHET	Bruno	17/03/2004	IP-AUT	MIORL	Courrier adressé à Lionel BENAICHE			
61603	FRACHET	Bruno	03/09/2002	IP-CF	UCB	Courrier à Lionel BENAICHE			
61603	FRACHET	Bruno	03/09/2002	IP-CF	Groupe Entendre - distributeur audioprothèses	Participation au Congrès International ORL du 27 septembre au 4 octobre 2002 (Le Caire)			
61603	FRACHET	Bruno	03/09/2002	IP-CF	OTOLOGICS	Cours sur la surdité à Prague : du 20 au 22 septembre 2002			
61603	FRACHET	Bruno	16/07/2001	IP-CF		Journée Information sur la prothèse MET le 7 septembre 2002			
61603	FRACHET	Bruno	17/10/2000	IF	SYMPHONIX	Cours de dissection appliqué à une prothèse auditive implantable (prothèse Symphonix - SIEMENS) - Aucun bénéfice n'est réalisé - a fortiori, il n'y a aucun honoraire pour les en			
61603	FRACHET	Bruno	17/10/2000	IF	SIEMENS SICO	Actions			
61603	FRACHET	Bruno	17/10/2000	VB	SERVIER	Actions			
61603	FRACHET	Bruno	17/10/2000	VB	SCHERING-PLOUGH	Association			
61603	FRACHET	Bruno	17/10/2000	VB	PHONAK	Association			
61603	FRACHET	Bruno	17/10/2000	(Autre)		Participation à un groupe de recherche (GIRA) sur l'audition soutenu par firme industrielle Phonak			
61603	FRACHET	Bruno	17/10/2000	(Autre)		Secrétaire général du Syndicat des médecins ORL			
61603	FRACHET	Bruno	17/10/2000	(Autre)	BMS	Conseil en R & D			
61603	FRACHET	Bruno	17/10/2000	(Autre)	DANONE	Membre d'un jury de bourse du centre Evian pour 1 réunion annuelle (activité encore en cours)	rémunération personnelle	01/2000	
10187	FRICKER	Jacques	20/10/2005	LD-AR	L'OREAL	Etude multicentrique sur un complément alimentaire	coordinateur principal	10/2005	06/2006
10187	FRICKER	Jacques	20/10/2005	EC-INV			co-expert , le protocole n'aura finalement pas été mis en pratique	04/2003	09/2003
10187	FRICKER	Jacques	20/10/2005	EC-CO	ABBOTT	Mise sur pied d'un protocole d'étude sur la multidisciplinarité dans la prise en charge de l'obésité	rémunération personnelle	05/2005	
10187	FRICKER	Jacques	20/10/2005	RE-DE	ALTIUS PHARMA pour les laboratoires ABBOTT	SIBUTRAL : rapport pour la commission d'AMM	rémunération personnelle	01/2004	
10187	FRICKER	Jacques	20/10/2005	CF-INT	ARKOPHARMA	Phytothérapie et perte de poids - Paris- mon intervention : contrôle comportemental de la surcharge pondéra	rémunération personnelle	02/2004	
10187	FRICKER	Jacques	20/10/2005	CF-INT	PFIZER	les maladies cardio-vasculaires	rémunération personnelle	11/2005	
10187	FRICKER	Jacques	20/10/2005	CF-INT	Syndicat des producteurs de yaourt	Intérêt nutritionel des yaourts - Paris			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10187	FRICKER	Jacques	20/10/2005	CF-INT	NOVARTIS	EPU Obésité	rémunération personnelle	01/2005	
10187	FRICKER	Jacques	20/10/2005	CF-AUD	SANOFI	congrès Européen sur l'obésité - Athènes		06/2005	
10187	FRICKER	Jacques	20/10/2005	CF-AUD	ABBOTT	Congrès Européen sur l'obésité - Helsinski		06/2003	
10187	FRICKER	Jacques	20/10/2005	IP-AUT	ABBOTT	rédaction d'un éditorial concernant les brochures d'informations sur la nutrition destinée aux médecins - pas de nom de produit associé		10/2005	01/2006
10187	FRICKER	Jacques	30/01/2004	IP-AUT	ABBOTT	invitation au congrès Européen sur l'obésité, juin 2003, Helsinki - Finlande			
10187	FRICKER	Jacques	12/10/2002	IP-AC	ARKO PHARMA	Conseil sur un protocole de recherche			
10187	FRICKER	Jacques	12/10/2002	IP-AC	ARTENAY AGRO DEVELOPPEMENT	Conseils sur produits			
10187	FRICKER	Jacques	12/10/2002	IP-CF	JONAS	Colloque de nutrition , coordonnateur scientifique			
10187	FRICKER	Jacques	12/10/2002	IP-CF	CNAM	Conférences dans le cadre du PNNS			
10187	FRICKER	Jacques	12/10/2002	IP-CF	PROTEIKA SA	Colloque, conférence			
10187	FRICKER	Jacques	12/10/2002	IP-AUT	EVIAN	Jury du prix de recherche Evian			
10187	FRICKER	Jacques	12/10/2002	IP-AUT		Rédacteur occasionnel d'un bulletin scientifique			
10187	FRICKER	Jacques	12/10/2002	IP-CF	ABBOTT (2003)	Réflexion sur la création d'une brochure destinée à solliciter la prise en charge de l'obésité par le médecin traitant			
10187	FRICKER	Jacques	17/02/2000	IP-RE	SANOFI	Médicament anti-obésité			
10187	FRICKER	Jacques	17/02/2000	IP-CF	FOURNIER	Conférence grand public sur la nutrition (1999)			
10187	FRICKER	Jacques	17/02/2000	IP-AUT	EVIC	Coordonnateur scientifique de congrès médicaux (Jonas 1999-2000 et Antilla 1999)			
10187	FRICKER	Jacques	01/01/1999	IP-AC	1996 : Conseil auprès de l'Agence de Communication DDW à propos d'un médicament commercialisé par la société Roche				
10187	FRICKER	Jacques	01/01/1999	IP-AUT	KNOLL-France	Prise en charge des frais de transport + hébergement des congrès européens sur l'obésité en 1995, 96 et 97			
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Merck-clevenot				
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Théranol				
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Roche				
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Nutricia				
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Searle				
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Servier Lipha				
10187	FRICKER	Jacques	01/01/1998	IP-AUT	Knoll				
63543	FRIOCOURT	Patrick	30/11/2010	CF-AUD	AVENTIS	Congrès Francophone de Gériatrie		10/2010	10/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-AUD	LUNDBECK	Saint Père/ azilect-ebixa		10/2010	10/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-AUD	NOVARTIS	Collège Professionnel Gériatres		05/2010	05/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-INT	NOVARTIS	Réunion régionale (modérateur)	Rémunération personnelle	05/2010	05/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-AUD	ESAI	Formation chefs de Pole		04/2010	04/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-AUD	AVENTIS	états généraux FA		03/2010	03/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-AUD	ESAI	Board Régional		02/2010	02/2010
63543	FRIOCOURT	Patrick	30/11/2010	CF-INT	NOVARTIS	Nouvelles dimensions en gériatrie (NDEG)□□éthique en gériatrie	Rémunération personnelle	01/2010	01/2010
63543	FRIOCOURT	Patrick	13/12/2009	CF-AUD	LUNDBECK	Paris/symposium/Ebixa		03/2009	03/2009
63543	FRIOCOURT	Patrick	13/12/2009	CF-AUD	SERVIER	Paris/IAGG		07/2009	07/2009
63543	FRIOCOURT	Patrick	13/12/2009	CF-INT	NOVARTIS	Contres/HTA/Rasilez	Rémunération personnelle	09/2009	09/2009
63543	FRIOCOURT	Patrick	13/12/2009	CF-AUD	NOVARTIS	Nantes/Congrès Alzheimer/exelon		10/2009	10/2009
63543	FRIOCOURT	Patrick	13/12/2009	CF-AUD	ESAI	Bordeaux/Formation chef de Pole		11/2009	11/2009
63543	FRIOCOURT	Patrick	13/12/2009	CF-AUD	SANOFI	Paris/états généraux de la FA/dronedarone		12/2009	12/2009
63543	FRIOCOURT	Patrick	13/12/2009	IP-AC	ESAI	Table ronde/ebixa	Rémunération personnelle	06/2009	06/2009
63543	FRIOCOURT	Patrick	13/12/2009	IP-AC	SANOFI	table ronde/dronedarone	Rémunération personnelle	07/2009	07/2009
63543	FRIOCOURT	Patrick	13/12/2009	IP-AC	SANOFI	Table ronde/idrabiotaparinux	Rémunération personnelle	07/2009	07/2009
63543	FRIOCOURT	Patrick	31/03/2009	VB	JANSSEN	subvention	AMIB	07/2008	07/2008
63543	FRIOCOURT	Patrick	31/03/2009	VB	MENARINI	subvention	APMIB	01/2009	01/2009
63543	FRIOCOURT	Patrick	31/03/2009	CF-AUD	JANSSEN	Montpellier, 24 heures Alzheimer		11/2008	11/2008
63543	FRIOCOURT	Patrick	31/03/2009	CF-AUD	LUNDBECK	Paris		03/2009	03/2009
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	NOVARTIS	Paris. Nouvelles dimensions en gériatrie (NDEG), observation clinique, exelon	Rémunération personnelle	01/2009	01/2009
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	SANOFI	orléans. Plavix. Prescription médicamenteuse	Rémunération personnelle	04/2008	04/2008
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	IPSEN	Vichy	Rémunération personnelle	11/2007	11/2007
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	NOVARTIS	Deauville, Exelon, bonnespratiques prescription anticholinestérasiques	Rémunération personnelle	09/2007	09/2007
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	JANSSEN	Toulouse, 24 heures Alzheimer, Syncope et démence	Rémunération institution	10/2007	10/2007
63543	FRIOCOURT	Patrick	31/03/2009	EC-CO	BAXTER	Clinimix N9G15E	coinvestigateur	01/2009	09/2010
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	JANSSEN	Toulouse. 24 heures Alzheimer	Rémunération personnelle/institution	10/2007	10/2007
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	IPSEN	Vichy	Rémunération personnelle	11/2007	11/2007
63543	FRIOCOURT	Patrick	31/03/2009	CF-INT	CIPEG	BNP Kenzen	Rémunération personnelle	12/2007	12/2007
63543	FRIOCOURT	Patrick	16/10/2006	CF-AUD	SERVIER	La Baule		01/2006	
63543	FRIOCOURT	Patrick	16/10/2006	IP-AC	LEO	étude IRIS	Rémunération institution	01/2006	
63543	FRIOCOURT	Patrick	16/10/2006	CF-INT	MSD	Conférence	Rémunération personnelle	01/2005	11/2006
63543	FRIOCOURT	Patrick	13/06/2006	EC-INV	SANOFI	- Lovenox□□- enquête MI	membre comité	01/2004	12/2006
63543	FRIOCOURT	Patrick	13/06/2006	EC-CO	LEO	Innovax	co-investigateur	01/2005	
63543	FRIOCOURT	Patrick	13/06/2006	CF-INT	MSD	2 soirées COZAAR	rémunération personnelle	01/2005	01/2005
63543	FRIOCOURT	Patrick	13/06/2006	CF-INT	MSD	2 soirées COZAAR	rémunération personnelle	01/2006	01/2006
63543	FRIOCOURT	Patrick	13/06/2006	CF-AUD	JANSSEN	Springfield alzheimer Genève		01/2006	01/2006
63543	FRIOCOURT	Patrick	13/06/2006	CF-AUD	SERVIER	Journées européenne cardiologie Paris	Rémunération personnelle		
63543	FRIOCOURT	Patrick	12/06/2005	IP-AC	AVENTIS	Lovenox - comité scientifique d'une étude (2004)			
63543	FRIOCOURT	Patrick	12/06/2005	(Autre)	SFGG / SFC	Groupe de travail de la SFGG (société française de gériatrie et gérontologie) et SFC (société française de c			
10188	FUNCK-BRENTANO	Christian	01/01/1999	IF	RHONE POULENC RORER				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IF	HYBRIDON				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	SERVIER				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	ROUSSEL				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	SYNTHELABO				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	KNOLL				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	BAYER				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	MERCK LIPHA SANTE				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-EC	DEBIOPHARM				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-RE	ROCHE				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-RE	MERCK LIPHA SANTE				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-AC	SYNTHELABO				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-AC	SERVIER				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-CF	MERCK SHARP DHOME				
10188	FUNCK-BRENTANO	Christian	01/01/1999	IP-AUT	PROCTER & GAMBLE				
10188	FUNCK-BRENTANO	Christian	01/01/1999	VB	BAYER, SERVIER, BEAUFOUR, DEBIOPHARM, NOVARTIS	Essais cliniques réalisés à l'Unité de pharmacologie clinique de l'Hôpital St-Antoine			
10188	FUNCK-BRENTANO	Christian	01/01/1999	VB	SERVIER				
10188	FUNCK-BRENTANO	Christian	01/01/1999	VB	BEAUFOUR				
10188	FUNCK-BRENTANO	Christian	01/01/1999	VB	DEBIOPHARM				
10188	FUNCK-BRENTANO	Christian	01/01/1999	VB	NOVARTIS				
10188	FUNCK-BRENTANO	Christian	31/01/1998	IF	RHONE POULENC RORER				
10188	FUNCK-BRENTANO	Christian	31/01/1998	IF	HYBRIDON				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	RDPC Europe				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	PARKE DAVIS				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	ROUSSEL				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	BIOPHARMA				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	BAYER				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	MERCK-CLEVENOT				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	SYNTHELABO				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	DEBIOPHARM				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	SERVIER				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	PIERRE FABRE MEDICAMENT				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	ROCHE				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	SANOFI				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	ASTRA				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	PROCTER GAMBLE				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	RHONE POULENC RORER				
10188	FUNCK-BRENTANO	Christian	01/01/1998	IP-AUT	KNOLL				
10188	FUNCK-BRENTANO	Christian	01/01/1998	VB	ROUSSEL	Pour l'association NEB			
10188	FUNCK-BRENTANO	Christian	01/01/1998	VB	SYNTHELABO	Pour l'association NEB			
10188	FUNCK-BRENTANO	Christian	01/01/1998	VB	DEBIOPHARM	Pour l'association NEB			
10188	FUNCK-BRENTANO	Christian	01/01/1998	VB	ROCHE	Pour l'association NEB			
10188	FUNCK-BRENTANO	Christian	01/01/1998	VB	PFIZER	Pour l'association NEB			
10188	FUNCK-BRENTANO	Christian	01/01/1998	VB	SERVIER	Pour l'association NEB			
63922	GAILLEDREAU	Joël	27/11/2005	EC-INV	SANOFI-AVENTIS	Etude randomisée en double aveugle Saredutant Vs paroxetin vs placebo	Investigateur coordonnateur	08/2004	
63922	GAILLEDREAU	Joël	27/11/2005	CF-INT	JANSSEN	Premiere rencontre de la psychiatrie libérale de l'Ouest	Rémunération personnelle	10/2003	10/2003
63922	GAILLEDREAU	Joël	27/11/2005	VB	GSK	Subvention GICIPI		10/2005	10/2005
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	PFIZER	RCT (Essai clinique randomisé) Pregabaline vs Venlafaxine vs placebo	Co-investigateur	06/2005	
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	PIERRE FABRE	RCT (essai clinique randomisé) FO 2625 vs placebo	Co-investigateur	10/2005	
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	BOEHRINGER	RCT (Essai clinique randomisé) Duloxetine vs placebo	Co-investigateur	05/2005	
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	SANOFI	RCT(Essai clinique randomisé) Saredutant vs placebo vs Paroxetine	Co-investigateur	02/2005	
63922	GAILLEDREAU	Joël	27/11/2005	VB	PFIZER	Subvention GICIPI		11/2005	11/2005
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	GSK	RCT (Essai clinique randomisé) AK130939 vs placebo	Co-investigateur	04/2004	02/2005
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	LUNDBECK	RCT (Essai clinique randomisé) Escitalopram vs placebo	Co-investigateur	03/2003	02/2005
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	LUNDBECK	RCT (Essai clinique randomisé) Escitalopram vs Citalopram	Co-investigateur	02/2005	04/2005
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	LUNDBECK	RCT (Essai clinique randomisé) Escitalopram vs placebo	Co-investigateur	11/2003	10/2004
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	SANOFI	RCT (Essai clinique randomisé) vs placebo / EDM	Co-investigateur	11/2003	03/2004
63922	GAILLEDREAU	Joël	27/11/2005	EC-CO	SERVIER	Agomelatine vs Venlafaxine	Co-investigateur	08/2003	12/2003
61785	GALINOWSKI	André	07/09/2007	CF-AUD	SERVIER	congrès de l'Encéphale (Paris) 2007			
61785	GALINOWSKI	André	07/09/2007	EC-CO	BIOPROJET	BP2.649	co-nvestigateur	01/2007	
61785	GALINOWSKI	André	07/09/2007	EC-CO	BMS	protocole clozapine aripiprarole	co-investigateur	01/2006	
61785	GALINOWSKI	André	16/01/2006	EC-CO	LILLY	Duloxetine	investigateur principal d'une étude multicentrique (dans notre centre)	01/2004	12/2005
61785	GALINOWSKI	André	16/01/2006	EC-CO	SERVIER	CL2.33138-006 FRA	Co-investigateur	01/2004	
61785	GALINOWSKI	André	16/01/2006	EC-CO	BMS	Aripiprozole - 2003-2004	Co-investigateur	01/2003	12/2004
61785	GALINOWSKI	André	16/01/2006	EC-CO	TOPAZE	Evaluation des pratiques-Enquêtes	Clinicien participant	01/2003	12/2003
61785	GALINOWSKI	André	16/01/2006	EC-CO	PFIZER	Observatoire troubles cognitifs sujet agé	Clinicien investigateur	01/2004	12/2004
61785	GALINOWSKI	André	16/01/2006	IP-RE	NOVARTIS	Clozapine dans maladies de parkinson	Rémunération aucune	01/2001	12/2001
61785	GALINOWSKI	André	16/01/2006	CF-INT	LUNDBECK	Escitalopram APA (Atlanta) Voyage-congrès-hébergement		01/2005	12/2005
61785	GALINOWSKI	André	16/01/2006	CF-INT	SANOFI	EPU sur Bipolarité (n°2)		01/2005	12/2005
61785	GALINOWSKI	André	16/01/2006	CF-AUD	LILLY	Congrès de l'encéphalé (Paris)		01/2006	12/2006
61785	GALINOWSKI	André	16/01/2006	CF-AUD	LUNDBECK	Congrès de l'Enceyglobe (Paris) - 2005			
61785	GALINOWSKI	André	14/12/2005	EC-INV	LILLY	Duluxetine	Investigateur principal	01/2005	12/2005
61785	GALINOWSKI	André	14/12/2005	EC-CO	SERVIER	CL2-33138-006-FRA	Co-investigateur	01/2004	
61785	GALINOWSKI	André	14/12/2005	EC-CO	BMS	Aripiprazole	Co-investigateur	01/2003	12/2005
61785	GALINOWSKI	André	14/12/2005	CF-INT	LUNDBECK	Invitation au congrès American Psychiatric Association - Atlanta Mai 2005 : Escitalopram	Acune rémunération	05/2005	
65869	GAROT	Jérôme	07/07/2010	EC-INV	SERVIER	Coordonnateur national "IVABRADINE"	Coordonnateur national	06/2008	09/2010
65869	GAROT	Jérôme	07/07/2010	IP-AUT	MSD	Atelier d'IRM cardiaque à l'hôpital J. Cartier - pas d'intervention sur un produit pharmacologique		03/2009	
64654	GAROT	Philippe	30/05/2007	CF-AUD	CORDIS	ACCardiology - mars 2007 - USA N.O		03/2007	03/2007
64654	GAROT	Philippe	30/05/2007	CF-AUD	BOSTON SC	TCT ASIA - Séoul (Korea) - avril 2006		04/2006	04/2006
64654	GAROT	Philippe	30/05/2007	CF-AUD	ABBOTT	CTO Club Japan Toyohashi		06/2006	06/2006
63062	GAUTIER	Sophie	23/09/2010	PAR	SERVIER	Service affaires réglementaires : sans produit en charge	belle-sœur	01/2007	
63062	GAUTIER	Sophie	04/05/2010	PAR	SERVIER	Service affaires réglementaires. Information sur la mise en notoriété du dossier d'AMM en Suède. GB. Pas de produits suivis		01/2007	
63062	GAUTIER	Sophie	23/03/2009	PAR	SERVIER	chef de projet affaires pharmaceutiques	belle sioeur (soeur du conjoint)	01/2007	
63062	GAUTIER	Sophie	07/02/2008	Néant					
63062	GAUTIER	Sophie	05/01/2005	Néant					
60151	GAYOT	Anne	24/06/2010	CF-INT	ANDRE REY	Développement pharmaceutique Process Analytical Technology	Rémunération personnelle	07/2008	07/2008
60151	GAYOT	Anne	24/06/2010	CF-AUD	THERAMEX	Académie Theramex		05/2009	05/2009
60151	GAYOT	Anne	24/06/2010	VB	ASTRA, MACO PHARMA, MERCK, TRADIPHAR, SERVIER, BOIRON, GSK, BMS	Taxe d'apprentissage	Bénéficiaire : Laboratoire de Pharmacotechnie Industrielle		
60151	GAYOT	Anne	17/06/2009	CF-INT	INTERNATIONAL DRUG DEVELOPMENT	Développement pharmaceutique validation du procédé	aucune rémunération	05/2007	05/2007
60151	GAYOT	Anne	17/06/2009	CF-INT	ANDRE REY	Développement pharmaceutique Process Analytical Technology	rémunération personnelle	07/2008	07/2008

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60151 GAYOT		Anne	17/06/2009	CF-AUD	THERAMEX	Académie Theramex		05/2009	05/2009
60151 GAYOT		Anne	17/06/2009	VB	ASTRA-MACO PHARMA-MERCK-TRADIPHAR-SERVIER-BOIRON	Taxe d'apprentissage	Laboratoire de pharmacotechnie industrielle		
60151 GAYOT		Anne	17/06/2009	VB	GSK - BMS	Taxe d'apprentissage	Laboratoire de pharmacotechnie industrielle		
60151 GAYOT		Anne	17/06/2009	VB	GENFIT	Etudes de caractérisation des matières premieres	Laboratoire de pharmacotechnie industrielle	01/2008	12/2008
60151 GAYOT		Anne	25/07/2008	CF-INT	INTERNATIONAL DRUG DEVELOPMENT	Développement pharmaceutique - validation du procédé	Aucune rémunération	05/2007	05/2007
60151 GAYOT		Anne	25/07/2008	CF-INT	ANDRE REY	Développement pharmaceutique - Process analytical technology	Rémunération personnelle	07/2008	07/2008
60151 GAYOT		Anne	25/07/2008	CF-AUD	THERAMEX	Académie Théramex		05/2008	05/2008
60151 GAYOT		Anne	25/07/2008	VB	ASTRA, MACO PHAMA, MERCK, TRADIPHAR, SERVIER, BOIRON, GSK, BMS	Taxe d'apprentissage	Laboratoire de pharmacotechnie		
60151 GAYOT		Anne	25/07/2008	VB	GENFIT	Etudes de caractérisation des matières premières			
60151 GAYOT		Anne	27/09/2007	CF-INT	INTERNATIONAL DRUG DEVELOPMENT	développement pharmaceutique - validation du procédé	aucune rémunération	05/2007	05/2007
60151 GAYOT		Anne	27/09/2007	CF-INT	ANDRE REY	Développement pharmaceutique - process analytical technology	Rémunération personnelle	07/2007	07/2007
60151 GAYOT		Anne	27/09/2007	CF-AUD	THERAMEX	Académie Theramex		05/2007	05/2007
60151 GAYOT		Anne	27/09/2007	VB	ASTRA, MACO PHARMA, MERCK, TRADIPHAR, SERVIER, BOIRON, GSK, BMS	Taxe d'apprentissage	Laboratoire pharmaceutique		
60151 GAYOT		Anne	27/09/2007	VB	GENFIT	Etude de caractérisation des matières premières	Laboratoire pharmaceutique		
60151 GAYOT		Anne	10/06/2006	RE-DE	MACO PHARMA	- Solutions de chlorure de sodium - Solutions de glucose - Eau pour préparations sinjectables	rémunération personnelle	01/2004	12/2006
60151 GAYOT		Anne	10/06/2006	RE-DE	BOIRON	Gélules de charbon végétal	rémunération personnelle	01/2004	12/2004
60151 GAYOT		Anne	10/06/2006	IP-AC	GENFIT	Développement de gélules de GFT 14	rémunération personnelle	01/2006	12/2006
60151 GAYOT		Anne	10/06/2006	CF-INT	International Drug Development	développement pharmaceutique validation du procédé	aucune rémunération	03/2005	03/2005
60151 GAYOT		Anne	10/06/2006	CF-INT	ANDRE REY	Développement pharmaceutique process analytical technology	rémunération personnelle	07/2005	07/2006
60151 GAYOT		Anne	10/06/2006	CF-INT	CEFIRA	Transposition industrielle	rémunération personnelle	06/2006	06/2006
60151 GAYOT		Anne	10/06/2006	CF-AUD	THERAMEX	Académie Theramex		05/2006	05/2006
60151 GAYOT		Anne	10/06/2006	IP-AUT	MACO PHARMA	Développement de comprimés de bleu de méthylène		01/2005	
60151 GAYOT		Anne	10/06/2006	VB	ASTRA, MACO PHARMA, MERCK, TRADIPHAR, SERVIER	Taxe d'apprentissage	laboratoire de pharmcacotechnie		
60151 GAYOT		Anne	15/03/2005	IP-AC	GENFIT	2003-2005			
60151 GAYOT		Anne	15/03/2005	IP-RE	MACO PHARMA	2004-2005			
60151 GAYOT		Anne	15/03/2005	IP-RE	BOIRON	2002			
60151 GAYOT		Anne	15/03/2005	IP-CF	IDD	Conférence, en qualité d'intervenant			
60151 GAYOT		Anne	15/03/2005	IP-CF	ANDRE REY	Conférence, en qualité d'intervenant, développement et validation			
60151 GAYOT		Anne	15/12/2003	VB	MACO PHARMA	Faculté de Pharmacie / labo de Pharmacotechnie			
60151 GAYOT		Anne	15/12/2003	VB	MERCK SANTE	Faculté de Pharmacie / labo de Pharmacotechnie			
60151 GAYOT		Anne	15/12/2003	VB	ABOTT	Faculté de Pharmacie / labo de Pharmacotechnie			
60151 GAYOT		Anne	15/12/2003	IP-RE	BOIRON	Dossier pharmaceutique			
60151 GAYOT		Anne	20/07/2002	IP-RE	BOIRON	Spécialités de comprimés			
60151 GAYOT		Anne	20/07/2002	IP-RE	SUBSTIPHARM	Poudre en sachet de PEG			
60151 GAYOT		Anne	20/07/2002	IP-CF	CEFIRA	Validation du procédé			
60151 GAYOT		Anne	20/07/2002	VB	MACO-PHARMA	Faculté de Pharmacie - Laboratoire de pharmacotechnie industrielle - Lille			
60151 GAYOT		Anne	20/07/2002	VB	ABBOTT	Faculté de Pharmacie			
60151 GAYOT		Anne	15/05/2000	IP-RE	BOIRON				
60151 GAYOT		Anne	15/05/2000	IP-CF	IFIP				
60151 GAYOT		Anne	15/05/2000	IP-CF	H.R. Limited (Londres)				
60151 GAYOT		Anne	15/05/2000	IP-CF	CEFIRA (Grasse)				
60151 GAYOT		Anne	15/05/2000	VB	KNOLL Valenciennes	Développement galénique			
64182 GIBAULT		Thierry	08/07/2010	CF-AUD	NOVARTIS	ALFEDIAM		01/2009	12/2009
64182 GIBAULT		Thierry	08/07/2010	CF-AUD	NOVARTIS	EASD		01/2009	12/2009
64182 GIBAULT		Thierry	31/07/2009	Néant					
64182 GIBAULT		Thierry	23/06/2008	CF-AUD	MSD	ALFEDIAM 2008		01/2008	12/2008
64182 GIBAULT		Thierry	23/06/2008	CF-AUD	MSD	EASD 2007		01/2007	12/2007
64182 GIBAULT		Thierry	11/06/2007	CF-AUD	SERVIER	Congrès de la SFE / ALFEDIAM		03/2007	03/2007
64182 GIBAULT		Thierry	19/06/2006	CF-AUD	SERVIER	congrès de l'ALFEDIAM - Paris		02/2006	
64182 GIBAULT		Thierry	19/06/2006	CF-AUD	SERVIER	CONGRES DE L'ALFEDIAM (PARIS)		02/2006	
62521 GIL		Sophie	26/03/2009	Néant					
62521 GIL		Sophie	12/06/2006	EC-INV	ABBOTT	Passage transplacentaire du Kaletra	Expérimentateur	09/2003	09/2006
62521 GIL		Sophie	12/06/2006	EC-INV	SERVIER	Mise en place d'un modèle Murin (Etudes toxicologiques)	Co-responsable de la thèse	05/2005	06/2008
62521 GIL		Sophie	12/06/2006	EC-INV	ROCHE	Passage transplacentaire du Fuzeon	Expérimentateur	06/2006	06/2007
62521 GIL		Sophie	12/06/2006	RE-DE	GT Grossesse - AFSSAPS	GTGP n° 17 du 10/01/02	Rémunération personnelle	01/2002	01/2002
55671 GILLET		Pierre	08/02/2010	CF-AUD	AERES	Expertise laboratoire LISBP - Toulouse		12/2009	12/2009
55671 GILLET		Pierre	08/02/2010	IP-AUT	TGI	Expertises médico-judiciaire en tant que sapiteur pour le TGI et la CRCI		12/2009	02/2010
55671 GILLET		Pierre	08/02/2010	CF-AUD	AERES	EXPERTISE LABORATOIRE LISBP TOULOUSE		12/2009	
55671 GILLET		Pierre	08/02/2010	IP-AUT	TGI	MEDICO- JUDICIAIRE, EXPERTISES EN TANT QUE SAPITEUR POUR LE TGI ET LA CRCI		12/2009	02/2010
55671 GILLET		Pierre	23/12/2008	CF-INT	MG FORM	EPU Grossesse et médicaments	Rémunération personnelle		
55671 GILLET		Pierre	23/12/2008	EC-CO	GENEVRIER	collaboration scientifique		01/2007	12/2008
55671 GILLET		Pierre	23/12/2008	EC-CO	DANONE	collaboration scientifique	expertise	01/2007	12/2009
55671 GILLET		Pierre	23/12/2008	EC-CO	BIOIBERICA	collaboration scientifique	expertise	01/2008	12/2009
55671 GILLET		Pierre	25/02/2008	CF-INT	AMPPU	EPU Interactions médicamenteuses	Rémunération personnelle		
55671 GILLET		Pierre	25/02/2008	CF-INT	AMPPU	EPU Interactions médicamenteuses	Rémunération personnelle		
55671 GILLET		Pierre	19/01/2007	CF-INT	BIOIBERICA	Barcelone : chondroprotection et acide hyaluronique	Aucune rémunération	01/2006	
55671 GILLET		Pierre	19/01/2007	EC-CO	FONDATION AVENIR	Mécanotransduction chondrocytaire	collaborateur	01/2005	01/2007
55671 GILLET		Pierre	19/01/2007	EC-CO	ANR JEUNE CHERCHEUR A WATRIN	Ingénierie du cartilage et cellules souches mésenchymateuses	collaborateur	01/2006	
55671 GILLET		Pierre	19/01/2007	EC-CO	ANR BLANCHE JC VOEGEL	Biopolymères multicouches et chondrogénèse	collaborateur	01/2007	
55671 GILLET		Pierre	19/01/2007	IP-AC	DANONE	Expertise données probiotiques	Rémunération institution		
55671 GILLET		Pierre	19/01/2007	IP-AC	PHARMASCIENCE	Expertise données précliniques	Rémunération institution	01/2006	
55671 GILLET		Pierre	12/10/2005	LD		Comité de Pilotage RATIO (actuel)			
55671 GILLET		Pierre	12/10/2005	EC-INV	GIP AVENTIS HMR	Contrat de recherches sur apoptose et arthrose (Contrat Université Industrie)	aucune rétribution directe		
55671 GILLET		Pierre	12/10/2005	EC-INV	IBSA	Chondrosulf et chondroprotection (Contrat Université Industrie)	aucune rétribution directe		
55671 GILLET		Pierre	12/10/2005	EC-CO	THERAPLIX (AVENTIS)	propriétés antalgiques centrales du Paracétamol (contrat université industrie)		01/2003	12/2003
55671 GILLET		Pierre	12/10/2005	CF-INT	IBSA	Congrès Européen de Rhumatologie / Lisbonne (participation symposium)		01/2004	12/2004

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
55671	GILLET	Pierre	12/10/2005	CF-INT	PFIZER	Congrès Américain de Rhumatologie (Financement PFIZER)		01/2005	12/2005
55671	GILLET	Pierre	12/10/2005	CF-AUD	MSD, PFIZER	Interventions ponctuelles dans le cadre d'EPU régionaux sur les AINS			
55671	GILLET	Pierre	12/10/2005	VB	CNRS	Pour le Laboratoire Faculté			
55671	GILLET	Pierre	12/10/2005	VB	MINISTERE DE L'EDUCATION NATIONALE				
55671	GILLET	Pierre	12/10/2005	VB		PHRC et Recherche Clinique Laboratoire Faculté (UMR) : - IBSA (projet en cours, IRM et cartilage) - Fondat	Financement <15% du budget du service		
55671	GILLET	Pierre	12/10/2005	IP-AUT	SOCIETE FRANCAISE DE PHARMACOLOGIE	Membre			
55671	GILLET	Pierre	12/10/2005	IP-AUT	SOCIETE FRANCAISE DE RHUMATOLOGIE	Membre			
55671	GILLET	Pierre	12/10/2005	CF-AUD	AVENTIS	EPU pour la Faculté de Médecine de Nancy (semaine médicale de Lorraine. Participation d'AVENTIS)			
55671	GILLET	Pierre	12/10/2005	VB	CNRS		pour le laboartoire de la faculté - ministère de l'éducation -IBSA (projet en cours, IRM et cartilage) -Fondation Avenir - AMGEN		
55671	GILLET	Pierre	12/10/2005	VB	PHRCET RECHERCHE CLINIQUE - LABORATOIRE FACULTé (UMR)				
55671	GILLET	Pierre	12/10/2005	(Autre)		Membre de la Société Française de Pharmacologie			
55671	GILLET	Pierre	12/10/2005	(Autre)		Membre de la Société Française de Rhumatologie			
55671	GILLET	Pierre	01/03/2005	LD		Comité de Pilotage RATIO (actuel)			
55671	GILLET	Pierre	01/03/2005	EC-INV	GIP AVENTIS HMR	Contrat de recherches sur apoptose et arthrose (contrat université industrie)	aucune rétribution directe - investigateur principal		
55671	GILLET	Pierre	01/03/2005	IP-EC	IBSA	Chondrosulf et chondroprotection (contrat université industrie)			
55671	GILLET	Pierre	01/03/2005	IP-RE		2003 Théraplix, propriétés antalgiques centrales du Paracétamol (contrat université industrie)			
55671	GILLET	Pierre	01/03/2005	IP-CF		Congrès Européen de Rhumatologie, Lisbonne 2004 (ISBA : participation symposium), en qualité d'interven			
55671	GILLET	Pierre	01/03/2005	IP-CF		Interventions ponctuelles dans le cadre d'EPU régionaux sur les AINS (MSD et Pfizer), DDEPU pour la Facu			
55671	GILLET	Pierre	01/03/2005	VB	CNRS	Pour le Laboratoire Faculté			
55671	GILLET	Pierre	01/03/2005	VB	MINISTERE DE L'EDUCATION NATIONALE				
55671	GILLET	Pierre	01/03/2005	IP-AUT	SOCIETE FRANCAISE DE PHARMACOLOGIE	Membre			
55671	GILLET	Pierre	01/03/2005	IP-AUT	SOCIETE FRANCAISE DE RHUMATOLOGIE	Membre			
55671	GILLET	Pierre	13/03/2004	IP-CF	MERCK SHARP DOHME	EPU AINS			
55671	GILLET	Pierre	13/03/2004	VB	AVENTIS	Univ Nancy I - CNRS			
55671	GILLET	Pierre	13/03/2004	VB	RODHIA	Univ Nancy I			
55671	GILLET	Pierre	13/03/2004	VB	THERAPLIX	Univ Nancy I			
55671	GILLET	Pierre	13/03/2004	VB	PFIZER - PHARMACIA	CHU Nancy - Assoc. Chef service			
55671	GILLET	Pierre	13/03/2004	VB	COGITOBIO	Univ Nancy I			
55671	GILLET	Pierre	13/03/2004	IP-CF	MSD	EPU AINS			
55671	GILLET	Pierre	13/03/2004	VB	AVENTIS	Univ Nancy I - CNRS			
55671	GILLET	Pierre	13/03/2004	VB	RODHIA	Univ. Nancy I			
55671	GILLET	Pierre	13/03/2004	VB	THERAPLIX	Univ. Nancy I			
55671	GILLET	Pierre	13/03/2004	VB	PFIZER - PHARMACIA	CHU Nancy - Assoc. Chef Service			
55671	GILLET	Pierre	13/03/2004	VB	COGITOBIO	Univ. Nancy I			
55671	GILLET	Pierre	31/01/2001	IP-AC	ROCHE	Tenaxicam injectable			
55671	GILLET	Pierre	31/01/2001	IP-CF	AVENTIS	EPU Leflunomide			
55671	GILLET	Pierre	31/01/2001	IP-CF	BIOCODEX	EPU inhibiteurs COX2			
55671	GILLET	Pierre	31/01/2001	IP-CF	ROCHE	Invitation congrès Rhumato USA			
55671	GILLET	Pierre	31/01/2001	IP-CF	AVENTIS	Invitation congrès Paris Rhumato			
55671	GILLET	Pierre	31/01/2001	VB	THERAMEX	Université Nancy I			
55671	GILLET	Pierre	31/01/2001	VB	RHODIA	Université Nancy I			
55671	GILLET	Pierre	31/01/2001	VB	GUERBET	Université Nancy I			
55671	GILLET	Pierre	31/01/2001	VB	AVENTIS - HMR (GIP)	CNRS			
55671	GILLET	Pierre	31/01/2001	(Autre)		Participation ponctuelle à des jurys de concours - Médecin de PMI, de la fonction territoriale...			
55671	GILLET	Pierre	10/03/2000	VB	SEARLE, HOESCHT MARION ROUSSEL (AVENTIS), GUERBET	Année 2000 : coresponsable scientifique des contrats Laboratoire de recherche (Université)/Industrie			
55671	GILLET	Pierre	30/09/1999	VB	SERVIER / SEARLE	Université Nancy 1			
55671	GILLET	Pierre	30/09/1999	VB	BELLON/BOEHRINGER	Université Nancy 1			
55671	GILLET	Pierre	30/09/1999	VB	GUERBET	Université Nancy 1			
55671	GILLET	Pierre	30/09/1999	VB	HOECHST-MARION-ROUSSEL	CNRS			
55671	GILLET	Pierre	30/09/1999	VB	ROCHE NICOLAS	Université Nancy 1			
62417	GILLET	Claudine							
10194	GINESTET	Daniel	11/10/2002	IP-AC	LILLY	Conseil et rapport (ti-Zyprexa"), juin 2002			
10194	GINESTET	Daniel	11/10/2002	IP-CF	LILLY	Présidence congrès sur schizophrénie, janvier 2002			
10194	GINESTET	Daniel	18/02/2002	IP-CF	LILLY	Présidence prévue pour Symposium Schizophénie - 23/03/2002			
10194	GINESTET	Daniel	18/02/2002	IP-AUT	LUNDBECK	Membre du jury "Psychose", bourse attribuée par le Laboratoire			
10194	GINESTET	Daniel	07/07/2000	IP-CF	LILLY	Présidence d'un atelier lors du symposium sur la schizophrénie - Paris, Janvier 2000			
10194	GINESTET	Daniel	01/01/1999	IP-RE	Lilly : Prozac (Prévention des récidives) 1996				
10194	GINESTET	Daniel	01/01/1999	IP-RE	Servier : Stablon LP* - 1996				
10194	GINESTET	Daniel	01/01/1999	IP-AC	Lilly : Lettre de la Schizophrénie (comité de rédaction depuis 1995)				
10194	GINESTET	Daniel	01/01/1999	IP-AC	Lundbeck : Bourses Recherche (conseil scientifique depuis 1990)				
10194	GINESTET	Daniel	01/01/1999	IP-CF	Présidence Congrès (nov. 96) : Lilly				
10194	GINESTET	Daniel	01/01/1999	IP-CF	mars 97 : Sandoz				
10194	GINESTET	Daniel	01/01/1998	IP-AUT	Servier				
10194	GINESTET	Daniel	01/01/1998	IP-AUT	Lilly				
10194	GINESTET	Daniel	01/01/1998	IP-AUT	Lundbeck				
10194	GINESTET	Daniel	01/01/1998	IP-AUT	Pfizer		CDI	01/1985	
64566	GINOT	Yves-Michel	24/03/2009	LD-ODE	TECHNOLOGIE SERVIER	salarié	CDI	01/1985	
64566	GINOT	Yves-Michel	12/09/2006	LD-ODE	TECHNOLOGIE SERVIER	salarié	Rémunération personnelle	01/2008	12/2009
60259	GIRERD	Xavier	04/11/2009	IP-AC	DAIICHI SANKYO	SEVIKAR	Rémunération personnelle	05/2009	10/2009
60259	GIRERD	Xavier	04/11/2009	CF-INT	CAISSE NATIONALE ASSURANCE MALADIE IDF	Médecins conseils de la CNAM	Rémunération personnelle	01/2007	12/2009
60259	GIRERD	Xavier	04/11/2009	CF-INT	BMS	COAPROVEL	Rémunération personnelle	01/2008	12/2009
60259	GIRERD	Xavier	04/11/2009	CF-INT	DAIICHI SANKYO	SEVIKAR	Rémunération personnelle	01/2007	12/2009
60259	GIRERD	Xavier	04/11/2009	CF-INT	IPSEN	Exforge			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60259	GIRERD	Xavier	04/11/2009	CF-INT	NOVARTIS	Rasilez, Exforge	Rémunération personnelle	01/2007	12/2009
60259	GIRERD	Xavier	04/11/2009	IP-AC	NOVARTIS	Rasilez, Exforge	Rémunération personnelle	01/2008	12/2009
60259	GIRERD	Xavier	20/04/2005	IP-AC	ABBOT	Membre d'un board national, Trandoplapril	Aucune rémunération		09/2006
60259	GIRERD	Xavier	20/04/2005	IP-AC	ASTRA ZENECA	Membre d'un board national, Rosuvastatine	Aucune rémunération		11/2007
60259	GIRERD	Xavier	20/04/2005	IP-AC	BMS	Irbesartan, Membre d'un board national	Aucune rémunération		03/2007
60259	GIRERD	Xavier	20/04/2005	IP-AC	BOERINGHER	Membre d'un board national? Telmisartan	Aucune rémunération		12/2008
60259	GIRERD	Xavier	20/04/2005	IP-AC	FOURNIER	Fénofibrate	Aucune rémunération		10/2006
60259	GIRERD	Xavier	20/04/2005	IP-AC	PFIZER	Amlodipine, Caduet (international)	Aucune rémunération		12/2007
60259	GIRERD	Xavier	20/04/2005	IP-AC	SANOFI AVENTIS	Irbesartan	Aucune rémunération		03/2007
60259	GIRERD	Xavier	20/04/2005	IP-AC	MENARINI	Zofénopril	Aucune rémunération		10/2007
60259	GIRERD	Xavier	20/04/2005	IP-AC	NOVARTIS	Valsartan	Aucune rémunération		01/2008
60259	GIRERD	Xavier	20/04/2005	IP-EC	ALTANA	Investigateur principal			01/2007
60259	GIRERD	Xavier	20/04/2005	IP-EC	BOEHRINGER	Conférences en France 2004-2005			12/2005
60259	GIRERD	Xavier	20/04/2005	IP-EC	GSK	Investigateur principal observatoire clinique			01/2006
60259	GIRERD	Xavier	20/04/2005	IP-EC	IPSEN BEAUFOUR	Investigateur principal observatoire clinique			09/2007
60259	GIRERD	Xavier	20/04/2005	IP-EC	SERVIER	Investigateur principal Périndopril et Rilménidine			04/2007
60259	GIRERD	Xavier	20/04/2005	IP-EC	MENARINI	Investigateur principal olmesartan			08/2007
60259	GIRERD	Xavier	20/04/2005	IP-EC	NOVARTIS	Investigateur principal aliskirene			05/2007
60259	GIRERD	Xavier	20/04/2005	IP-EC	TAKEDA	Investigateur principal d'une étude clinique en 2003			12/2005
60259	GIRERD	Xavier	20/04/2005	IP-CF	ABBOTT	Conférences en France en 2004, en qualité d'intervenant			12/2005
60259	GIRERD	Xavier	20/04/2005	IP-CF	ASTRA ZENECA	Conférences en France en 2004, en qualité d'intervenant			12/2005
60259	GIRERD	Xavier	20/04/2005	IP-CF	BMS	Conférences en France en 2004; en qualité d'intervenant			12/2005
60259	GIRERD	Xavier	20/04/2005	IP-CF	PFIZER	Conférences en France et en Europeen 2004-2005, en qualité d'intervenant			12/2008
60259	GIRERD	Xavier	20/04/2005	IP-CF	NOVARTIS	Conférences en France et en Europe en 2004-2005, en qualité d'intervenant			12/2008
60259	GIRERD	Xavier	20/04/2005	IP-CF	TAKEDA	Conférences en Europe en 2004			12/2008
60259	GIRERD	Xavier	01/10/2003	LD	PFIZER	Conseil (Amlodipine) pour 2002 et 2003			
60259	GIRERD	Xavier	01/10/2003	IP-EC	NOVARTIS	Investigateur			
60259	GIRERD	Xavier	01/10/2003	IP-AC	SANOFI SYNTHELABO	Membre d'un board			
60259	GIRERD	Xavier	01/10/2003	IP-AC	BRISTOL MYERS SQUIBB	Membre d'un board			
60259	GIRERD	Xavier	01/10/2003	IP-AC	ASTRA ZENECA	Membre d'un board			
60259	GIRERD	Xavier	01/10/2003	IP-CF	PFIZER	HTA (2003)			
60259	GIRERD	Xavier	01/10/2003	IP-CF	NOVARTIS	HTA (2003)			
60259	GIRERD	Xavier	01/10/2003	IP-CF	BAYER	HTA (2003)			
60259	GIRERD	Xavier	01/10/2003	IP-CF	TAKEDA	HTA (2003)			
60259	GIRERD	Xavier	01/10/2003	IP-CF	BEAUFOUR	HTA (2003)			
60259	GIRERD	Xavier	10/04/2003	LD	PFIZER	Conseil scientifique (2002,2003)			
60259	GIRERD	Xavier	10/04/2003	IP-EC	NOVARTIS	Investigateur essai clinique (2002, 2003)			
60259	GIRERD	Xavier	10/04/2003	IP-EC	TAKEDA	Investigateur essai clinique (2003)			
60259	GIRERD	Xavier	10/04/2003	IP-EC	MENARINI	Coordinateur enquête scientifique (2002, 2003)			
60259	GIRERD	Xavier	10/04/2003	IP-EC	THERVAL	Coordinateur enquête scientifique (2002, 2003)			
60259	GIRERD	Xavier	10/04/2003	IP-CF	PFIZER, BAYER, TAKEDA, ASTRA-ZENECA	Conférences			
60259	GIRERD	Xavier	21/09/2000	IP-EC	MSD	Essai phase IV - coordinateur			
60259	GIRERD	Xavier	21/09/2000	IP-EC	NOVARTIS	Coordinateur étude internationale			
60259	GIRERD	Xavier	21/09/2000	IP-EC	MONSANTO	Essai phase III B - investigateur			
60259	GIRERD	Xavier	21/09/2000	IP-EC	PIERRE FABRE	Essai phase IV - coordinateur			
60259	GIRERD	Xavier	21/09/2000	IP-EC	ASTRA-ZENECA	Essai phase IV - coordinateur			
60259	GIRERD	Xavier	21/09/2000	IP-CF	ASTRA-ZENECA	Conférence(s)			
60259	GIRERD	Xavier	21/09/2000	IP-CF	MERCK-LIPHA	Conférence(s)			
60259	GIRERD	Xavier	21/09/2000	IP-CF	BAYER	Conférence(s)			
60259	GIRERD	Xavier	21/09/2000	VB	PFIZER	Association			
65480	GIROUD	Maurice	09/06/2009	EC-INV	REGISTRE DIJONNAIS DES AVC (INSERM + INVS)	épidémiologie des AVC dans la ville de Dijon intra-muros	coordonnateur	01/1985	
65480	GIROUD	Maurice	09/06/2009	IP-AC	DHOS / HAS	Comité de pilotage sur les AVC	aucune rémunération	01/2009	
65480	GIROUD	Maurice	09/06/2009	CF-INT	SERVIER	European Stroke Conférence - Stockholm	aucune rémunération	05/2009	05/2009
65480	GIROUD	Maurice	09/06/2009	CF-INT	SOCIETE FRANCAISE NEURO-VASCULAIRE	European Stroke Conference - Nice	aucune rémunération	05/2008	05/2008
65480	GIROUD	Maurice	09/06/2009	CF-AUD	SERVIER	Stockholm		05/2009	05/2009
65480	GIROUD	Maurice	09/06/2009	CF-AUD	SOCIETE FRANCAISE NEURO-VASCULAIRE	Nice		05/2008	05/2008
65480	GIROUD	Maurice	09/06/2009	VB	WYETH	honoraires	Registre Dijonnais des AVC	01/2009	01/2009
65480	GIROUD	Maurice	09/06/2009	VB	SERVIER	Honoraires	Associations pour le Développement des Sciences Neurologiques en Bourgogne	01/2008	12/2009
64693	GLACET-BERNARD	Agnès	02/07/2008	PAR	LABORATOIRES SERVIER	veille technologique	soeur	01/1986	
64693	GLACET-BERNARD	Agnès	02/07/2008	CF-AUD	ALCON	visite de l'usine Grieschaber en Suisse (instrument chirurgicaux)		09/2008	09/2008
64693	GLACET-BERNARD	Agnès	02/07/2007	EC-INV	HOPITAL INTERCOMMUNAL (promoteur)	Traitement des occlusions veineuses par hémodilution (érythro-aphérèse)	Investigateur coordonnateur	11/2003	12/2007
64693	GLACET-BERNARD	Agnès	02/07/2007	EC-INV	HEMOTECH	Traitement de la DMLA par rhéophérèse	Investigateur coordonnateur	01/2007	12/2010
64693	GLACET-BERNARD	Agnès	02/07/2007	EC-CO	ALLERGAN	Traitement des occlusions veineuses par Posurdex	Co-investigateur	01/2004	12/2008
64693	GLACET-BERNARD	Agnès	02/07/2007	EC-CO	EYETECH / PFIZER	Traitement des occlusions veineuses par Macugen (étude 1011)	Co-investigateur	01/2003	12/2005
64693	GLACET-BERNARD	Agnès	02/07/2007	RE-AUT	PHRC	Avis pour le projet "recherche de thrombophilie dans les occlusions veineuses rétiniennes"	Aucune rémunération	01/2005	12/2005
62374	GODEBERGE	Philippe	22/08/2002	IP-EC	SERVIER	Conduite essai clinique (1994)			
62374	GODEBERGE	Philippe	22/08/2002	IP-CF	SERVIER	Traitement maladie Hénumudane (94-95)			
64969	GODEFROY	Olivier	08/03/2009	EC-INV	SERVIER	PERFORM/ accident vasculaire cérébral	investigateur principal	01/2006	
64969	GODEFROY	Olivier	08/03/2009	EC-INV	BIOGEN	BG12/sclérose en plaques	investigateur principal	03/2009	
64969	GODEFROY	Olivier	08/03/2009	EC-INV	ESAI	Hippocampe/ trouble cognitif léger-M Alzheimer	Investigateur principal	01/2008	
64969	GODEFROY	Olivier	08/03/2009	CF-INT	EISAI, NOVARTIS, JANSSEN, LUNDBECK, GSK, SERVIER/EUTHERAPIE, BIOGEN	EPU dans les domaines de la neurologie	rémunération institution	01/2001	
64969	GODEFROY	Olivier	08/03/2009	CF-AUD	EISAI, NOVARTIS, JANSSEN, LUNDBECK, GSK, SERVIER/EUTHERAPIE, BIOGEN, SCHERING	EPU participation congrès		01/2001	
64969	GODEFROY	Olivier	08/03/2009	VB	EISAI, NOVARTIS, JANSSEN, LUNDBECK, GSK, SERVIER/EUTHERAPIE, BIOGEN	versement <15% du budget de fonctionnement de l'association "ADER"		01/2001	12/2006
64969	GODEFROY	Olivier	22/08/2007	EC-INV	NOVARTIS	démence vasculaire - Rivastigmine	investigateur principal	01/2003	12/2006
64969	GODEFROY	Olivier	22/08/2007	EC-INV	SERVIER	PERFORM / accident vasculaire cérébral		01/2006	12/2007
64969	GODEFROY	Olivier	22/08/2007	IP-AC	NOVARTIS	Avis expert sur médicament / études cliniques	rémunération personnelle et institution	01/2003	12/2003

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64959	GODEFROY	Olivier	22/08/2007	CF-INT	EISAI - NOVARTIS - JANSSEN - LUNDBECK - GSK - SERVIER /EUTHERAPIE - BIOGEN	EPU dans les domaines de la neurologie	rémunération institution	01/2001	12/2001
64969	GODEFROY	Olivier	22/08/2007	CF-AUD	EISAI - NOVARTIS - JANSSEN - LUNDBECK - GSK - SERVIER /EUTHERAPIE - BIOGEN	EPU - participation au congrès		01/2001	12/2001
64969	GODEFROY	Olivier	22/08/2007	VB	EISAI - NOVARTIS - JANSSEN - LUNDBECK - GSK - SERVIER /EUTHERAPIE - BIOGEN	versements <15 % au budget de fonctionnement de l'association « ADER »		01/2001	12/2001
64338	GOLDBERG	Danièle	12/04/2010	CF-AUD	WYETH	Congrès européen de rhumatologie ENBREL		06/2010	
64338	GOLDBERG	Danièle	12/04/2010	CF-AUD	ABBOTT	Congrès américain de rhumatologie		10/2010	
64338	GOLDBERG	Danièle	27/04/2009	EC-CO	ABBOTT	Humira phase IV suivi du produit	étude multicentrique investigateur principal d'un centre	01/2004	12/2007
64338	GOLDBERG	Danièle	27/04/2009	CF-INT	IPSEN	Réunion médicale (1 soirée) Hôtel Mariott Association des Médecins du 17ème - ostéoporose et vitamine D	rémunération personnelle	03/2009	03/2009
64338	GOLDBERG	Danièle	27/04/2009	CF-AUD	EXPANSCIENCE	Congrès COFIPO de rhumatologie - Bruxelles		04/2009	04/2009
64338	GOLDBERG	Danièle	27/04/2009	CF-AUD	WYETH	Congrès européen de rhumatologie - Copenhague		06/2009	06/2009
64338	GOLDBERG	Danièle	08/04/2009	EC-INV	ABBOTT	essai clinique phase IV HUMIRA	expérimentateur principal	01/2003	12/2007
64338	GOLDBERG	Danièle	08/04/2009	CF-INT	IPSEN	réunion de médecins Association Médicale Amicale du 17ème : 1 soirée thème : ostéoporose	rémunération personnelle	03/2009	03/2009
64338	GOLDBERG	Danièle	08/04/2009	CF-AUD	EXPANSCIENCE	congrès Cofipo Bruxelles		04/2009	04/2009
64338	GOLDBERG	Danièle	08/04/2009	CF-AUD	WYETH	congrès européen de rhumatologie (Enbrel)		06/2009	06/2009
64338	GOLDBERG	Danièle	31/03/2008	LD-AR	PROCTER & GAMBLE	Je faisais partie d'un groupe d'experts	aucune rémunération	01/1995	12/2007
64338	GOLDBERG	Danièle	31/03/2008	EC-CO	ROCHE	Essai clinique phase IV MABTHERA	expérimentateur non principal - étude multicentrique	01/2005	05/2007
64338	GOLDBERG	Danièle	31/03/2008	EC-CO	ABBOTT	essai clinique phase IV HUMIRA	expérimentateur non principal - étude multicentrique	01/2005	05/2007
64338	GOLDBERG	Danièle	31/03/2008	CF-AUD	PROCTER & GAMBLE	Congrès : AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH - Actonel / USA		10/2007	10/2007
64338	GOLDBERG	Danièle	31/03/2008	CF-AUD	WYETH	Congrès : AMERICAN COLLEGE OF RHUMATOLOGY / USA		11/2007	11/2007
64338	GOLDBERG	Danièle	27/09/2007	EC-INV	ABOTT	HUMIRA	Investigateur principal	01/2004	05/2007
64338	GOLDBERG	Danièle	27/09/2007	EC-INV	ROCHE	MABTHERA	Investigateur principal	01/2005	05/2007
64338	GOLDBERG	Danièle	27/09/2007	IP-AC	PROCTER	ACTONEL participation au groupe d'experts réunions de trveil (en cours)	aucune rémunération	01/1992	
64338	GOLDBERG	Danièle	27/09/2007	VB	SCHERING PLOUGH	Achat de 2 fauteuils de perfusion	CMCPP	01/2005	05/2007
64338	GOLDBERG	Danièle	25/04/2007	LD-AR	PROCTER ET GAMBLE	Groue d'experts "Ostéoporoae" - "ACTONEL"	Aucune rémunération	01/1995	
64338	GOLDBERG	Danièle	25/04/2007	EC-CO	ROCHE	MABTHERA	Co-investigateur	10/2005	10/2007
64338	GOLDBERG	Danièle	25/04/2007	EC-CO	ABOTT	HUMIRA polyarthrite		01/2004	12/2007
64338	GOLDBERG	Danièle	21/03/2006	LD-AR	PROCTER / AVENTIS	Organisation du groupe d'experts sur l'ostéoporose (GESO)	aucune rémunération	01/1991	
64338	GOLDBERG	Danièle	21/03/2006	EC-CO	SFR SOCIETE FRANCAISE DE RHUMATOLOGIE	Etude médico-economique / protocole EMER pour infliximab (Schering Plough)	expérimentateur non principal	01/2000	12/2003
64338	GOLDBERG	Danièle	21/03/2006	EC-CO	ABBOTT	suivi des effets secondaires REALISE Adalimumab	expérimentateur non principal	01/2003	12/2006
64338	GOLDBERG	Danièle	21/03/2006	CF-AUD	SERVIER	5ème congrès Européen ostéoporose - Mars 2005 / Protelos		03/2005	03/2005
64338	GOLDBERG	Danièle	21/03/2006	CF-AUD	PROCTER	journée Franco-Tunisienne ACTONEL		05/2005	05/2005
64338	GOLDBERG	Danièle	21/03/2006	CF-AUD	PROCTER	American Society for bone and mineral research		09/2005	09/2005
64338	GOLDBERG	Danièle	21/03/2006	CF-AUD	SCHERING PLOUGH	American college of rhumatology - REMICADE		11/2005	11/2005
61795	GOMPEL	Anne	17/10/2007	PAR	HRA PHARMA	développement de la contraception d'urgence par RU486	belle-fille, contrat en cours		
61795	GOMPEL	Anne	17/10/2007	CF-INT	NOVARTIS	salon de gynécologie pratique□□table ronde sur suivi après cancer du sein	Rémunération institution	03/2007	03/2007
61795	GOMPEL	Anne	17/10/2007	EC-INV	NOVARTIS	recherche sur isoformes du récepteur de la progestérone dans le cancer du sein	responsable recherche	12/2004	12/2008
61795	GOMPEL	Anne	17/10/2007	IP-AC	PROCTER ET GAMBLE	Patch testostérone Workshop à Reims sur recommandations d'utilisation	Rémunération institution	03/2007	03/2007
61795	GOMPEL	Anne	19/06/2006	LD-AR	SCHERING	membre d'un groupe d'expert ma FHS "Advisory Council"	rémunération institution	01/2008	
61795	GOMPEL	Anne	19/06/2006	LD-AR	PFIZER	Steering committee étude clinique	rémunération institution	01/2003	
61795	GOMPEL	Anne	19/06/2006	IP-AC	PROCTER ET GAMBLE	Patch testostérone Workshop à Londres	rémunération institution		
61795	GOMPEL	Anne	19/06/2006	IP-AC	SHIRE FRANCE	Vaccina - participation à une réunion comme expert	rémunération institution	01/2006	
61795	GOMPEL	Anne	19/06/2006	CF-INT	NOVARTIS	Talon de gynécologie - modérateur inhibiteur	rémunération institution	01/2005	12/2005
61795	GOMPEL	Anne	19/06/2006	CF-INT	BESINS	journée de gynécologie	rémunération institution	01/2006	12/2006
61795	GOMPEL	Anne	19/06/2006	VB	BESINS	recherche biologique cellules mammaires		01/2005	12/2006
61795	GOMPEL	Anne	19/06/2006	VB	ORGANON	recherche biologique cellules mammaires	INSERM	01/2004	12/2006
61795	GOMPEL	Anne	19/06/2006	VB	NOVARTIS	recherche biologique cellules mammaires□□PR dans cancer du sein	INSERM	01/2005	12/2006
61795	GOMPEL	Anne	19/06/2006	VB	BROSC	recherche biologique cellules mammaires		01/2004	
61795	GOMPEL	Anne	19/06/2006	PAR	HRA PHARMA		belle fille	01/2004	
61795	GOMPEL	Anne	27/10/2005	LD-AR	PFIZER	Participation au steering committee etud costumers (en cours)	rémunération versée à une association	01/2003	
61795	GOMPEL	Anne	27/10/2005	EC-INV	SERVIER	Etude Aerodiol	Coordonnateur	01/2002	12/2003
61795	GOMPEL	Anne	27/10/2005	EC-INV	IPRAD	XXX	Coordonnateur	01/2003	12/2004
61795	GOMPEL	Anne	27/10/2005	IP-AC	PROCTER ET GAMBLE	Conseil workshop	Rémunération versée à une association	04/2005	
61795	GOMPEL	Anne	27/10/2005	CF-INT	SERVIER	Cardiologie Est Parisien	Rémunération personnelle	01/2005	12/2005
61795	GOMPEL	Anne	27/10/2005	CF-INT	AVENTIS	Contraception du lupus	Rémunération pesonnelle	01/2004	12/2004
61795	GOMPEL	Anne	27/10/2005	VB	ORGANON	Recherche sur cellules mamaires	INSERM	01/2000	12/2005
61795	GOMPEL	Anne	27/10/2005	VB	NOVARTIS	Recherche sur PR INSERM		01/2005	12/2006
61795	GOMPEL	Anne	27/10/2005	VB	PANRENHEE BIOTECH	Recherches sur cellules mammaires		01/2003	
61795	GOMPEL	Anne	27/10/2005	VB	BESINS	Recherches sur cellules mammaires		11/2005	05/2006
61795	GOMPEL	Anne	27/10/2005	PAR	HRA PHARMA		Salariée - compagne de mon fils	01/2004	
61795	GOMPEL	Anne	20/06/2005	IP-EC	SERVIER	Investigateur principal - Dopergine (aerodiol) - 2004-2005			
61795	GOMPEL	Anne	20/06/2005	IP-AC	PROCTER & GAMBLE	Participation à un groupe de travail (avril 2005)			
61795	GOMPEL	Anne	20/06/2005	IP-AC	HRA Pharma	Participation à un groupe de travail (2004)			
61795	GOMPEL	Anne	20/06/2005	IP-CF	NOVARTIS	Breast Cancer - San Antonio (invitation en qualité d'auditeur)			
61795	GOMPEL	Anne	20/06/2005	VB	ORGANON	INSERM contrat de recherche association 1901			
61795	GOMPEL	Anne	20/06/2005	VB	NOVARTIS	INSERM contrat de recherche association 1901 (en cours)			
61795	GOMPEL	Anne	20/06/2005	VB	SERVIER	INSERM contrat de recherche association 1901 (2001-2002)			
61795	GOMPEL	Anne	20/06/2005	VB	LILLY	INSERM contrat de recherche association 1901 (2002-2003)			
61795	GOMPEL	Anne	20/06/2005	PAR	HRA Pharma	Compagne de mon fils employée en Chine			
61795	GOMPEL	Anne	05/03/2005	IP-EC	ORGANON INTERNATIONAL	Recherche			
61795	GOMPEL	Anne	05/03/2005	IP-AC	PFIZER	Conseil scientifique étude sur statine			
61795	GOMPEL	Anne	05/03/2005	IP-EC	NOVARTIS	Recherche			
61795	GOMPEL	Anne	10/09/2003	IP-CF	SOLYMES				
61795	GOMPEL	Anne	10/09/2003	IP-CF	BESINS	Participation livre			

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61795	GOMPEL	Anne	10/09/2003	VB	ORGANON, AKZO NOBEL, SERVIER	Association (Travaux de recherche)			
61795	GOMPEL	Anne	10/09/2003	VB	PFIZER	Conseil scientifique essai clinique			
61795	GOMPEL	Anne	18/03/2003	IP-EC	ORGANON				
61795	GOMPEL	Anne	18/03/2003	IP-CF	BESINS	Livre			
61795	GOMPEL	Anne	18/03/2003	IP-EC	SERVIER				
61795	GOMPEL	Anne	18/03/2003	IP-EC	IPRAD				
61795	GOMPEL	Anne	18/03/2003	IP-EC	SOLYMES - AVENTIS				
61795	GOMPEL	Anne	18/03/2003	IP-EC	AVENTIS	Reprise d'observation clinique - rémunération association			
61795	GOMPEL	Anne	18/03/2003	IP-EC	SERVIER	Coordination étude clinique sur aerodiol (11/2002)			
63709	GORWOOD	Philip	30/09/2008	LD-AR	BRISTOL MYERS SQUIBB	Membre du board CAMPUS PSY	Rémunération personnelle	01/2005	12/2009
63709	GORWOOD	Philip	30/09/2008	VB	ARDIX	Pharmacogénétique de la réponse au Stablon	INSERM U675	01/2008	12/2010
63709	GORWOOD	Philip	30/09/2008	VB	EUTHéRAPIE	Analyse pharmacogénétique des protocoles de développement de l'Agomélatine	INSERM U675 (Contrat INSERM)	01/2008	12/2010
63709	GORWOOD	Philip	30/09/2008	CF-AUD	JANSSEN	Naples, symoslum national (Italien/□□Antipsychotiques/Risperdal		04/2008	04/2008
63709	GORWOOD	Philip	30/09/2008	CF-AUD	EUTHéRAPIE	Munich, symposium satellite du CINP/□□Antidépresseurs/Agomélatine		07/2008	07/2008
63709	GORWOOD	Philip	30/09/2008	CF-AUD	EUTHéRAPIE	Barcelone, symposium satellite de l'ECNP/ Antidépresseurs/Agomelatine		08/2008	09/2008
63709	GORWOOD	Philip	30/09/2008	IP-AC	LILLY	Conseil scientifique	Rémunération personnelle	10/2008	
63709	GORWOOD	Philip	30/09/2008	IP-AC	UCB	Conseil scientifique	Rémunération personnelle	01/2005	12/2009
63709	GORWOOD	Philip	30/09/2008	LD-AR	JANSSEN EMEA	Conseil Scientifique	Rémunération personnelle	01/2006	12/2010
63709	GORWOOD	Philip	30/09/2008	LD-AR	JANSSEN (JOHNSON & JOHNSON)	Conseil scientifique	Rémunération personnelle	01/2007	12/2009
63709	GORWOOD	Philip	30/09/2008	LD-AR	SERVIER/ARDIX/EUTHéRAPIE	Conseil scientifique	Rémunération personnelle	01/2006	12/2009
63709	GORWOOD	Philip	02/11/2005	VB	LILLY	Réalisation d'une étude pharmacogénétique sur l'efficacité d'un traitement dans l'hyperactivité avec déficit d	INSERM	09/2003	09/2006
63709	GORWOOD	Philip	02/11/2005	VB	BMS	Réalisation d'une étude pharmacogénétique sur l'efficacité de la Naltrexone dans l'alcoolo-dépendance	CNRS	12/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	CF-INT	BMS	Participation à un groupe de travail sur la communication pour les internes de psychiatrie	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	CF-INT	LILLY	Participation à un groupe d'expert sur les troubles bipolaires	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	CF-INT	GSK	Week-end "Emotions"	Vous	01/2004	05/2006
63709	GORWOOD	Philip	02/11/2005	CF-INT	BMS	ECNP 2005, Amsterdam, Hollande	Vous	10/2005	10/2005
63709	GORWOOD	Philip	02/11/2005	CF-INT	SERVIER	WCP 2005, Le Caire-Egypte	Vous	10/2005	10/2005
63709	GORWOOD	Philip	02/11/2005	IP-AC	JANSSEN	Rédaction de notes de lecture pour des journaux sponsorisés par l'industrie	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	IP-AC	SANOFI-SYNTHELABO	Rédaction de notes de lecture pour des journaux sponsorisés par l'industrie	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	IP-AC	CHIESI	Réalisation d'une veille scientifique mensuelle des revues en psychiatrie de langue anglaise	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	IP-AC	WYETH	Réalisation d'une veille scientifique mensuelle des revues en psychiatrie de langue anglaise	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	IP-AC	GSK	Réalisation d'une veille scientifique mensuelle des revues en psychiatrie de langue anglaise	Vous	09/2003	09/2006
63709	GORWOOD	Philip	02/11/2005	EC-INV	LUNDBECK	Coordinateur européen pour l'étude de l'Escitalopram dans la prévention des rechutes dépressives chez les	Coordinateur européen	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	EC-INV	JANSSEN	Coordinateur national pour l'étude sur l'efficacité du Palmitate de Risperidone dans la schizophrénie	Coordinateur national	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	EC-INV	SANOFI-AVENTIS	Coordinateur national pour l'étude sur l'efficacité du Saredutent dans la dépression	Coordinateur national	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	EC-INV	LILLY	Etude de pharmacogénétique d'une étude européenne d'efficacité d'un produit de l'entreprise	Coordinateur de la partie pharmacogénétique	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	SERVIER	Conseiller pour le développement de nouveaux produits	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	WYETH	Conseiller pour le développement de nouveaux produits	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	SERVIER	Membre d'une association sponsorisée par l'entreprise	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	LILLY	Membre d'une association sponsorisée par l'entreprise	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	BMS	Membre d'une association sponsorisée par l'entreprise	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	UCB	Membre d'une association sponsorisée par l'entreprise	Vous	09/2003	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	JANSSEN	Expert-Conseil	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	SERVIER	Expert-conseil	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	GSK	Expert-conseil	Vous	09/2004	09/2006
63709	GORWOOD	Philip	02/11/2005	LD-AR	CHIESI	Expert-conseil	Vous	09/2004	09/2006
63709	GORWOOD	Philip	25/10/2005	CF-INT	BMS	ECNP 2005/ place des antipsychotiques	Vous	10/2005	10/2005
63709	GORWOOD	Philip	25/10/2005	EC-INV	SERVIER	Coordination d'une étude sur mémoire et dépression (ACTUEL2)	Coordinateur national	09/2004	01/2006
10205	GOUYETTE	Alain	31/01/2001	IF	IGRXD SA	10 actions à 20 E			
10205	GOUYETTE	Alain	01/01/1999	IP-EC	RPR	Contrats de recherche académique dans le cadre de l'IGR et du CNRS.			
10205	GOUYETTE	Alain	01/01/1999	IP-EC	SERVIER				
10205	GOUYETTE	Alain	01/01/1999	IP-EC	BEAUFOUR				
10205	GOUYETTE	Alain	01/01/1999	IP-EC	SYNTHELABO				
10205	GOUYETTE	Alain	01/01/1998	IF	RPR				
10205	GOUYETTE	Alain	01/01/1998	IP-AUT	Institut Henri Beaufour				
10205	GOUYETTE	Alain	01/01/1998	IP-AUT	RPR (Bellon)				
10205	GOUYETTE	Alain	01/01/1998	IP-AUT	Ethypharm				
10205	GOUYETTE	Alain	01/01/1998	IP-AUT	Synthélabo				
61237	GRIMALDI	André	24/09/2004	IP-EC	AVENTIS	Etude aladin, tulip			
61237	GRIMALDI	André	24/09/2004	IP-EC	LABORATOIRE TAKEDA	Etude direct			
61237	GRIMALDI	André	24/09/2004	IP-EC	LABORATOIRE SERVIER				
61237	GRIMALDI	André	24/09/2004	IP-AC	AVENTIS	Board lantus			
61237	GRIMALDI	André	24/09/2004	IP-AC	GLAXO SMITH KLINE	Board avandia			
61237	GRIMALDI	André	24/09/2004	IP-AC	MSD	Board losartan			
61237	GRIMALDI	André	24/09/2004	IP-AC	LIPHA	Board glicovare			
61237	GRIMALDI	André	24/09/2004	IP-CF	GLAXO SMITH KLINE	Diabète de type 2			
61237	GRIMALDI	André	24/09/2004	IP-CF	AVENTIS	Diabète de type 2			
61237	GRIMALDI	André	01/02/2004	IP-EC	AVENTIS	Etude Aladin - Etude Tulip			
61237	GRIMALDI	André	01/02/2004	IP-EC	ASTRA ZENECA - TAKEDA	Etude DIRECT			
61237	GRIMALDI	André	01/02/2004	IP-RE	MSD	Etude HPS - VAMIT			
61237	GRIMALDI	André	01/02/2004	IP-AC	MSD	Risque cardio-vasculaire			
61237	GRIMALDI	André	01/02/2004	IP-AC	AVENTIS	Alliance 7 -Board Lantus			
61237	GRIMALDI	André	01/02/2004	IP-AC	GLAXO SMITHKLINE	Board Avandia			
61237	GRIMALDI	André	01/02/2004	IP-CF	GLAXO SMITHKLINE	MEDEC 2003 - Société Européenne de Cardio (2004) - Thèse : Stratégie thérapeutique diabète type 2			
61237	GRIMALDI	André	01/02/2004	IP-CF	MERCK LIPHA	Alfediam 2003 : Vivre avec un diabète 2			
61237	GRIMALDI	André	20/10/2002	IP-EC	ASTRA ZENECA	Etude DIRECT			
61237	GRIMALDI	André	20/10/2002	IP-EC	AVENTIS	Etude ALADIN			
61237	GRIMALDI	André	20/10/2002	IP-AC	NOVO NORDISK	Conseil insuline et DB type 2			
61237	GRIMALDI	André	20/10/2002	IP-AC	AVENTIS	Conseil LANTUS			
61237	GRIMALDI	André	20/10/2002	IP-AC	MSD	Conseil LOSARTAN			

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61237	GRIMALDI	André	20/10/2002	IP-AC	GLAXO SMITHKLINE	Glitazone Avandia			
61237	GRIMALDI	André	20/10/2002	IP-CF	SERVIER, GLAXO SMITHKLINE, MERCK LIPHA, MSD				
61237	GRIMALDI	André	13/06/2001	IP-EC	LILLY	Hémalog			
61237	GRIMALDI	André	13/06/2001	IP-EC	NOVO	Aspart			
61237	GRIMALDI	André	13/06/2001	IP-AC	NOVO	Insuline diabète type 2			
61237	GRIMALDI	André	13/06/2001	IP-AC	LIPHA	Insulinorésistance			
61237	GRIMALDI	André	13/06/2001	IP-AC	AVENTIS	Insuli Lautus			
61237	GRIMALDI	André	13/06/2001	IP-CF	NOVO	MEDEC			
61237	GRIMALDI	André	13/06/2001	IP-CF	LIPHA	MEDEC : Conférence diabète type 2			
61237	GRIMALDI	André	13/06/2001	IP-CF	SERVIER	Observance			
61237	GRIMALDI	André	13/06/2001	IP-CF	SMITHKLINE BEECHAM	Observance			
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	WYETH-PFIZER	Membre d'un comité d'évaluation de la tolérance d'un essai en cours sur Temsirolimus	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	EXPANSCIENCES	Conseil en méthodologie : piascledine .	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	WYETH-PFIZER	Membre d'un comité d'évaluation de la tolérance d'un essai en cours : Temsirolimus	Aucune rémunération		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	GSK	Conseil en méthodologie:□□Duodart	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	LFB	Conseil en méthodologie: produits en développement (blood products)	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	RE-DE	IRIS	Expertise sur l'essai ADVANCE	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC			Aucune rémunération		
60409	GROUIN	Jean-Marie	21/09/2010	RE-DE	IRIS	Expertise sur l'essai ADVANCE	Aucune rémunération		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	THEA	Conseil en méthodologie : □□T2380	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	IRI SERVIER	Conseil en méthodologie : □□preterax, diamicron, vastarel,	Rémunération personnelle		
60409	GROUIN	Jean-Marie	21/09/2010	IP-AC	GENZYME	Conseil en méthodologie : Periflaxor , Myozyme, Sepraspray, Seprafilm	Rémunération personnelle		
60409	GROUIN	Jean-Marie	26/03/2009	LD-AR	LFB	Membre groupe experts	Rémunération personnelle	01/2004	
60409	GROUIN	Jean-Marie	26/03/2009	IP-AC	GENZYME-LFB-STALLERGES-MAIOLI-SPINDLER-IR FABRE -NOVARTIS-PFIZER-CHIESI-EXPANSCIENCES-BOEHRINGER-WYETH-THEA-GUERBET-GLAXO-SERVIER-ALLERGAN-JANSEN	Conseil ponctuel en en méthodologie et en statistiques sur les essais cliniques	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	IP-AC	MAILOI SPINDLER	Activités de conseil ponctuelles en méthodologie et en statistiques portant sur le plan de développement, les	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	IP-AC	PAREXEL	Formation en méthodologie statistique des essais cliniques	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	IP-AC	GENZYME, STALLERGENES	Activités de conseils ponctuels en méthodologie et en statistiques portant sur le plan de développement, les	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	IF			<5000 € ou <5% du capital		
60409	GROUIN	Jean-Marie	22/03/2008	IP-AC	EXPANSCIENCES, 3M SANTE, GSK, STALLERGENES, CHIESI, WYETH, FOURNIER, GENZYME, FAUST PHARMACEUTICALS, GALDERMA, ARKOPHARMA, GILEAD SCIENCES, SANOFI SYNTHELABO, GUERBET, INNOTHERA, MERCK LIPHA	Activités de conseil ponctuelles en méthodologie et en statistiques portant sur le plan de développement, les	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	IP-AC	GSK, TAKEDA, IFIS	Formation en méthodologie statistique des essais cliniques	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	RE-DE	ARKOPHARMA	Méta-analyse de l'efficacité d'Hypericum vs placebo	Rémunération personnelle		
60409	GROUIN	Jean-Marie	22/03/2008	LD-AR	LFB - IR PIERRE FABRE - IRI SERVIER - THEA	Consultation individuelle en méthodologie et statistiques de façon régulière	Rémunération personnelle		
60409	GROUIN	Jean-Marie	17/01/2007	LD-AR	LFB - IR PIERRE FABRE - IRI SERVIER - THEA	Consultation individuelle en méthodologie et statistiques de façon régulière	Rémunération personnelle		
60409	GROUIN	Jean-Marie	17/01/2007	RE-DE	ARKOPHARMA	Méta-analyse de l'efficacité d'Hypericum vs placebo	Rémunération personnelle		
60409	GROUIN	Jean-Marie	17/01/2007	IP-AC	EXPANSCIENCES, 3M SANTE, GSK, STALLERGENES, CHIESI, WYETH, FOURNIER, GENZYME, FAUST PHARMACEUTICAL, GALDERMA, ARKOPHARMA, GILEAD SCIENCES, SANOFI SYNTHELABO, GUERBET, INNOTHERA, MERCK LIPHA	Activités de conseil ponctuelles en méthodologie et en statistiques portant sur le plan de développement, les	Rémunération personnelle		
60409	GROUIN	Jean-Marie	17/01/2007	IP-AC	GSK, TAKEDA, IFIS	Formation en méthodologie statistique des essais cliniques	Rémunération personnelle		
60409	GROUIN	Jean-Marie	17/01/2007	IP-AUT	GSK	Intervention dans un procès sur Seretide (essai Concept) comme témoin pour GSK		01/2006	06/2006
60409	GROUIN	Jean-Marie	05/10/2005	IP-AC	IRI SERVIER, IR PIERRE FABRE, INNOTHERA, LFB, THEA, GILEAD WYETH, FOURNIER, 3M SANTE, GUERBET, SANOFI SYNTHELABO, SMITH & NEPHEW, ISOCELL, PHARMASCIENCES, GLAXO, NUKLEUS	Actions de conseils en méthodologie statistiques	Rémunération personnelle		
60409	GROUIN	Jean-Marie	30/08/2005	RE-DE	3 M SANTE, IRI SERVIER		rémunération personnelle		
60409	GROUIN	Jean-Marie	30/08/2005	IP-AC	IR PIERRE FABRE, LFB, THEA, GILEAD, WYETH, FOURNIER, IRI SERVIER, M SANTE, GUERBET, SANOFI, DANONE, ISOCELL, PHARMASCIENCE, GLAXO	Patch testosterone, Mienaciman (Pierre Fabre)	Conseil en statistiques - rémunération personnelle		
60409	GROUIN	Jean-Marie	30/08/2005	CF-INT	SANOFI, IRI SERVIER, IR PIERRE FABRE, GUERBET, IFIS, 3M SANTE	Formation en méthodologie des essais cliniques ou en statistiques	Rémunération personnelle		
60409	GROUIN	Jean-Marie	20/10/2003	LD	LFB	Actions de conseil en méthodologie répétées			
60409	GROUIN	Jean-Marie	20/10/2003	IP-AC	LFB, IR PIERRE FABRE, IRI SERVIER, DANONE SANTE, PHARMASCIENCES, 3M SANTE, THEA, MAYOLI-SPINDLER, GUERBET, THERABEL, NOVARTIS, FOURNIER, ARKOPHARMA, BAYER, PALBIAN, SCHERING, INNOTHERA, ISOCELL	Depuis le 01/01/2001 - Actions de conseil en statistiques et méthodologie			
60409	GROUIN	Jean-Marie	20/10/2003	IP-CF	IRIS, IFIS, WYETH	Cours de méthodologie statistique			
60409	GROUIN	Jean-Marie	20/10/2003	IP-CF	GLAXO	Prévention des exacerbations dans la BPCO			
60409	GROUIN	Jean-Marie	20/10/2003	LD	Institut de Recherche PIERRE FABRE	Actions de conseil en méthodologie répétées			
60409	GROUIN	Jean-Marie	20/10/2003	LD	IRI SERVIER	Actions de conseil en méthodologie répétées			
63656	GUERET	Pascal	23/03/2005	IP-EC	SERVIER				
63656	GUERET	Pascal	23/03/2005	IP-EC	TAKEDA				
63656	GUERET	Pascal	23/03/2005	IP-EC	BMS				
63656	GUERET	Pascal	23/03/2005	IP-AC	SERVIER	Conseil			
63656	GUERET	Pascal	23/03/2005	IP-CF		Très variables d'une année sur l'autre			
62694	GUEX	Jean-Jérôme	26/05/2004	IP-EC	PIERRE FABRE				
62694	GUEX	Jean-Jérôme	26/05/2004	IP-AC	BEAUFOUR IPSEN PHARMA				
62694	GUEX	Jean-Jérôme	26/05/2004	IP-CF	BEAUFOUR IPSEN PHARMA, SERVIER, PIERRE FABRE				
62694	GUEX	Jean-Jérôme	26/05/2004	VB	PIERRE FABRE				

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62694	GUEX	Jean-Jérôme	22/02/2003	IP-EC	BNITN/ISTH	Contrôle étude clinique			
62694	GUEX	Jean-Jérôme	22/02/2003	IP-AC	BRENFERISSA PHARM	Comité éditorial revue communication entreprise			
60991	GUEYFFIER	François	12/07/2006	VB	PERSÉE MEDICA	Essai clinique conduit au CIC	Hospices Civils de Lyon	04/2006	01/2007
60991	GUEYFFIER	François	12/07/2006	VB	CREAPHARM				
60991	GUEYFFIER	François	12/07/2006	VB	BOIRON				
60991	GUEYFFIER	François	12/07/2006	VB	ROCHE				
60991	GUEYFFIER	François	12/07/2006	VB	LIPHA MERCK		Hospices Civils de Lyon		
60991	GUEYFFIER	François	12/07/2006	CF-INT	SERVIER	Journées de l'hypertension artérielle, Paris 2005	Aucune rémunération	12/2005	12/2005
60991	GUEYFFIER	François	12/07/2006	IP-AC	GSK	Membre du Conseil Scientifique d'une étude épidémiologique	Rémunération personnelle	07/2002	07/2006
60991	GUEYFFIER	François	12/07/2006	IP-AC	AVENTIS	Membre du Conseil Scientifique d'un observatoire du médicament	Rémunération institution	07/2004	07/2010
60991	GUEYFFIER	François	12/07/2006	EC-CO	MSD	Essai Clinique	Co-investigateur	05/2003	07/2010
60991	GUEYFFIER	François	12/07/2006	EC-CO	GSK	Essai clinique	Co-investigateur	01/2006	03/2006
60991	GUEYFFIER	François	03/11/2003	VB	MERCK SHARP & DOHME, PFIZER, GENZYME, LIPHA, NOVARTIS, GLAXO SMITHKLINE, SERVIER	Hospices Civils de Lyon et Association ALECA			
60991	GUEYFFIER	François	25/10/2000	VB	SEARLE MONSANTO	Investigateur essai clinique phase III			
60991	GUEYFFIER	François	25/10/2000	VB	SOLVAY	Investigateur étude épidémiologique			
60991	GUEYFFIER	François	25/10/2000	VB	SOLVAY	Comité scientifique étude épidémiologique			
60991	GUEYFFIER	François	25/10/2000	VB	BAYER	Comité préparatoire d'un essai clinique			
60991	GUEYFFIER	François	25/10/2000	VB	GLAXO WELLCOME	Comité scientifique étude épidémiologique			
60991	GUEYFFIER	François	25/10/2000	VB	SCHWARZ PHARMA	Conseil méthodologique			
60991	GUEYFFIER	François	25/10/2000	VB	MSD, AVENTIS, SEARLE, SOLVAY, SERVIER, BOEHRINGER INGELHEIM	Aide au financement de réunions scientifiques autour du projet de recherche INDANA			
60991	GUEYFFIER	François	29/06/1999	Néant					
60055	GUILLAUME	Jean-Claude	02/05/2004	IP-EC	JANSSEN-CILAG	Regranex UdJ			
60055	GUILLAUME	Jean-Claude	02/05/2004	IP-AC	SANOFI SYNTHELABO	Conseil ponctuel			
60055	GUILLAUME	Jean-Claude	03/09/2003	IP-AC	SANOFI SYNTHELABO	Conseil ponctuel			
60055	GUILLAUME	Jean-Claude	03/09/2003	IP-CF	AVENE	Rencontre des Dermatologues des hôpitaux généraux			
60055	GUILLAUME	Jean-Claude	03/09/2003	IP-CF	GLAXO SMITHKLINE	Forum interdisciplinaire sur les herpes veridae			
60055	GUILLAUME	Jean-Claude	03/09/2003	(Autre)	JANSSEN-CILAG	Essai ERAN (coinvestigateur)			
60055	GUILLAUME	Jean-Claude	03/09/2003	(Autre)	ROCHE	Essai Rituximab dans pemphigus (co-investigateur)			
60055	GUILLAUME	Jean-Claude	03/09/2003	(Autre)	NOVARTIS	Etude Cyclosporine tolérance psoriasis			
60055	GUILLAUME	Jean-Claude	14/10/2002	IP-EC	LABCATAL	Gluconate de Zn dans l'acné			
60055	GUILLAUME	Jean-Claude	14/10/2002	IP-EC	NOVARTIS	Cyclosporine tolérance psoriasis			
60055	GUILLAUME	Jean-Claude	14/10/2002	IP-EC	JANSSEN-CILAG	Regranex ulcère de jambe			
60055	GUILLAUME	Jean-Claude	14/10/2002	IP-AC	SANOFI-SYNTHELABO	Conseil ponctuel			
60055	GUILLAUME	Jean-Claude	02/05/2000	IP-EC	AVENTIS	Essai Pyostacine			
60055	GUILLAUME	Jean-Claude	02/05/2000	IP-EC	NOVARTIS (SANDOZ)	Essai Néoral (suivi à long terme psoriasis)			
60055	GUILLAUME	Jean-Claude	02/05/2000	IP-EC	PIERRE FABRE	Essai gel RV 2455			
60055	GUILLAUME	Jean-Claude	02/05/2000	IP-EC	NOVARTIS	Leucomax (ulcères)			
60055	GUILLAUME	Jean-Claude	02/05/2000	IP-EC	SERVIER	Daflon (ulcères veineux)			
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	EC-CO	LILLY France	Ruboxistaurin (en cours)	co-investigateur		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	EC-CO	ASTRA ZENECA / TAKEDA	Candesartan (en cours)	co-investigateur		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	RE-DE	LILLY France	Transparence / Exenatide	rémunération personnelle	06/2006	
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	IP-AC	GLAXO - TAKEDA	Groupe d'expert / Rosiglitazone	rémunération personnelle		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	IP-AC	GSK	Conseil scientifique - conférences	rémunération personnelle		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	IP-AC	ASTRA ZENECA	Conférences	rémunération personnelle		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	IP-AC	SANOFI-AVENTIS	Groupe d'expert	rémunération personnelle		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	IP-AC	SERVIER	Conférences, rédaction d'articles et de brochures	rémunération personnelle		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	IP-AC	THERVAL MEDICAL	Conférences - rédaction d'articles	rémunération personnelle		
10219	GUILLAUSSEAU	Pierre-Jean	14/06/2006	CF-AUD	SERVIER	Prise en charge congrès de l'EASD			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	IP-EC	GLAXO/TAKEDA	Groupe d'experts			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	IP-EC	GLAXO	Conseil scientifique			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	IP-EC	THERVAL	Conférences/Textes			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	IP-EC	ELI LILLY	Conférences			
10219	GUILLAUSSEAU	Pierre-Jean	29/06/2003	IP-EC	SERVIER	Conférences/Textes			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	IP-AC	GLAXO	Conseil scientifique (Protocole)			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	IP-CF	AVENTIS	Conférence			
10219	GUILLAUSSEAU	Pierre-Jean	26/06/2003	VB	ASTRA ZENECA	Etude DIRECT . Association Claude Bernard			
10219	GUILLAUSSEAU	Pierre-Jean	29/09/2000	IP-AC	RHONE POULENC				
10219	GUILLAUSSEAU	Pierre-Jean	29/09/2000	IP-CF	SERVIER	Conférences			
10219	GUILLAUSSEAU	Pierre-Jean	29/09/2000	IP-CF	SERVIER	Réalisation d'un CD-Rom			
10219	GUILLAUSSEAU	Pierre-Jean	29/09/2000	IP-CF	ADIR	Rédaction de textes scientifiques			
10219	GUILLAUSSEAU	Pierre-Jean	29/09/2000	(Autre)	ROCHE DIAGNOSTIC	Subvention à l'Association de Recherche Claude Bernard de l'Assistance Publique			
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-AC	RHONE POULENC RORER	Conseil scientifique			
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-CF	SERVIER	Conférences d'enseignement post universitaire			
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-CF	Société ARTEM	Rédaction d'articles, de brochures d'enseignement scientifiques et médicaux			
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-AUT	BAYER	Prise en charge de congrès médicaux			
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-AUT	SERVIER				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-AUT	LILLY				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	IP-AUT	BOEHRINGER-MANNHEIM				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1999	VB	LILLY France	Association Claude Bernard de l'assistance publique - Université de Paris			
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	Lilly France				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	Servier				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	ADIR				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	ARTEM				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	Bristol Myers Squibb				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	RPR				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	IP-AUT	Sanofi Wintrop				
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	VB	Lilly France		Association Claude Bernard		
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	VB	Sandoz		Association Claude Bernard		
10219	GUILLAUSSEAU	Pierre-Jean	01/01/1998	VB	ADIR		Association Claude Bernard		
63529	GUILLOUZO	André	30/07/2010	IP-AC	IRIS	Consultance sur la génomique	Rémunération personnelle	09/2009	08/2010

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63529	GUILLOUZO	André	30/07/2010	IF	BIOPPREDIC		>=5000 € ou >=5% du capital	11/1987	
63529	GUILLOUZO	André	15/01/2008	LD-AR	SERVIER	Consultance, tous produits	Rémunération personnelle	01/2006	12/2008
10221	GUILMOT	Jean-Louis	13/01/2000	IP-EC	SANOFI	Phénomène de Raynaud			
10221	GUILMOT	Jean-Louis	13/01/2000	IP-EC	SCHERING	Hypertension artérielle pulmonaire			
10221	GUILMOT	Jean-Louis	13/01/2000	IP-EC	SANDOZ NOVARTIS	Antidiabétique oral			
10221	GUILMOT	Jean-Louis	13/01/2000	IP-AC	SCHERING SA	Prostacycline			
10221	GUILMOT	Jean-Louis	13/01/2000	IP-CF	AVENTIS	Antithromboliques			
10221	GUILMOT	Jean-Louis	13/01/2000	IP-CF	SANOFI	Antithromboliques			
10221	GUILMOT	Jean-Louis	13/01/2000	IP-AUT	LAFON	Membre Safety Committee essai clinique AOMI			
10221	GUILMOT	Jean-Louis	13/01/2000	(Autre)	LAFON	Fille			
10221	GUILMOT	Jean-Louis	01/01/1999	IP-AC	Schering SA une réunion annuelle 96, deux réunions annuelles 97				
10221	GUILMOT	Jean-Louis	01/01/1999	IP-CF	Rhône Poulenc Rohrer : 4 conférences en 97				
10221	GUILMOT	Jean-Louis	01/01/1999	IP-CF	Zénéca : une conférence en 97				
10221	GUILMOT	Jean-Louis	01/01/1999	IP-CF	Novartis : une conférence en 97				
10221	GUILMOT	Jean-Louis	01/01/1999	IP-CF	Sanofi : une conférence le 31 janvier 98				
10221	GUILMOT	Jean-Louis	01/01/1999	VB	Versement à l'ADERMI - Association pour la recherche et le Développement en médecine interne : Servier.		ADERMI		
10221	GUILMOT	Jean-Louis	01/01/1999	VB	Sigma Tau		ADERMI		
10221	GUILMOT	Jean-Louis	01/01/1999	VB	Bayer Diagnostics		ADERMI		
10221	GUILMOT	Jean-Louis	01/01/1999	PAR	LAFON	Fille - depuis le 1er novembre 1997			
10221	GUILMOT	Jean-Louis	01/01/1998	IP-AUT	Sanofi Choay				
10221	GUILMOT	Jean-Louis	01/01/1998	IP-AUT	Schering SA				
10221	GUILMOT	Jean-Louis	01/01/1998	IP-AUT	Sandoz				
10221	GUILMOT	Jean-Louis	01/01/1998	IP-AUT	Bellon				
10221	GUILMOT	Jean-Louis	01/01/1998	VB	Schering		Association pour développement et recherche en médecine interne		
10221	GUILMOT	Jean-Louis	01/01/1998	VB	Houdé		Association pour développement et recherche en médecine interne		
10221	GUILMOT	Jean-Louis	01/01/1998	VB	Sigma Tau		Association pour développement et recherche en médecine interne		
64260	GUYADER	Dominique	13/07/2010	EC-INV	IDERA	IMO 2125 (Inhibiteur du taux de proprioceptéur)	Investigateur principal	07/2009	
64260	GUYADER	Dominique	13/07/2010	EC-CO	PFIZER	PF-00868554	co-investigateur	07/2009	
64260	GUYADER	Dominique	13/07/2010	EC-CO	BOEHRINGER-INGELHEIM	BI 201335 NA	co-investigateur	09/2009	
64260	GUYADER	Dominique	13/07/2010	EC-CO	ROCHE	NEORECORMON	co-investigateur		
64260	GUYADER	Dominique	13/07/2010	RE-AUT	SERVIER	Membre du groupe d'expertise de l'Agomélatine	Rémunération personnelle	01/2006	
64260	GUYADER	Dominique	13/07/2010	IP-AC	BIOTRIAL	Conseil dans la réalisation d'études cliniques de phase I-II	Rémunération personnelle	01/2008	
64260	GUYADER	Dominique	13/07/2010	CF-INT	ROCHE	Réunions EPU post congrès	Rémunération personnelle	01/2005	
64260	GUYADER	Dominique	13/07/2010	CF-INT	SCHERING	Réunions EPU post congrès et intervention dans le cadre du projet ProspectH	Rémunération personnelle	01/2005	
64260	GUYADER	Dominique	13/07/2010	CF-INT	BMS	Réunions EPU	Rémunération personnelle	01/2009	
64260	GUYADER	Dominique	13/07/2010	CF-INT	GILEAD	Réunions EPU	Rémunération personnelle	01/2008	
64260	GUYADER	Dominique	13/07/2010	CF-AUD	ROCHE	AASLD (Boston)□□EASL (Milan)		01/2005	
64260	GUYADER	Dominique	13/07/2010	CF-AUD	SCHERING	EASL (Copenhague)□□AASLD (St Francisco)		01/2005	
64260	GUYADER	Dominique	13/07/2010	CF-AUD	BMS	APASL (Hong-Kong)		01/2009	
64260	GUYADER	Dominique	13/07/2010	CF-AUD	GILEAD	EASL (Milan)		01/2008	
64260	GUYADER	Dominique	13/07/2010	VB	ROCHE	Subvention pour Etude Epidémiologique	Association Fer et Foie		
64260	GUYADER	Dominique	13/07/2010	LD-AR	GSK	Board d'une étude clinique Elthrombopag + contrat de recherche clinique	Rémunération personnelle	01/2010	
64260	GUYADER	Dominique	17/04/2009	VB	ROCHE	Subvention pour Etude Epidémiologique	Association Fer et Foie		
64260	GUYADER	Dominique	17/04/2009	CF-AUD	GILEAD	EASL (Milan)		01/2008	
64260	GUYADER	Dominique	17/04/2009	CF-AUD	BMS	APASL (Hong-Kong)		01/2009	
64260	GUYADER	Dominique	17/04/2009	CF-AUD	SCHERING	EASL (Copenhague)□□AASLD (St Francisco)		01/2005	
64260	GUYADER	Dominique	17/04/2009	CF-AUD	ROCHE	AASLD (Boston)□□EASL (Milan)		01/2005	
64260	GUYADER	Dominique	17/04/2009	CF-INT	GILEAD	Réunions EPU	Rémunération personnelle	01/2008	
64260	GUYADER	Dominique	17/04/2009	CF-INT	BMS	Réunions EPU	Rémunération personnelle	01/2009	
64260	GUYADER	Dominique	17/04/2009	CF-INT	SCHERING	Réunions EPU post congrès et intervention dans le cadre du projet ProspectH	Rémunération personnelle	01/2005	
64260	GUYADER	Dominique	17/04/2009	CF-INT	ROCHE	Réunions EPU post congrès	Rémunération personnelle	01/2005	
64260	GUYADER	Dominique	17/04/2009	IP-AC	BIOTRIAL	Conseil dans la réalisation d'études cliniques de phase I-II	Rémunération personnelle	01/2008	
64260	GUYADER	Dominique	17/04/2009	RE-AUT	SERVIER	Membre du groupe d'expertise de l'Agomélatine	Rémunération personnelle	01/2006	
64260	GUYADER	Dominique	17/04/2009	EC-CO	ROCHE	NEORECORMON	co-investigateur		
64260	GUYADER	Dominique	17/04/2009	EC-INV	IDERA	IMO 2125	investigateur principal	07/2009	
64260	GUYADER	Dominique	17/04/2009	EC-CO	BOEHRINGER-INGELHEIM	BI 201335 NA	co-investigateur	09/2009	
64260	GUYADER	Dominique	17/04/2009	EC-CO	PFIZER	PF-00868554	co-investigateur	07/2009	
64260	GUYADER	Dominique	17/04/2009	EC-CO	SCHERING-PLOUGH	BOCEPREVIR	co-investigateur	09/2009	04/2010
64260	GUYADER	Dominique	04/12/2007	RE-AUT	SERVIER	Rapport Hepatotoxicité de l'Agomelatine	Rémunération personnelle	11/2007	02/2008
64260	GUYADER	Dominique	04/12/2007	EC-CO	INTERMUNE	ITMN191	co-investigateur	09/2007	09/2009
64260	GUYADER	Dominique	05/09/2006	EC-CO	SCHERING PLOUGH	Antiprotease SP	co-investigateur	01/2004	12/2005
64260	GUYADER	Dominique	05/09/2006	EC-CO	GILEAD	TDF/ FTC / ETV	co-investigateur	01/2006	12/2007
64260	GUYADER	Dominique	05/09/2006	EC-CO	ROCHE	Pegasys	co-investigateur	01/2005	12/2006
64260	GUYADER	Dominique	05/09/2006	RE-AUT	SERVIER	Mélatonine : expertise de cas cliniques d'hépato-toxicité	rémunération personnelle	01/2006	12/2006
64260	GUYADER	Dominique	05/09/2006	IP-AC	SCHERING PLOUGH	Expertise virus C en pratique quotidienne (projet PROSPECTH)	rémunération personnelle	01/2005	
64260	GUYADER	Dominique	05/09/2006	CF-INT	ROCHE	Symposium AFEF	Rémunération personnelle		
64260	GUYADER	Dominique	05/09/2006	CF-AUD	SCHERING PLOUGH	AASLD - AFEF - EASL		01/2006	12/2006
64260	GUYADER	Dominique	05/09/2006	CF-AUD	ROCHE	AASLD - AFEF - EASL		01/2005	12/2005
64260	GUYADER	Dominique	05/09/2006	VB	ROCHE	étude épidémiologique virus C	Association Fer et Foie	01/2004	12/2006
64260	GUYADER	Dominique	05/09/2006	VB	SCHERING PLOUGH	Observatoire Addiction virus C	Association Fer et Foie	01/2004	12/2006
10223	GUYOT	Jean-Claude	13/09/2002	IF	SARL OPTITAB (Compiègne)	Associé à hauteur de 10%			
10223	GUYOT	Jean-Claude	13/09/2002	IP-AC	GLAXO SMITHKLINE BEECHAM - LCO	Instrumentation de machines à comprimer			
10223	GUYOT	Jean-Claude	13/09/2002	IP-CF	ARCHIMEX - L'OREAL	Agglomération des poudres par compression			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10223	GUYOT	Jean-Claude	25/06/2001	IF	SARL OPTITAB - 26 rue Notre Dame du Bon Secours - 60200 Compiègne (sté créée le 12.09.2000)	Associé à hauteur de 10 % - Objet : conseil et formation pour optimisation des procédés de fabrication. Aucune répartition des bénéfices jusque là			
10223	GUYOT	Jean-Claude	25/06/2001	IP-AC	SOLVAY PHARMA, VETOQUINOL, PARKE DAVIS, SKYC PHARMA (Suisse), URIACH (Espagne)	Fabrication des comprimés ; conseil en formulation, instrumentation, validation des chaines de mesure			
10223	GUYOT	Jean-Claude	25/06/2001	IP-CF	RHODIA, SANOFI SYNTHELABO, L OREAL, VETOQUINOL, AVENTIS (Maroc)	Agglomération des poudres par compression : mécanisme de la formation des comprimés, évaluation aptitude à la compression, amélioration aptitude à la compression			
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	HOECHST MARION ROUSSEL				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	NOVARTIS				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	BEAUFOUR IPSEN				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	JOUVEINAL				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	SANOFI SA				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	LIPHA				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	SERVIER				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	VETOQUINOL				
10223	GUYOT	Jean-Claude	01/01/1999	IP-CF	institut de formation permanente Univ. Lille II				
10223	GUYOT	Jean-Claude	01/01/1999	IP-CF	Centre de perfectionnement des industries chimiques (ENSIC- NANCY)				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	JAGO PHARMA				
10223	GUYOT	Jean-Claude	01/01/1999	IP-AC	JAGO PHARMA				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Roussel Uclaf				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Nestlé				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Glaxo				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Dior				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	l'Oréal				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	LTM				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Jouveinal				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Roquette				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Sandoz				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Synthélabo				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Lipha				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Servier				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Roussel				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	UPSA				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Seppic				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Cassenne				
10223	GUYOT	Jean-Claude	01/01/1998	IP-AUT	Beecham				
10223	GUYOT	Jean-Claude	01/01/1998	VB	Roussel		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Beaufour		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Sanofi		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Synthélabo		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Sandoz		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Picot		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Roquette		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Lipha		Facturation par l'Adrinord de travaux à		
10223	GUYOT	Jean-Claude	01/01/1998	VB	Servier		Facturation par l'Adrinord de travaux à		
61238	HALIMI	Serge	08/01/2004	LD	ROCHE DIAGNOSTICS				
61238	HALIMI	Serge	08/01/2004	IP-EC	TAKEDA - SERVIER - AVENTIS	Essais cliniques			
61238	HALIMI	Serge	08/01/2004	IP-EC	GLAXO SMITHKLINE - ROCHE PHARMA	Essais cliniques			
61238	HALIMI	Serge	08/01/2004	IP-RE	AVENTIS	Board nouvelles molécules			
61238	HALIMI	Serge	08/01/2004	IP-AC	JANSSEN CILAG				
61238	HALIMI	Serge	08/01/2004	IP-AC	LILLY				
61238	HALIMI	Serge	08/01/2004	IP-CF	TOUS !				
61238	HALIMI	Serge	26/06/2003	LD	ROCHE DIAGNOSTICS				
61238	HALIMI	Serge	26/06/2003	IP-EC	GLAXO SMITHKLINE				
61238	HALIMI	Serge	26/06/2003	IP-EC	TAKEDA				
61238	HALIMI	Serge	26/06/2003	IP-EC	BAYER				
61238	HALIMI	Serge	26/06/2003	IP-RE	YAMANOUCHI				
62017	HANAIRE	Hélène	16/12/2009	LD-AR	SANOFI-AVENTIS	GROUPE D EXPERTS/ INSULINE (POURSUIVIES)	REMUNERATION INSTITUTION		
62017	HANAIRE	Hélène	16/12/2009	LD-AR	NOVO-NORDISK	GROUPE D'EXPERTS/INSULINE (POURSUIVIES)	REMUNERATION INSTITUTION		
62017	HANAIRE	Hélène	16/12/2009	LD-AR	MEDTRONIC	GROUPE D'EXPERTS/TECHNOLOGIES INNOVANTES (POURSUIVIES)	REMUNERATION INSTITUTION		
62017	HANAIRE	Hélène	16/12/2009	EC-INV	SANOFI-AVENTIS	RIMONABANT	IC	01/2006	12/2007
62017	HANAIRE	Hélène	16/12/2009	EC-INV	SANOFI-AVENTIS	LANTUS	IP	01/2006	12/2007
62017	HANAIRE	Hélène	16/12/2009	EC-INV	MEDTRONIC	PARADIGM RT	IP		12/2008
62017	HANAIRE	Hélène	16/12/2009	EC-INV	METACURE	TANTALUS	IP		12/2007
62017	HANAIRE	Hélène	16/12/2009	EC-INV	NOVONORDISK	LEVEMIR (EN COURS)	IP		
62017	HANAIRE	Hélène	16/12/2009	EC-INV	NOVONORDISK	LEVEMIR ET GROSSESSE (EN COURS)	IP		
62017	HANAIRE	Hélène	16/12/2009	EC-INV	SAFONI AVENTIS	GLULIZINE (EN COURS)	IP		
62017	HANAIRE	Hélène	16/12/2009	EC-INV	NOVONORDISK	INSULININE INHALEE			12/2008
62017	HANAIRE	Hélène	16/12/2009	EC-CO	LILLY	INSULINE INHALEE	COI		12/2008
62017	HANAIRE	Hélène	16/12/2009	EC-CO	LILLY	BYETTA	COI		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62017	HANAIRE	Hélène	16/12/2009	IP-AC	GSK	GROUPE DE REFLEXION GLITAZONES	AUCUNE REMUNERATION		
62017	HANAIRE	Hélène	16/12/2009	IP-AC	MSD	GROUPE DE REFLEXION GLIPTINES	AUCUNE REMUNERATION		
62017	HANAIRE	Hélène	16/12/2009	CF-INT	LILLY	JLD PARIS 2007, INSULINOTHERAPIE MODERNE DIABETE DE TYPE 2	REMUNERATION PERSONNELLE		
62017	HANAIRE	Hélène	16/12/2009	CF-INT	LILLY	JLD PARIS 2008-05-26, QUELLE TECHNIQUE POUR QUEL PATIENT?	REMUNERATION PERSONNELLE		
62017	HANAIRE	Hélène	16/12/2009	CF-INT	MEDTRONIC	PARIS 2006, ORGANISATION DU TRAITEMENT PAR POMPE A INSULINE.	REMUNERATION PERSONNELLE		
62017	HANAIRE	Hélène	16/12/2009	CF-AUD	ABBOTT	PARTICIPATION AU CONGRES DE L ALFEDIAM BRUXELLES		01/2008	12/2008
62017	HANAIRE	Hélène	16/12/2009	CF-AUD	SERVIER	PARTICIPATION AU CONGRES DE L EASD ROME		01/2008	12/2008
62017	HANAIRE	Hélène	16/12/2009	VB	NOVONORDISK	GIS : GROUPE D INTERETS SCIENTIFIQUES ; STRATEGIES THERAPEUTIQUES DU DIABETE;	CHU DE TOULOUSE	01/1996	12/2010
62017	HANAIRE	Hélène	16/12/2009	VB	LIFESCAN	GIS : GROUPE D INTERETS SCIENTIFIQUES ; STRATEGIES THERAPEUTIQUES DU DIABETE;	CHU DE TOULOUSE	01/1996	12/2010
62017	HANAIRE	Hélène	16/12/2009	VB	MEDTRONIC	RECHERCHES SUR LE TRAITEMENT PAR POMPE	ASSOCIATION GEDEC		12/2009
62017	HANAIRE	Hélène	27/05/2008	LD	SANOFI AVENTIS	Groupe d'experts/ Insuline	rémunération institution		
62017	HANAIRE	Hélène	27/05/2008	LD	NOVO NORDISK	Groupe d'experts/ Insuline	rémunération institution		
62017	HANAIRE	Hélène	27/05/2008	LD	MEDTRONIC	Groupe d'experts/ Technologies innovantes	rémunération institution		
62017	HANAIRE	Hélène	27/05/2008	EC-INV	SANOFI AVENTIS	Rimonabant	investigateur coordonnateur	01/2006	12/2007
62017	HANAIRE	Hélène	27/05/2008	EC-INV	SANOFI AVENTIS	LANTUS	investigateur principal	01/2006	12/2007
62017	HANAIRE	Hélène	27/05/2008	EC-INV	MEDTRONIC	Paradigm RT	investigateur principal		12/2008
62017	HANAIRE	Hélène	27/05/2008	EC-INV	METACURE	TANTALUS	investigateur principal		12/2007
62017	HANAIRE	Hélène	27/05/2008	EC-INV	NOVO NORDISK	Levemir (en cours)	investigateur principal		
62017	HANAIRE	Hélène	27/05/2008	EC-INV	NOVO NORDISK	Levemir et grossesse (en cours)	investigateur principal		
62017	HANAIRE	Hélène	27/05/2008	EC-INV	SANOFI AVENTIS	Glulizine (en cours)	investigateur principal		
62017	HANAIRE	Hélène	27/05/2008	EC-INV	NOVO NORDISK	Insuline inhalée			12/2008
62017	HANAIRE	Hélène	27/05/2008	EC-CO	LILLY	Insuline inhalée	co-investigateur		12/2008
62017	HANAIRE	Hélène	27/05/2008	EC-CO	LILLY	BYETTA	co-investigateur		12/2008
62017	HANAIRE	Hélène	27/05/2008	IP-AC	GSK	Groupe de reflexion glitazones	aucune rémunération		
62017	HANAIRE	Hélène	27/05/2008	IP-AC	MSD	Groupe de reflexion Gliptines	aucune rémunération		
62017	HANAIRE	Hélène	27/05/2008	IP-CF	LILLY	JLD - Insulinotherapie moderne diabète de type 2 - Paris	rémunération personnelle	01/2007	12/2007
62017	HANAIRE	Hélène	27/05/2008	IP-CF	LILLY	JLD Paris - Quelle technique pour quel patient ?	rémunération personnelle	05/2008	05/2008
62017	HANAIRE	Hélène	27/05/2008	IP-CF	MEDTRONIC	Organisation du traitement par pompe insuline - Paris	Rémunération personnelle	01/2006	12/2006
62017	HANAIRE	Hélène	27/05/2008	CF-INT	ABBOTT	Participation au congrès de l'ALFEDIAM - Bruxelles		01/2008	12/2008
62017	HANAIRE	Hélène	27/05/2008	CF-INT	SERVIER	Participation au congrès de l'EASD - Rome		01/2008	12/2008
62017	HANAIRE	Hélène	27/05/2008	VB	NOVONORDISK - LIFESCAN	GIS : Groupe d'interêts scientifiques : stratégies thérapeutiques du diabète	CHU Toulouse	01/1996	12/2010
62017	HANAIRE	Hélène	27/05/2008	VB	MEDTRONIC	Recherches sur le traitement par pompe	Association GEDEC		12/2009
62017	HANAIRE	Hélène	11/10/2006	LD-AR	NOVONORDISK	Board diabète de type 1 " changing diabetes"	rémunération versée à une institution	01/2002	
62017	HANAIRE	Hélène	11/10/2006	LD-AR	SANOFI AVENTIS	Groupe d'experts " Insuline 7 "	rémunération partagée personnelle/institution	01/2003	
62017	HANAIRE	Hélène	11/10/2006	EC-INV	ASTRA ZENECA		investigateur coordonnateur	01/2005	12/2006
62017	HANAIRE	Hélène	11/10/2006	EC-INV	SANOFI AVENTIS	Rimonabant	investigateur coordonnateur	01/2006	
62017	HANAIRE	Hélène	11/10/2006	EC-CO	MEDTRONIC	Pompe injectable insuline	Co-investigateur		12/2006
62017	HANAIRE	Hélène	11/10/2006	EC-CO	NOVONORDISK	Insuline inhalée (en cours)	co-investigateur	01/2006	
62017	HANAIRE	Hélène	10/03/2003	VB	MINIMED - MEDTRONIC	Association Gedic : élaboration et suivi d'une base de données en Midi Pyrénées			
62017	HANAIRE	Hélène	10/03/2003	VB	NOVO-NORDISK	Association ADAC : Participation à un board sur le diabète			
62017	HANAIRE	Hélène	10/03/2003	VB	LILLY, AVENTIS, NOVO, LIFESCAN, BAYER, DISTRONIC	Association ADAC: activité de formation, recherche, conseil, expertises...			
62017	HANAIRE	Hélène	10/03/2003	VB	NOVONORDISK et LIFESCAN	CHU Toulouse. Partenariat dans un GIS. Etude des pratiques thérapeutiques dans le diabète de type 2			
10227	HAZEBROUCQ	Georges	07/07/2010	PAR	AIR LIQUIDE SANTé INTEZRNATIONAL	médecin spécialiste thérapie inhalée	frère	02/2009	
10227	HAZEBROUCQ	Georges	07/07/2010	LD-ODE	LABORATOIRE EXELGYN	pharmacien responsable intérimaire	consultant à temps partiel	09/2006	12/2009
10227	HAZEBROUCQ	Georges	07/07/2010	LD-ODE	LABORATOIRE EXELGYN	, pharmacien responsable intérimaire	consultant à temps partiel	09/2006	12/2009
10227	HAZEBROUCQ	Georges	07/07/2010	LD-AR	LABORATOIRE EXELGYN	Pharmacien responsable intérimaire (statut de consultant à temps partiel)	Rémunération personnelle	09/2006	12/2009
62992	HAZEBROUCQ	Vincent	17/10/2003	LD	MINISTERE EDUCATION NATIONALE ET RECHERCHE	Chargé de mission DT AS			
62992	HAZEBROUCQ	Vincent	17/10/2003	IP-RE	MINISTERE DELEGUE A LA RECHERCHE	Télémédecine			
62992	HAZEBROUCQ	Vincent	17/10/2003	PAR	SERVIER	Oncle			
62992	HAZEBROUCQ	Vincent	17/10/2003	(Autre)		Réalisation d'expertises judiciaires pour les tribunaux pouvant éventuellement impliquer une entreprise de la liste ci-dessus			
10227	HAZEBROUCQ	Georges	29/12/1999	IP-EC	LOUIS LAFON	expertise pharmaceutique (2)			
10227	HAZEBROUCQ	Georges	29/12/1999	IP-EC	B. BRAUN	expertise pharmaceutique (1)			
10227	HAZEBROUCQ	Georges	29/12/1999	IP-EC	SCHERING PLOUGH	expertise pharmaceutique (1)			
10227	HAZEBROUCQ	Georges	29/12/1999	IP-CF	SANOFI	conférence			
10227	HAZEBROUCQ	Georges	29/12/1999	VB	SERVIER	conférence : Association			
10227	HAZEBROUCQ	Georges	29/12/1999	PAR	SERVIER	frère			
10227	HAZEBROUCQ	Georges	29/12/1999	(Autre)	SCHERING PLOUGH	invitation à un congrès aux USA			
10227	HAZEBROUCQ	Georges	01/01/1999	IP-RE	SCHERING-PLOUGH				
10227	HAZEBROUCQ	Georges	01/01/1999	IP-RE	BRAUN				
10227	HAZEBROUCQ	Georges	01/01/1999	IP-RE	GAMBRO				
10227	HAZEBROUCQ	Georges	01/01/1999	IP-RE	L. LAFON				
10227	HAZEBROUCQ	Georges	01/01/1999	IP-AUT	CONGRèS à L'éTRANGER L. LAFON				
10227	HAZEBROUCQ	Georges	01/01/1999	IP-AUT	CONGRèS à L'éTRANGER SCHERING-PLOUGH				
10227	HAZEBROUCQ	Georges	01/01/1999	VB	VIA UNE ASSOCIATION, SOCIéTé D'éTUDES ODONTOPHARMACOLOGIQUES : AGA		Société d'études odontopharmacologiques		
10227	HAZEBROUCQ	Georges	01/01/1999	VB	SERVIER		Société d'études odontopharmacologiques		
10227	HAZEBROUCQ	Georges	01/01/1999	VB	JOURNEES PHARMACEUTIQUES MSD CHIBRET				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	Schering-Plough				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	Braun				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	Gambro				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	Lafon				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	Aga				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	SKB				
10227	HAZEBROUCQ	Georges	01/01/1998	IP-AUT	Roche				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10227	HAZEBROUCQ	Georges	01/01/1998	VB	Servier	Action de formation pour une association			
10227	HAZEBROUCQ	Georges	01/01/1998	VB	Société d'Etude des Thérapeutiques Odonto Pharmacologique				
10227	HAZEBROUCQ	Georges	01/01/1998	PAR	Frère chez Servier				
63004	HENRY	Patrick	09/10/2003	IP-EC	MERCK SHARP & DOHME				
63004	HENRY	Patrick	09/10/2003	IP-EC	ORION				
63004	HENRY	Patrick	09/10/2003	IP-EC	SHERING PLOUGH				
63004	HENRY	Patrick	09/10/2003	IP-AC	ABBOTT				
63004	HENRY	Patrick	09/10/2003	IP-AC	MERCK - LIPHA				
63004	HENRY	Patrick	09/10/2003	IP-CF	PFIZER				
63004	HENRY	Patrick	09/10/2003	IP-CF	SERVIER				
63004	HENRY	Patrick	09/10/2003	IP-CF	ASTRA ZENECA				
63004	HENRY	Patrick	09/10/2003	IP-CF	GLAXO				
63004	HENRY	Patrick	09/10/2003	IP-CF	AVENTIS				
10229	HERSON	Serge	24/09/2007	LD-AR	ASSOCIATION FRANCAISE CONTRE LA MYOPATHIE	Conseil scientifique, groupe innovations thérapeutiques (en cours)	aucune rémunération	01/1993	
10229	HERSON	Serge	24/09/2007	EC-INV	TRANSGENE	Thérapie génique par un plasmide codant la dystrophine de la Myopathie de Duchenne	Investigateur principal	01/2003	12/2005
10229	HERSON	Serge	24/09/2007	EC-INV	GENETHON	Thérapie génique par vecteur AAV1-Gamma sarcoglycan dans la sarcoglycanopathie (LGMD 2C)	investigateur principal	12/2006	
10229	HERSON	Serge	24/09/2007	EC-CO	ROCHE	Rituximab for the teatment of refractory inflammatory myopathies and myasthenia gravis	co-investigateur	09/2007	
10229	HERSON	Serge	24/09/2007	EC-CO	GENZYME	Myozyme au cours des Myopathies par déficit en maltase acide chez l'adulte	co-investigateur	10/2005	
10229	HERSON	Serge	24/09/2007	RE-DE	ANRS	président du comité indépendant des essais vaccinaux	Aucune rémunération	01/2005	
10229	HERSON	Serge	24/09/2007	RE-DE	AGEPS-APHP	Président du comité de développement scientifique de l'AGEPS		01/2003	
10229	HERSON	Serge	24/09/2007	RE-AUT	PGR X	Expert maladies auto immunes	Aucune rémunération	05/2007	
10229	HERSON	Serge	03/09/2004	Néant					
10229	HERSON	Serge	01/01/1999	IP-EC	Bristol (D4T 2 doses, Altis)				
10229	HERSON	Serge	01/01/1999	IP-EC	Roche				
10229	HERSON	Serge	01/01/1999	IP-AC	Amgen				
10229	HERSON	Serge	01/01/1999	IP-AC	Membre de l'équipe du service : Bioderma				
10229	HERSON	Serge	01/01/1999	IP-AC	Janssen				
10229	HERSON	Serge	01/01/1999	IP-AC	Cilag				
10229	HERSON	Serge	01/01/1999	IP-AC	Labcatal				
10229	HERSON	Serge	01/01/1999	IP-AC	Lipha				
10229	HERSON	Serge	01/01/1999	IP-AC	Lederlé				
10229	HERSON	Serge	01/01/1999	IP-AC	Liphaderm				
10229	HERSON	Serge	01/01/1999	IP-AC	Negma				
10229	HERSON	Serge	01/01/1999	IP-AC	Pierre Fabre				
10229	HERSON	Serge	01/01/1999	IP-AC	Roussel				
10229	HERSON	Serge	01/01/1999	IP-AC	Servier				
10229	HERSON	Serge	01/01/1999	IP-AC	Smith Kline Beecham				
10229	HERSON	Serge	01/01/1999	IP-AC	Spécia				
10229	HERSON	Serge	01/01/1999	IP-CF	Bristol				
10229	HERSON	Serge	01/01/1999	IP-CF	Roche				
10229	HERSON	Serge	01/01/1999	IP-CF	Lederle				
10229	HERSON	Serge	01/01/1999	IP-AUT	Abonnements : Bristol				
10229	HERSON	Serge	01/01/1999	IP-AUT	Janssen				
10229	HERSON	Serge	01/01/1999	IP-AUT	Sanofi				
10229	HERSON	Serge	01/01/1999	IP-CF	Roche				
10229	HERSON	Serge	01/01/1999	VB	Glaxo-Roche				
61084	HERVE	Allain	30/10/1999	IP-EC	LILLY France	Un essai Pergolide (Parkinson)			
61084	HERVE	Allain	30/10/1999	IP-EC	SYNTHELABO	Un essai multicentrique (TIAGE)			
61084	HERVE	Allain	30/10/1999	IP-EC	SCHERING	Un essai Lisuride (Parkinson)			
61084	HERVE	Allain	30/10/1999	IP-EC	ZENECA	Migraine Pharmacoépidémiologie			
61084	HERVE	Allain	30/10/1999	IP-AC	GLAXO-WELLCOME	Observatoire KOEMIE (Rennes) - Migraine à Citroën			
61084	HERVE	Allain	30/10/1999	IP-CF	SERVIER	Conférence sur l'ischémie cérébrale et le Parkinson			
61084	HERVE	Allain	30/10/1999	IP-CF	NOVARTIS	Conférence sur les ICOMT			
63870	HITTINGER	Luc	29/08/2005	IP-EC	BMS- SANOFI AVENTIS	Travaux préclinique et de phase I			
63870	HITTINGER	Luc	29/08/2005	IP-AC	PFIZER	Développement de produit			
63870	HITTINGER	Luc	29/08/2005	IP-CF	BMS, SANOFI AVENTIS,PFIZER, SERVIER, ASTRA ZENECA	Insuffisance cardiaque			
60031	HOUIN	Georges	28/04/2010	RE-DE	KEOCYT	Essi d'une forme pédiatrique de cyclophosphamide et d'une seconde de Temozolomide	Rémunération personnelle	01/2009	
60031	HOUIN	Georges	09/03/2009	RE-DE	KEOCYT	Essai d'une forme pédiatrique de cyclophosphamide et d'une seconde de Temozolomide	Rémunération personnelle	01/2009	
60031	HOUIN	Georges	30/09/2008	CF-INT	MYLAN	Alger: Essais de Bioéquivalence	Rémunération personnelle		
60031	HOUIN	Georges	13/07/2007	VB	ASSOCIATION JURIPHARM	Subvention des laboratoires SERVIER, AVENTIS, FABRE (aux alentours de 1990)		01/1990	
60031	HOUIN	Georges	13/07/2007	IP-AC	RANBAXY	Contrat de collaboration	Rémunération personnelle	01/2005	
60031	HOUIN	Georges	13/07/2007	IP-AC	IDD (PARIS)	Développement d'un dossier	Rémunération personnelle	01/2000	
60031	HOUIN	Georges	13/07/2007	IP-AC	GUERBET, IDD, IVAX, MERCK GéNéRIQUES, RIVOPHARM, SANOFI AVENTIS, SERVIER, SUBSTIPHARM, TROPHOS, ARROW GENERIQUE, ESTEVE, EXONHIT, FERRING, GALENIC		Rémunération personnelle		
60031	HOUIN	Georges	13/07/2007	RE-DE	GUERBET, IDD, IVAX, MERCK GéNéRIQUES, RIVOPHARM, SANOFI AVENTIS, SERVIER, SUBSTIPHARM, TROPHOS, ARROW GENERIQUE, ESTEVE, EXONHIT, FERRING, GALENIC				
60031	HOUIN	Georges	13/07/2007	LD-AR	ADME BIOANALYSES	depuis 1990	Consultant régulier	01/1990	
60031	HOUIN	Georges	12/05/2006	IP-AC	RANBAXY	Contrat de collaboration	Rémunération personnelle	01/2005	
60031	HOUIN	Georges	12/05/2006	VB	ASSOCIATION JURIPHARM	Subvention des laboratoires SERVIER, AVENTIS, FABRE (aux alentours de 1990)		01/1990	
60031	HOUIN	Georges	12/05/2006	IP-AC	IREX	Interventions ponctuelles	Rémunération personnelle	01/2000	04/2004
60031	HOUIN	Georges	12/05/2006	IP-AC	IDD (PARIS)	Développement d'un dossier	Rémunération personnelle	01/2000	
60031	HOUIN	Georges	12/05/2006	IP-AC	GUERBET, IDD, IVAX, MERCK GéNéRIQUES, RIVOPHARM, SANOFI AVENTIS, SERVIER, SUBSTIPHARM, TROPHOS, ARROW GENERIQUE, ESTEVE, EXONHIT, FERRING, GALENIC		Rémunération personnelle		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60031	HOUIN	Georges	12/05/2006	RE-DE	GUERBET, IDD, IVAX, MERCK GéNéRIQUES, RIVOPHARM, SANOFI AVENTIS, SERVIER, SUBSTIPHARM, TROPHOS, ARROW GENERIQUE, ESTEVE, EXONHIT, FERRING, GALENIC				
60031	HOUIN	Georges	12/05/2006	LD-AR	THERAMEX	Monaco	Consultant régulier	01/2000	01/2006
60031	HOUIN	Georges	12/05/2006	LD-AR	ADME BIOANALYSES	depuis 1990	Consultant régulier	01/1990	
60031	HOUIN	Georges	22/04/2005	IP-AC	IDD (PARIS)	Développement d'un dossier	Rémunération personnelle		
60031	HOUIN	Georges	22/04/2005	IP-AC	IREX	Interventions ponctuelles	Rémunération personnelle		
60031	HOUIN	Georges	22/04/2005	IP-AC	RIBAXY	Contrat de collaboration	Rémunération personnelle		
60031	HOUIN	Georges	11/02/2005	LD	ADME BIOANALYSES	depuis 1990	Consultant régulier	01/1990	
60031	HOUIN	Georges	11/02/2005	LD	FOURNIER	Dijon	Consultant régulier	01/2001	12/2001
60031	HOUIN	Georges	11/02/2005	LD	THERAMEX	Monaco	Consultant régulier	01/2000	
60031	HOUIN	Georges	11/02/2005	LD	ZYDUS	Aubervilliers	Consultant régulier	01/2004	12/2004
60031	HOUIN	Georges	11/02/2005	LD	PIERRE FABRE	Castres (aux alentours de 1995)		01/1995	12/1995
60031	HOUIN	Georges	11/02/2005	IP-AC	GUERBET, IDD, IVAX, MERCK GENERIQUES, RIVOPHARM, SANOFI AVENTIS, SERVIER, SUBSTIPHARM, TROPHOS, ARROW GENERIQUE, ESTEVE, EXONHIT, FERRING, GALENIC		Rémunération personnelle		
60031	HOUIN	Georges	11/02/2005	VB	ASSOCIATION JURIPHARM	Subvention des laboratoires SERVIER,ROCHE, AVENTIS, FABRE (aux alentours de 1990)		01/1990	
60031	HOUIN	Georges	11/02/2005	IP-RE	GUERBET, IDD, IVAX, MERCK GENERIQUES, RIVOPHARM, SANOFI AVENTIS, SERVIER, SUBSTIPHARM, TROPHOS, ARROW GENERIQUE, ESTEVE, EXONHIT, FERRING, GALENIC				
60031	HOUIN	Georges	02/07/2004	IP-EC	SERVIER	Etudes absorption animales, contrat faculté			
60031	HOUIN	Georges	02/07/2004	IP-EC	EXONHIT	Participation à un DSMB (2003-2004)			
60031	HOUIN	Georges	02/07/2004	IP-RE	ARROW, GENERIQUES	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	ESTEVE (Espagne)	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	GALENIX	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	GUERBET	Expertises en pharmacocinétique			
60031	HOUIN	Georges	02/07/2004	IP-RE	IDD	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	IREX	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	MERCK, GENERIQUES	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	RIBOPHARMA	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-RE	SUBSTIPHARM	Expertises en pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	IP-CF	SERVIER	Pharmacocinétique clinique			
60031	HOUIN	Georges	02/07/2004	VB	SERVIER	Association NEB (support d'une thèse)			
60031	HOUIN	Georges	20/08/2003	IP-EC	EXORHIT	Membre DSMB, étude pentoxifylline			
60031	HOUIN	Georges	20/08/2003	IP-RE	ARROW, ESTEVE, GALENIX, IDD, IREX	Rapports pharmacocinétiques			
60031	HOUIN	Georges	20/08/2003	IP-RE	MERCK GENERIQUES, RIVOPHARM, SUBSTIPHARM	Rapports pharmacocinétiques			
60031	HOUIN	Georges	20/08/2003	IP-AC	FOURNIER	Réunions sur dossiers pharmacocinétiques			
60031	HOUIN	Georges	20/08/2003	IP-AC	THERAMEX	Réunions sur dossiers pharmacocinétiques			
60031	HOUIN	Georges	20/08/2003	IP-AC	FABRE	Réunions sur dossiers pharmacocinétiques			
60031	HOUIN	Georges	20/08/2003	VB	AVENTIS	Association Juripharm			
60031	HOUIN	Georges	20/08/2003	VB	FABRE	Association Juripharm			
60031	HOUIN	Georges	03/07/2000	IP-EC	PIERRE FABRE				
60031	HOUIN	Georges	03/07/2000	IP-EC	SERVIER				
60031	HOUIN	Georges	03/07/2000	IP-RE	BAYER				
60031	HOUIN	Georges	03/07/2000	IP-RE	MERCK GENERIQUES				
60031	HOUIN	Georges	03/07/2000	IP-RE	SUBSTIPHARM				
60031	HOUIN	Georges	03/07/2000	IP-RE	THERAMEX				
60031	HOUIN	Georges	03/07/2000	IP-AC	CHIESI				
60031	HOUIN	Georges	03/07/2000	IP-AC	PIERRE FABRE				
60031	HOUIN	Georges	03/07/2000	IP-AC	FOURNIER				
60031	HOUIN	Georges	03/07/2000	IP-AC	GUERBET				
60031	HOUIN	Georges	03/07/2000	IP-AC	THERAMEX				
60031	HOUIN	Georges	03/07/2000	IP-AC	UPSA-BMS				
60031	HOUIN	Georges	03/07/2000	VB	PIERRE FABRE				
60031	HOUIN	Georges	03/07/2000	VB	AVENTIS				
60031	HOUIN	Georges	03/07/2000	VB	SERVIER				
61529	HUET DE BAROCHEZ	Bruno	23/11/2009	LD-ODE	SERVIER INDUSTRIE	Employé	CDI	01/2009	
61529	HUET DE BAROCHEZ	Bruno	23/11/2009	LD-ODE	SERVIER INDUSTRIE	Employé	CDI	01/2009	
61529	HUET DE BAROCHEZ	Bruno	25/03/2009	LD-ODE	SERVIER INDUSTRIE	Employé	CDI	01/2004	12/2008
61529	HUET DE BAROCHEZ	Bruno	10/02/2008	LD-ODE	SERVIER INDUSTRIE	Employé	CDI	01/2004	
61529	HUET DE BAROCHEZ	Bruno	21/08/2006	LD-ODE	SERVIER INDUSTRIE	Employé	CDI	01/2004	
61529	HUET DE BAROCHEZ	Bruno	02/05/2005	LD-AR	SERVIER INDUSTRIE	CDI		01/2003	
61529	HUET DE BAROCHEZ	Bruno	08/12/2004	LD	SERVIER INDUSTRIE	CDI			
61529	HUET DE BAROCHEZ	Bruno	18/12/2003	LD	SERVIER INDUSTRIE	Salarié			
61529	HUET DE BAROCHEZ	Bruno	08/09/2002	LD	TECHNOLOGIE SERVIER	CDI			
61529	HUET DE BAROCHEZ	Bruno	23/10/2001	LD	TECHNOLOGIE SERVIER	CDI			
64322	HULOT	Jean-Sébastien	02/10/2010	CF-AUD	SERVIER	ESC Heart Failure 2010 Berlin		05/2010	06/2010
64322	HULOT	Jean-Sébastien	02/10/2010	CF-AUD	ELI LILLY	ESC 2010 Stockholm		08/2010	09/2010
64322	HULOT	Jean-Sébastien	02/10/2010	CF-INT	ELI LILLY	Urgencos 2010/ Paris / Nouveaux anti-plaquettaires	Rémunération personnelle		
64322	HULOT	Jean-Sébastien	02/10/2010	IP-AC	SANOFI AVENTIS	Conseil Pharmacocinétique	Aucune rémunération	05/2010	05/2010
64322	HULOT	Jean-Sébastien	02/10/2010	IP-AC	BIOTRONIK	Mise en place étude pharmacogénétique	Rémunération personnelle	11/2009	
64322	HULOT	Jean-Sébastien	02/10/2010	RE-DE	BAYER	Nouvelle aspirine gastro-résistante	Rémunération personnelle	09/2010	09/2010
64322	HULOT	Jean-Sébastien	02/10/2010	EC-CO	NOVARTIS	cuto Parité	expérimenteteur non principal	06/2010	06/2010
64322	HULOT	Jean-Sébastien	02/10/2010	EC-CO	BIOTRONIK	Tests génétiques	co-investigateur	05/2010	
64322	HULOT	Jean-Sébastien	02/10/2010	EC-INV	MEDCO HEALTH SOLUTIONS	Etude interaction clopidogrel/prasugrel et IPP	Investigateur principal	08/2010	
64322	HULOT	Jean-Sébastien	04/12/2007	EC-CO	SOCIETE FRANCAISE DE CARDIOLOGIE	essai clinique / Enoxaparine	co-investigateur	01/2007	01/2008
64322	HULOT	Jean-Sébastien	26/10/2006	EC-INV	AP-HP	essai clinique / Méthotrexate	investigateur principal	07/2003	10/2005
64322	HULOT	Jean-Sébastien	26/10/2006	EC-INV	AP-HP	essai clinique / Clopidogrel	investigateur principal	12/2006	08/2007
64322	HULOT	Jean-Sébastien	26/10/2006	EC-INV	GILEAD SCIENCES	étude pharmacologique / Ténofovir	responsable scientifique	08/2004	01/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64322	HULOT	Jean-Sébastien	26/10/2006	EC-CO	SOCIETE FRANCAISE DE CARDIOLOGIE	essai clinique / Enoxaparine	co-investigateur	01/2007	01/2008
64322	HULOT	Jean-Sébastien	26/10/2006	EC-CO	AP-HP	essai clinique : Venlafaxine	responsable étude pharmacologique	08/2004	08/2007
64322	HULOT	Jean-Sébastien	26/10/2006	EC-CO	GERCOR	essai clinique / Oxaliplatine	responsable étude pharmacologique	08/2005	08/2007
64322	HULOT	Jean-Sébastien	26/10/2006	RE-DE	SPACECODE	étude stabilité pharmacologique Tacrolimus	rémunération institution	11/2005	01/2006
64322	HULOT	Jean-Sébastien	26/10/2006	IP-AC	SANOFI AVENTIS	groupe experts, Etats généraux de la thrombose / Enoxaparine	rémunération personnelle	09/2004	01/2007
64322	HULOT	Jean-Sébastien	26/10/2006	CF-INT	ASTRA-ZENECA	Paris / congrès médicaux / pharmacologie des statines / Rosuvastatine	rémunération personnelle	01/2005	12/2006
64322	HULOT	Jean-Sébastien	26/10/2006	CF-INT	B.M.S	Paris / congrès médicaux / lecture critique d'un article médical / pas de produit en particulier	rémunération personnelle	01/2005	12/2006
64322	HULOT	Jean-Sébastien	26/10/2006	CF-AUD	B.M.S	Congrès European Society of Cardiology / Barcelone		09/2006	09/2006
64322	HULOT	Jean-Sébastien	26/10/2006	IP-AUT	UNAFORMEC	Formation Médicale Continue / médicaments et sujets âgés		06/2006	06/2006
60744	HUMBERT	Philippe	28/04/2010	IF	SKINEXIGENCES	Parts sociales	5000€ ou 5% du capital	01/2007	
60744	HUMBERT	Philippe	28/04/2010	IF	BIOEXIGENCE	Parts sociales	5000€ ou 5% du capital	01/2006	
60744	HUMBERT	Philippe	28/04/2010	IF	DERMATERRA	Parts sociales	5000€ ou 5% du capital	01/2000	
60744	HUMBERT	Philippe	28/04/2010	LD-AR	LA ROCHE POSAY	Conseil scientifique	rémunération personnelle	01/2004	
60744	HUMBERT	Philippe	28/04/2010	LD-AR	MEDA PHARMA	Conseil scientifique	rémunération personnelle	01/2008	
60744	HUMBERT	Philippe	28/04/2010	LD-AR	YVES ROCHER	Conseil scientifique	rémunération personnelle	01/2000	
60744	HUMBERT	Philippe	28/04/2010	EC-INV	GENEVRIER		investigateur	01/2009	
60744	HUMBERT	Philippe	28/04/2010	CF-INT	BAILLEUL	Congrès - orateur	rémunération personnelle	01/2008	12/2009
60744	HUMBERT	Philippe	28/04/2010	CF-INT	NOREVA	Conférence de presse	rémunération personnelle	01/2010	12/2010
60744	HUMBERT	Philippe	28/04/2010	CF-INT	SANOFI	Intervenant		01/2010	12/2010
60744	HUMBERT	Philippe	30/09/2008	IP-AC	EXPANSCIENCE	conseil scientifique	Rémunération personnelle	01/2005	
60744	HUMBERT	Philippe	30/09/2008	IP-AC	WYETH	conseil scientifique	Rémunération personnelle	01/2008	
60744	HUMBERT	Philippe	30/09/2008	IP-AC	YVES ROCHER	cosmétovigilance	Rémunération personnelle	01/2008	
60744	HUMBERT	Philippe	30/09/2008	IP-AC	LA ROCHE POSAY	conseil scientifique	Rémunération personnelle	01/2008	
60744	HUMBERT	Philippe	30/09/2008	EC-INV	IDENOV	essais cliniques/cosmétiques	investigateur principal	01/2005	
60744	HUMBERT	Philippe	30/09/2008	EC-INV	CHANEL	essais cliniques/cosmétiques	investigateur principal	01/2008	
60744	HUMBERT	Philippe	30/09/2008	EC-INV	L'OREAL	essais cliniques/cosmétiques	investigateur principal	01/2008	
60744	HUMBERT	Philippe	30/09/2008	EC-INV	BAILLEUL	essais cliniques/ médicaments	investigateur principal	01/2008	
60744	HUMBERT	Philippe	09/12/2007	IF	DERMATICA	capitaux	>=5000 € ou >=5% du capital	10/2003	
60744	HUMBERT	Philippe	15/09/2006	LD-AR	LABORATOIRES YVES ROCHER	Consultant en cosmétovigilance	rémunération personnelle	01/2000	
60744	HUMBERT	Philippe	15/09/2006	LD-AR	LABORATOIRES LA ROCHE POSAY	Groupe d'experts scientifiques	rémunération personnelle / institution	01/2005	
60744	HUMBERT	Philippe	15/09/2006	LD-AR	LABORATOIRE WYETH	Conseil scientifique	rémunération personnelle	01/2004	
60744	HUMBERT	Philippe	15/09/2006	LD-AR	LABORATOIRE SHIRE	Conseil scientifique	rémunération personnelle	01/2004	03/2007
60744	HUMBERT	Philippe	15/09/2006	EC-INV	GALDERMA	Essais cliniques	investigateur principal	01/2006	
60744	HUMBERT	Philippe	15/09/2006	EC-INV	LA ROCHE POSAY	Essais cliniques	investigateur principal	01/1998	
60744	HUMBERT	Philippe	15/09/2006	EC-INV	MERCK MEDICATION FAMILIALE	Essais cliniques	investigateur principal	01/2003	
60744	HUMBERT	Philippe	15/09/2006	EC-CO	SERONO	Biothérapies		01/2003	
60744	HUMBERT	Philippe	15/09/2006	EC-CO	UCB PHARMA	Biothérapies		01/2005	
60744	HUMBERT	Philippe	15/09/2006	EC-CO	WYETH	Biothérapies		01/2003	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	GALERMA	Essais cliniques	rémunération personnelle	01/2006	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	LA ROCHE POSAY	Essais cliniques	rémunération personnelle	01/1998	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	MERCK MEDICATION FAMILIALE	Essais cliniques	rémunération personnelle	01/2003	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	LABORATOIRES YVES ROCHER	Consultant en cosmétovigilance	rémunération personnelle	01/2000	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	LABORATOIRES LA ROCHE POSAY	Groupe d'experts scientifiques	rémunération personnelle	01/2005	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	LABORATOIRE WYETH	Conseil scientifique	rémunération personnelle	01/2004	
60744	HUMBERT	Philippe	15/09/2006	IP-AC	LABORATOIRE SHIRE	Conseil scientifique	rémunération personnelle	01/2004	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	LABORATOIRES YVES ROCHER	Consultant en cosmétovigilance	rémunération personnelle	01/2000	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	LABORATOIRES LA ROCHE POSAY	groupe d'experts scientifiques	rémunération personnelle	01/2005	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	LABORATOIRE WYETH	Conseil scientifique	rémunération personnelle	01/2004	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	LABORATOIRE SHIRE	Conseil scientifique	rémunération personnelle	01/2004	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	GALDERMA	Essais cliniques	rémunération personnelle	01/2006	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	LA ROCHE POSAY	Essais cliniques	rémunération personnelle	01/1998	
60744	HUMBERT	Philippe	15/09/2006	CF-INT	MERCK MEDICATION FAMILIALE	Essais cliniques	rémunération personnelle	01/2003	
60744	HUMBERT	Philippe	25/02/2006	VB	INTERUNEC	Toutes les sociétés suscitées, association 1901 partenaire de l'université			
60744	HUMBERT	Philippe	25/02/2006	IP-AC	GENEVRIER - MERCK MEDICATION FAM - LABORATOIRE SHIRE	Conseil scientifique			
60744	HUMBERT	Philippe	25/02/2006	IP-AC	YVES ROCHER - COSMETIQUE ACTIVE - GALDERMA	Conseil scientifique			
60744	HUMBERT	Philippe	25/02/2006	IP-EC	L'OREAL - INNEOV - EXPANSCIENCE - SERONO - WYETH				
60744	HUMBERT	Philippe	27/01/2005	IP-EC	L'OREAL - INNEOV - EXPANSCIENCE - SERONO - WYETH				
60744	HUMBERT	Philippe	27/01/2005	IP-AC	YVES ROCHER - COSMETIQUE ACTIVE - GALDERMA	Conseil scientifique			
60744	HUMBERT	Philippe	27/01/2005	IP-AC	GENEVRIER - MERCK MEDICATION FAM - LABORATOIRE SHIRE	Conseil scientifique			
60744	HUMBERT	Philippe	27/01/2005	VB	INTERUNEC	Toutes les sociétés suscitées, association 1901 partenaire de l'université			
60744	HUMBERT	Philippe	07/02/2004	LD	YVES ROCHER	Conseil en cosmetovigilance			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	PIERRE FABRE	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	L'OREAL	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	MERCKMED FAM	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	LA ROCHE POSAY	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	DANONE	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	LABCATAL	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	SERVIER	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	ARKO	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	URGO	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-AC	GALDERMA	Conseils sur protocoles (Psoriasis)			
60744	HUMBERT	Philippe	07/02/2004	IP-AC	PIERRE FABRE	Activité éditoriale			
60744	HUMBERT	Philippe	07/02/2004	IP-AC	GENEVRIER	Activité éditoriale			

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60744	HUMBERT	Philippe	07/02/2004	IP-CF	COSMETIQUE ACTIVE	Conférences - Formations en Bioingénieurie et Physiopathologie cutanée			
60744	HUMBERT	Philippe	07/02/2004	VB	PIERRE FABRE ; L'OREAL ; MERCKMED FAM. ; LA ROCHE POSAY ; DANONE ; LABCATAL ; SERVIER ; ARKO ; URGO	INTERUNEC Association			
60744	HUMBERT	Philippe	07/02/2004	VB	DANONE ; LABCATAL ; SERVIER ; ARKO ; URGO	INTERUNEC Association			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	PIERRE FABRE ; L'OREAL ; MERCK MED.FAM	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	LA ROCHE POSAY ; DANONE ; URGO	Investigateur principal			
60744	HUMBERT	Philippe	07/02/2004	IP-EC	ARKO ; SERVIER ; LABCATAL	Investigateur principal			
60744	HUMBERT	Philippe	04/04/2000	LD	YVES ROCHER	Consultant en cosmétovigilance			
60744	HUMBERT	Philippe	04/04/2000	IP-EC	LABCATAL	Essai clinique			
60744	HUMBERT	Philippe	04/04/2000	IP-CF	LA ROCHE POSAY - CS DERMATO	Conférence en BIOINGENIERIE/Conférence sur travaux de recherche			
60744	HUMBERT	Philippe	04/04/2000	IP-CF	LEO	FMC			
60744	HUMBERT	Philippe	04/04/2000	VB	ROCHE POSAY/PIERRE FABRE/THERVAL FOURNIER/CS DERMATO.GALDERMA/LEO/ L OREAL/PHARMA SCIENCES/AGCE MEDICT	Association de recherche INTERUNEC			
10236	IMBS	Jean-Louis	08/06/2010	IP-AC	SANOFI-AVENTIS	Comité de suivi de sécurité et d'essai clinique international du salavaptan	Rémunération personnelle	06/2009	
10236	IMBS	Jean-Louis	25/03/2010	IP-AC	SANOFI-AVENTIS	Comité de suivi de sécurité et d'essai clinique international du salavaptan	Rémunération personnelle	06/2009	
10236	IMBS	Jean-Louis	03/11/2008	CF-INT	LABORATOIRE SERVIER	Invitation Congrès 5 et 6 novembre 2008 - Paris	Aucune rémunération	11/2008	11/2008
10236	IMBS	Jean-Louis	27/05/2008	CF-INT	LABORATOIRES ROCHE - PARIS	4èmes journées d'échanges sur la recherche clinique	Aucune rémunération	12/2007	12/2007
10236	IMBS	Jean-Louis	26/03/2007	CF-INT	ASTRAZENECA	Formation délégués médicaux□□(1 séance à Strasbourg)	Rémunération personnelle	01/2006	12/2006
10236	IMBS	Jean-Louis	21/03/2007	EC-INV	TAKEDA	Efficacité tolérance du Candesartan en médecine de ville	Investigateur principal	01/2004	12/2004
10236	IMBS	Jean-Louis	21/03/2007	EC-CO	MERCK LIPHA	Effets rénaux de la metformine chez le rat diabétique	Expérimentateur	01/2004	12/2004
10236	IMBS	Jean-Louis	21/03/2007	VB	SANOFI-AVENTIS	Membre de cinq comités de suivi de sécurité et d'essais cliniques internationaux (Xaliproden, rimonabant, s	Association Naturalia et Biologia □ ou□ Université Louis Pasteur		
10236	IMBS	Jean-Louis	21/03/2007	CF-AUD	PHARMACEUTIQUE	Lourmarin			
10236	IMBS	Jean-Louis	21/03/2007	CF-INT	MSD CHIBRET	Conférences de formation médicale continue : hypertension artérielle	Rémunération personnelle	11/2006	12/2006
10236	IMBS	Jean-Louis	21/03/2007	IP-AC	SERVIER	Protelos (dossier de présentation à la Commission de la transparence)	Rémunération institution	01/2005	12/2005
10236	IMBS	Jean-Louis	21/03/2007	RE-AUT	FAUST PHARMACEUTICAL	Sécurité d'emploi d'un produit potentiellement neurotrophe.	Rémunération institution	11/2006	01/2007
10236	IMBS	Jean-Louis	23/01/2006	VB	SANOFI-AVENTIS	Membre de 4 comités de sécurité et essais cliniques (xaliproden-rimonabant). Association Naturalia et Biolo		01/2002	
10236	IMBS	Jean-Louis	23/01/2006	VB	SERVIER	Expert pharmacovigilant Protelos. Association Naturalia et Biologia et Université Louis Pasteur		01/2005	12/2005
10236	IMBS	Jean-Louis	18/11/2004	VB	TAKEDA - UNIVERSITE LOUIS PASTEUR	1 étude clinique, essai clinique: efficacité tolérance du Candersartan en médecine de ville			
10236	IMBS	Jean-Louis	18/11/2004	VB	SERVIER - NATURALIA et BIOLOGIA	Réunions programmées, conseil : sécurité d'emploi du PROTELOS			
10236	IMBS	Jean-Louis	18/11/2004	VB	SANOFI SYNTHELABO - NATURALIA et BIOLOGIA	Expertise : participation à 3 comités de sécurité (DSMB) d'essais cliniques internationaux (Rimonabant, Xaliproden, vs antagoniste)			
10236	IMBS	Jean-Louis	18/11/2004	VB	PFIZER - NATURALIA et BIOLOGIA	Conférence sur invitation			
10236	IMBS	Jean-Louis	18/11/2004	VB	MERCK LIPHA - NATURALIA et BIOLOGIA	Expérimentation : effets rénaux de la metformine chez le rat diabétique			
10236	IMBS	Jean-Louis	29/02/2004	VB	TAKEDA	(Une étude clinique) Conseil : efficacité tolérance du Candesartan en médecine de ville - Université Louis Pasteur (Strasbourg)			
10236	IMBS	Jean-Louis	29/02/2004	VB	SERVIER	(Réunions programmées) Conseil : sécurité d'emploi du protos - Universié L. Pasteur			
10236	IMBS	Jean-Louis	29/02/2004	VB	SANOFI-SYNTHELABO	Expertise : participation à 3 comités de sécurité (DSMB) d'essais cliniques internationaux (Rimonabant, Xaliproden, SR12H63) - Université L. Pasteur			
10236	IMBS	Jean-Louis	29/02/2004	VB	MERCK LIPHA	Expérimentation : effets rénaux de la Metformine chez le rat diabétique - Université L. Pasteur			
10236	IMBS	Jean-Louis	29/02/2004	VB	PHARMACEUTIQUE	Congrès : frais de déplacement journées de Lourmarin - Université L. Pasteur			
10236	IMBS	Jean-Louis	28/07/2003	IP-CF		Invité (transport-hébergement) aux Universités d'été de Pharmaceutiques (Lourmarin) du 12 au 14/09/2003/Economie du médicaments (pharmaceutiques)			
10236	IMBS	Jean-Louis	28/07/2003	VB	SANOFI-SYNTHELABO	Membre de 2 comités de sécurité (DSMB) d'essais cliniques internationaux du RIMONABANT/Association Naturalia Biologica à destination du Laboratoire de Pharmacologie de			
10236	IMBS	Jean-Louis	28/07/2003	VB	SERVIER	Membre d'un groupe d'expert conseil du STRONIUM Ranelate/Association Naturalia Biologica			
10236	IMBS	Jean-Louis	08/01/2003	VB	SANOFI-SYNTHELABO	Participation à 2 comités de sécurité (DSMB) pour des essais internationaux multicentriques : Université L. Pasteur (Strasbourg)			
10236	IMBS	Jean-Louis	08/01/2003	VB	MERCK-LIPHA	Etude expérimentale des effets rénaux de la Metformine cf l'animal : Université L. Pasteur (Strasbourg)			
10236	IMBS	Jean-Louis	08/01/2003	VB	TRANSGENE	Evaluation d'une observation d'effet indésirable : Université L. Pasteur (Strasbourg)			
10236	IMBS	Jean-Louis	10/02/2002	VB	SANOFI-SYNTHELABO	Membre "Comité de sécurité" produit en phases II-III à compter de juin 2002 : versement université	Rectificatif : déclaré en IP essais cliniques = erreur VB (courrier du 10/01/2003)		
10236	IMBS	Jean-Louis	10/02/2002	VB		Journées pharmaceutiques : participation au colloque du 21/09/2001 (Lubéron) : versement Université	Rectificatif : déclaré en IP Conférences = erreur VB (courrier du 10/01/2003)		
10236	IMBS	Jean-Louis	27/10/2001	IP-AUT	PHARMACEUTIQUES	Prise en charge transport et hébergement : Université d'été de Pharmaceutiques (21-22/09/2001)			
10236	IMBS	Jean-Louis	27/10/2001	IP-AUT	SERVIER	Prise en charge transport et hébergement : Réunion de gérontologie (18-19/10/2001)			
10236	IMBS	Jean-Louis	18/06/2001	Néant					
10236	IMBS	Jean-Louis	26/06/2000	VB	SERVIER	Convention de recherche - bourse pour une thèse en pharmacologie clinique			
10236	IMBS	Jean-Louis	01/01/2000	IP-EC	LAFON	Collaboration à propos du bufiomédil (Fonzylane®) - coordonne le Comité de suivi de sécurité d'un essai clinique multicentrique international controlé contre placebo en la matièr			
10236	IMBS	Jean-Louis	01/01/2000	IP-CF	LIPHA	(1conférence en 1999) : association d'antihypertenseurs à doses faibles			
10236	IMBS	Jean-Louis	01/01/2000	IP-CF	SANOFI	(1 conférence en 1999) : antagonistes des récepteurs de l'angiotensine I			
10236	IMBS	Jean-Louis	01/01/2000	VB	LIPHA	Participation à un comité de suivi, ou à la coordination, ou à l'investigation d'essais cliniques - honoraires versés à l'Agent comptable de l'Univ. L. Pasteur, à destination du lab.			
10236	IMBS	Jean-Louis	01/01/2000	VB	MERCK	Même participation			
10236	IMBS	Jean-Louis	01/01/2000	VB	LAFON	Même participation			
10236	IMBS	Jean-Louis	01/01/2000	VB	SERVIER	Même participation			
10236	IMBS	Jean-Louis	01/01/2000	VB	TAKEDA	Même participation			
10236	IMBS	Jean-Louis	01/01/2000	VB	SANOFI	Même participation			
10236	IMBS	Jean-Louis	01/01/2000	VB	SEARLES	Même participation			
10236	IMBS	Jean-Louis	01/01/2000	VB	LIPHA	Contrat de recherche : versements identiques (Louis Pasteur...)			
10236	IMBS	Jean-Louis	01/01/2000	VB	MERCK	Contrat de recherche : versements identiques (Louis Pasteur...)			
10236	IMBS	Jean-Louis	01/01/2000	VB	SANOFI	Contrat de recherche : versements identiques (Louis Pasteur...)			
10236	IMBS	Jean-Louis	27/04/1999	IP-CF	LIPHA	une conférence en 1999 : association d'antihypertenseurs à doses faibles			
10236	IMBS	Jean-Louis	27/04/1999	IP-CF	SANOFI	Une conférence en 1999 : antagonistes des récepteurs de l'angiotensine I			
10236	IMBS	Jean-Louis	27/04/1999	VB	LIPHA MERCK, LAFON, SERVIER, TAKEDA, SANOFI, SEARLES	Participation à un Comité de suivi, ou à la coordination, ou à l'investigation d'essais cliniques : honoraires versés à l'agent comptable de l'université Louis Pasteur, à destination			
10236	IMBS	Jean-Louis	27/04/1999	VB	LIPHA MERCK, SANOFI	Contrat de recherche			
10236	IMBS	Jean-Louis	01/01/1999	IP-EC	RCD				
10236	IMBS	Jean-Louis	01/01/1999	IP-EC	BRISTOL MYERS SQUIBB				
10236	IMBS	Jean-Louis	01/01/1999	IP-EC	LIPHA MERCK				
10236	IMBS	Jean-Louis	01/01/1999	IP-EC	NOVARTIS				
10236	IMBS	Jean-Louis	01/01/1999	IP-EC	SERVIER (IRIS)				
10236	IMBS	Jean-Louis	01/01/1999	IP-EC	TAKEDA				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10236	IMBS	Jean-Louis	01/01/1999	IP-AC	SANOFI Recherche				
10236	IMBS	Jean-Louis	01/01/1999	IP-CF	MSD CHIBRET				
10236	IMBS	Jean-Louis	01/01/1999	IP-CF	ZENECA				
10236	IMBS	Jean-Louis	01/01/1999	VB		Les honoraires résultant de l'ensemble de ces activités sont versés à l'agent comptable de l'Université Louis Pasteur à destination de l'Institut de Pharmacologie (Faculté de méc			
10236	IMBS	Jean-Louis	01/01/1999	PAR	NOVARTIS	Enfant médecin employé			
10236	IMBS	Jean-Louis	01/01/1998	VB	Servier (IRIS)		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Sanofi Recherche		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Pharmacia		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Schering		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Lipha		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Sandoz		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Bayer		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Hoechst		pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	VB	Ambard	actions de formation dans le cadre de la conférence Léo	pour l'université Louis Pasteur à destination de l'institut de pharmacologie		
10236	IMBS	Jean-Louis	01/01/1998	PAR	Enfant CDD chez Ciba-Geigy				
63621	IUNG	Bernard	10/01/2009	IP-AC	EUROPEAN SOCIETY OF CARDIOLOGY	participation au groupe de travail sur l'élaboration des recommandations sur la prise en charge des valvulop	aucune rémunération	01/2005	01/2007
63621	IUNG	Bernard	10/01/2009	IP-AC	EUROPEAN SOCIETY OF CARDIOLOGY	participation au groupe de travail sur l'élaboration des recommandations sur la chirurgie non-cardiaque des p	aucune rémunération	05/2007	
63621	IUNG	Bernard	10/01/2009	IP-AC	HAS	participation au groupe de travail sur l'élaboration du guide patients sur les valvulopathies et cardiopathies c	aucune rémunération	06/2007	11/2008
63621	IUNG	Bernard	10/01/2009	IP-AC	HAS	participation au groupe de travail de relecture sur les recommandations pour la pratique clinique concernant	aucune rémunération	10/2008	05/2009
63621	IUNG	Bernard	10/01/2009	IP-CF	EDWARDS LIFESCIENCES	communication à des symposia sur les prothèses valvulaires ((3 à 5 fois par an de 2005 à 2008)	rémunération personnelle	01/2005	12/2008
63621	IUNG	Bernard	10/01/2009	IP-CF	SANOFI AVENTIS	participation au programme "inpulse in french cardiology" (formation de jeunes cardiologues à la rédaction s	rémunération personnelle	01/2005	12/2008
63621	IUNG	Bernard	10/01/2009	IP-CF	MERCK SERONO	6th international heart failure symposium - Bruxelles	rémunération personnelle	10/2007	10/2007
63621	IUNG	Bernard	10/01/2009	IP-CF	SFC	session organisée par la SFC avec le soutien de plusieurs laboratoires : le traitement antithrombotique de la	rémunération personnelle	11/2008	11/2008
63621	IUNG	Bernard	08/09/2005	IP-RE	SANOFI-AVENTIS Oncologie	Rapport d'expertise sur la tolérance cardiovasculaire d'un cytostatique (essai de phase I) AVE 8062 A (activité actuelle)		01/2004	
63621	IUNG	Bernard	08/09/2005	IP-AC	SANOFI-AVENTIS Oncologie	Conseil ponctuel sur l'analyse de la tolérance cardiovasculaire d'un cytostatique en phase I (AVE 8062 A) (activité actuelle)		01/2001	
63621	IUNG	Bernard	08/09/2005	IP-CF	EDWARDS LIFESCIENCES	Orateur dans des colloques et des cours de formation sur les cardiopathies valvulaires (activité actuelle)			
63621	IUNG	Bernard	08/09/2005	IP-CF	SAINT-JUDE MEDICAL	Orateur dans des colloques sur les cardiopathies valvulaires		01/2001	12/2003
63621	IUNG	Bernard	08/09/2005	IP-AUT	SERVIER	Prise en charge régulière des congrès de l'European Society of Cardiology			
10238	JACQUOT	Christian	12/03/2010	RE-DE	PHARMA-DEV Genève	Bioéquivalence Ribavirine (2 jours) EE/Desogestrel - Ribavirine CP	Rémunération personnelle	10/2009	10/2009
10238	JACQUOT	Christian	12/03/2010	RE-DE	PHARMA-DEV Genève	EE/Desogestrel (4 jours)	Rémunération personnelle	07/2009	07/2009
10238	JACQUOT	Christian	12/03/2010	RE-DE	PHARMA-DEV	Ribavirine CP (2 jours)	Rémunération personnelle	01/2010	01/2010
10238	JACQUOT	Christian	12/03/2010	RE-DE	AXCAN PHARMA	Rapport bioéquivalence Acide Ursodexoycholique 500 versus 2x250 (3 jours)	Rémunération personnelle	08/2009	08/2009
10238	JACQUOT	Christian	12/03/2010	RE-AUT	LAFON-CEPHALON	Exemptir. Etude bioéquivalence pour Spafon Lyoc 160mg (1 jour)	Rémunération personnelle	11/2009	11/2009
10238	JACQUOT	Christian	12/03/2010	IP-AC	SANOFI AVENTIS, BIOGARAN	Conseils sur protocoles génériques (4h par trimestre pour Sanofi Aventis - 5 demi-journées en 2009 pour Bi	Rémunération personnelle		
10238	JACQUOT	Christian	12/03/2010	IP-AC	RECORDATI	Conseils sur projet cinétique (2,5 demi-journées entre avril et décembre 2009)	Rémunération personnelle		
10238	JACQUOT	Christian	12/03/2010	PAR	JANSSEN CILAG	Directeur Marketing	Fils	02/2008	
10238	JACQUOT	Christian	12/03/2010	PAR	AFSSAPS	Rédacteur Pharma	Belle-fille		
10238	JACQUOT	Christian	24/03/2009	RE-DE	STRAGEN PHARMA	Bioéquivalence EE/Desogestrel	Rémunération personnelle	01/2009	01/2009
10238	JACQUOT	Christian	24/03/2009	RE-AUT	INNOTHERA	Diosmine cp 500mg - En cours de validation	rémunération personnelle	02/2009	
10238	JACQUOT	Christian	24/03/2009	RE-AUT	LAFON	Phloroglucinol 160 mg	Rémunération personnelle	02/2009	02/2009
10238	JACQUOT	Christian	24/03/2009	IP-AC	SANOFI	Conseils protocole générique - 1/2 journée	Rémunération personnelle	03/2009	03/2009
10238	JACQUOT	Christian	24/03/2009	IP-AC	BIOGARAN	Conseils protocole générique - 1/2 journée	Rémunération personnelle	03/2009	03/2009
10238	JACQUOT	Christian	24/03/2009	IP-AC	RECORDATI	Conseils en pharmacocuipés	1/2 journée□ Rémunération personnelle	03/2009	03/2009
10238	JACQUOT	Christian	24/03/2009	PAR	JANSSEN CILAG	Responsable marketing (en cours)	Enfant	02/2008	
10238	JACQUOT	Christian	24/03/2009	PAR	AFSSAPS	Rédacteur Pharma (en cours)	Belle-fille		
10238	JACQUOT	Christian	15/01/2009	RE-DE	STRAGEN PHARMA	Bioéquivalence EE/ gestodene (2 jours)	rémunération personnelle	07/2008	07/2008
10238	JACQUOT	Christian	15/01/2009	RE-DE	STRAGEN PHARMA	Bioéquivalence adapalene gel/ crème (2 jours)	rémunération personnelle	08/2008	08/2008
10238	JACQUOT	Christian	15/01/2009	RE-DE	ARMEES	Bioéquivalence doxycycline (1 jour)	rémunération partagée personnelle/institution	05/2008	05/2008
10238	JACQUOT	Christian	15/01/2009	RE-DE	GALENIX	Bioéquivalence gluconnage (1 jour)	rémunération personnelle	04/2008	04/2008
10238	JACQUOT	Christian	15/01/2009	RE-AUT	SERVIER	Biodisponibilité diosmine pour Belgique et Espagne (1 jour)	rémunération personnelle	12/2008	12/2008
10238	JACQUOT	Christian	15/01/2009	IP-AC	SANOFI	Conseils sur protocole générique (2 x 1/2 journée)	rémunération personnelle	10/2008	10/2008
10238	JACQUOT	Christian	15/01/2009	IP-AC	SANOFI	Conseils sur protocole générique (2 x 1/2 journée)	rémunération personnelle	12/2008	12/2008
10238	JACQUOT	Christian	15/01/2009	IP-AC	BIOGARAN	Conseils sur protocole générique (4 x 1/2 journée)	rémunération personnelle	01/2008	03/2008
10238	JACQUOT	Christian	15/01/2009	IP-AC	RECORDATI	Conseils en cinétique humaine (2 x 2 heures)	rémunération personnelle	04/2008	04/2008
10238	JACQUOT	Christian	15/01/2009	IP-AC	RECORDATI	Conseils en cinétique humaine (2 x 2 heures)	rémunération personnelle	05/2008	05/2008
10238	JACQUOT	Christian	15/01/2009	IP-AC	RECORDATI	Conseils en cinétique humaine (2 x 2 heures)	rémunération personnelle	11/2008	11/2008
10238	JACQUOT	Christian	15/01/2009	PAR	JANSSEN CILAG	Responsable marketing Europe	fils	02/2008	
10238	JACQUOT	Christian	15/01/2009	PAR	AFSSAPS	rédacteur pharmaceutique	Belle-fille	04/1998	
10238	JACQUOT	Christian	15/01/2009	(Autre)	ERREKATA (Italie)	Rapport bioéquivalence sur manidipine générique (2 jours 1/2)		09/2008	09/2008
65163	JACQUOT	Christian	12/08/2008	EC-CO	ROCHE	MIRCERA	co-investigateur	01/2005	
65163	JACQUOT	Christian	12/08/2008	CF-INT	NOVARTIS - ROCHE - AMGEN	Interventions sur les sujets indépendants des produits commercialisés par les firmes	soit aucune rémunération - soit rémunération personnelle	01/2005	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10238	JACQUOT	Christian	13/02/2008	IP-RE	BESINS	Expertise dossier TOX Progestérone (2 jours)	rémunération partagée personnelle/institution		
10238	JACQUOT	Christian	13/02/2008	IP-RE	STRAGEN	Expertise diclofenac gel / arbidol (7 jours)	rémunération partagée personnelle/institution		
10238	JACQUOT	Christian	13/02/2008	IP-RE	EXPANSCIENCE	Expertise dossier TOX existant pour Piascledine (2 jours)	rémunération partagée personnelle/institution		
10238	JACQUOT	Christian	13/02/2008	IP-RE	BAYER PHARMA	Expertise sur impuretés dans gipso-hydralin OTC (2 jours)	rémunération personnelle		
10238	JACQUOT	Christian	13/02/2008	IP-AC	SANOFI	Conseil cinétique NASACORT (1 jour)	rémunération personnelle	12/2007	12/2007
10238	JACQUOT	Christian	13/02/2008	IP-AC	BIOGARAN	Conseils sur protocole cinétique (les 12/12/07 - 14/01/08 - 22/02/08) 3 x 1/2 journée	rémunération personnelle		
10238	JACQUOT	Christian	13/02/2008	IP-AC	GALENIX	Conseils sur développement générique METFORMINE pour Europe (2 jours)	rémunération personnelle	01/2008	01/2008
10238	JACQUOT	Christian	13/02/2008	IP-AC	STRAGEN	Conseils développement cinétique ARBIDOL (1 jour)	rémunération personnelle	10/2007	10/2007
10238	JACQUOT	Christian	13/02/2008	IP-CF	PAREXEL (Paris)	Conférence sur biosimilaires / génériques	aucune rémunération	01/2008	01/2008
10238	JACQUOT	Christian	13/02/2008	IP-CF	ARC (Paris)	conférence sur biosimilaires	aucune rémunération	09/2007	09/2007
10238	JACQUOT	Christian	13/02/2008	VB	JANSSEN CILAG	Responsable marketing Europe	fils	02/2008	
10238	JACQUOT	Christian	13/02/2008	VB	AFSSAPS	Rédacteur pharmaceutique	belle-fille		
10238	JACQUOT	Christian	14/03/2006	RE-DE	STRAGEN (Suisse)	Bioéquivalence Ethynilerhatrol-gestoden	Aucune rémunération	12/2005	12/2005
10238	JACQUOT	Christian	14/03/2006	RE-DE	STRAGEN	Bioéquivalence Cyproterone 100mg	Rémunération personnelle	04/2005	05/2005
10238	JACQUOT	Christian	14/03/2006	RE-DE	KELLER	Bioéquivalence ovule econazole		09/2005	09/2005
10238	JACQUOT	Christian	14/03/2006	RE-DE	GALENIC	Bioéquivalence Metformine 500mg		01/2006	03/2006
10238	JACQUOT	Christian	14/03/2006	RE-DE	M.CLARET	Exemption bioéquivalence phloroglucinol		07/2005	08/2005
10238	JACQUOT	Christian	14/03/2006	RE-AUT	AVENTIS-SANOFI	Evaluation impuretés Hexomedine	Rémunération personnelle	01/2006	02/2006
10238	JACQUOT	Christian	14/03/2006	IP-AC	ALTANA	Conseils ponctuels en préclinique	Rémunération institution	01/2006	02/2006
10238	JACQUOT	Christian	14/03/2006	IP-AC	UPSA/BMS	Conseils ponctuels en toxicologie d'impuretés	Rémunération institution	02/2006	02/3006
10238	JACQUOT	Christian	14/03/2006	IP-AC	PIERRE FABRE	Conseils ponctuels en préclinique sur primatan, veybirol	Rémunération personnelle	10/2005	11/2005
10238	JACQUOT	Christian	14/03/2006	IP-AC	RECORDATI	Conseils en développement générique methadone orale	Rémunération personnelle	10/2005	01/2006
10238	JACQUOT	Christian	14/03/2006	VB		demande en commun avec d'autres collègues = taxe d'apprentissage mutualisée <15% du budget global du laboratoire - Université Paris XI	01/2005	12/2005	
10238	JACQUOT	Christian	14/03/2006	PAR	ASTRA ZENECA	Marketing Europe siège Bruxelle (Belgique) et bureau Manchester (UK)	Enfant	01/2003	
10238	JACQUOT	Christian	01/06/2005	IF	BNP	SICAV - action française			
10238	JACQUOT	Christian	01/06/2005	IP-RE	CLIPA	Bioéquivalence setralme		01/2004	
10238	JACQUOT	Christian	01/06/2005	IP-RE	STRAGEN	Androcur 100		01/2004	
10238	JACQUOT	Christian	01/06/2005	IP-RE	IVAX	Econazole bioequivalence		01/2004	
10238	JACQUOT	Christian	01/06/2005	IP-RE	ASTELLAS PHARMA	Locoid - rapport toxicologique		01/2005	
10238	JACQUOT	Christian	01/06/2005	IP-AC	BIOGARAN			01/2003	12/2004
10238	JACQUOT	Christian	01/06/2005	VB	ALTANA	conseils en préclinique	versement à ADEBIOPHARM		
10238	JACQUOT	Christian	01/06/2005	VB	BMS	Conseils en préclinique	versement à ADEBIOPHARM		
10238	JACQUOT	Christian	01/06/2005	PAR	ASTRA ZENECA	fils	marketing		
10238	JACQUOT	Christian	12/03/2005	IP-AC	BIOGARAN	Conseil ponctuel pour le développement bioéquivalence générique	Consultant	01/2003	12/2003
10238	JACQUOT	Christian	12/03/2005	IP-RE	CLIPA	Sertraline générique		01/2003	12/2003
10238	JACQUOT	Christian	12/03/2005	VB	ALTANA	Financement < 15% du budget du service			
10238	JACQUOT	Christian	12/03/2005	VB	UPSA/BMS	Financement < 15% du budget du service			
10238	JACQUOT	Christian	12/03/2005	PAR	ASTRA ZENECA	Fils / marketing			
10238	JACQUOT	Christian	12/03/2005	IP-RE	M.CLARET	Phloroglucinol		01/2003	12/2003
10238	JACQUOT	Christian	12/03/2005	IP-RE	STRAGEN (SUISSE)	Androcur		01/2003	12/2003
10238	JACQUOT	Christian	29/06/2004	IP-RE	SANDOZ	Bioéquivalence (générique)			
10238	JACQUOT	Christian	29/06/2004	IP-RE	GENEVRIER	Cinétique du Flector			
10238	JACQUOT	Christian	29/06/2004	IP-AC	SOLVAY France	Conseils en pharmacologie préclinique			
10238	JACQUOT	Christian	29/06/2004	IP-AC	PIERRE FABRE	Conseils en préclinique			
10238	JACQUOT	Christian	29/06/2004	IP-AC	BIOGARAN	Conseils en bioéquivalence			
10238	JACQUOT	Christian	29/06/2004	IP-AC	RECORDATI	Conseil en cinétique			
10238	JACQUOT	Christian	29/06/2004	VB	ALTANA	Adebiopharma			
10238	JACQUOT	Christian	29/06/2004	VB	UPSA	Adebiopharma			
10238	JACQUOT	Christian	20/04/2003	IP-RE	STRAGEN (Société suisse)	Un rapport sur étude bioéquivalence			
10238	JACQUOT	Christian	20/04/2003	IP-AC	BIOGARAN	Audit de protocole			
10238	JACQUOT	Christian	20/04/2003	IP-AC	SOLVAY	Conseil en pharmacologie animale			
10238	JACQUOT	Christian	20/04/2003	IP-AC	PIERRE FABRE	Audit sur dossiers			
10238	JACQUOT	Christian	20/04/2003	IP-AC	RECORDATI	Conseil en cinétique, protocole			
10238	JACQUOT	Christian	20/04/2003	IP-CF	ARC (Boulevard Malesherbes)	Actualités précliniques règlementaires			
10238	JACQUOT	Christian	20/04/2003	VB	UPSA/BRISTOL MYERS SQUIBB	Adebiopharm			
10238	JACQUOT	Christian	20/04/2003	VB	ALTANA	Adebiopharm			
10238	JACQUOT	Christian	20/04/2003	PAR	ASTRA ZENECA	Fils			
10238	JACQUOT	Christian	02/05/2000	IP-AC	SOLVAY France	Conseils en préclinique pour le Développement			
10238	JACQUOT	Christian	02/05/2000	IP-AC	BIOGARAN	Conseils en préclinique pour le Développement			
10238	JACQUOT	Christian	02/05/2000	IP-AC	WYETH	Conseils en préclinique pour le Développement			
10238	JACQUOT	Christian	02/05/2000	IP-AC	DOMS-RECORDATI	Conseils en préclinique pour le Développement			
10238	JACQUOT	Christian	02/05/2000	IP-AC	PIERRE FABRE	Conseils en préclinique pour le Développement			
10238	JACQUOT	Christian	02/05/2000	IP-CF	ANDRE REY CONSULTANTS	Colloques : actualités scientifiques et réglementaires sur le médicament			
10238	JACQUOT	Christian	02/05/2000	VB	UPSA	ADEBIOPHARM - ER 77 - Université Paris XI			
10238	JACQUOT	Christian	02/05/2000	VB	BYK-GULDEN PHARMA	ADEBIOPHARM - ER 77 - Université Paris XI			
10238	JACQUOT	Christian	01/01/1999	IP-RE	GENEVRIER				
10238	JACQUOT	Christian	01/01/1999	IP-RE	AIR LIQUIDE Santé				
10238	JACQUOT	Christian	01/01/1999	IP-AC	WYETH				
10238	JACQUOT	Christian	01/01/1999	IP-AC	SOLVAY France				
10238	JACQUOT	Christian	01/01/1999	IP-AC	DOMS ADRIAN				
10238	JACQUOT	Christian	01/01/1999	IP-AC	PIERRE FABRE MEDICAMENT				
10238	JACQUOT	Christian	01/01/1999	IP-AC	INNOTHERA				
10238	JACQUOT	Christian	01/01/1999	IP-AC	BIOGARAN				
10238	JACQUOT	Christian	01/01/1999	IP-AC	PROGRAPHARM				
10238	JACQUOT	Christian	01/01/1999	IP-CF	IFIP				
10238	JACQUOT	Christian	01/01/1999	IP-CF	ARC (Aurore Rey Consultant)				
10238	JACQUOT	Christian	01/01/1999	VB	UPSA	Association Adébiopharm			
10238	JACQUOT	Christian	01/01/1999	VB	LAFON	Ass. Adébiopharm			
10238	JACQUOT	Christian	01/01/1999	VB	BYK	Ass. Adébiopharm			

Id	Nom	Prenom	Date de déclaration	Type d'Intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10238	JACQUOT	Christian	01/01/1999	PAR	Fils				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Solvay France				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Doms				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Wyeth				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Innothéra				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Cassenne				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Pierre Fabre Médicament				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Progrepharm				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Genevrier				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Genevrier				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	GNR				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Lundbeck				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	Irex				
10238	JACQUOT	Christian	01/01/1998	IP-AUT	André Rey Consultant (Arc)				
10238	JACQUOT	Christian	01/01/1998	VB	Byk France		Association Adebiopharm et Université		
10238	JACQUOT	Christian	01/01/1998	VB	Upsa		Association Adebiopharm et Université		
10238	JACQUOT	Christian	01/01/1998	VB	Lafon		Association Adebiopharm et Université		
10238	JACQUOT	Christian	01/01/1998	PAR	PARKE-DAVIS	Enfant			
10240	JAILLON	Patrice	22/05/2006	IF	SANOFI SYNTHELABO	Valeurs en bourse			
10240	JAILLON	Patrice	22/05/2006	LD-AR	ROCHE, MSD, SERVIER,PIERRE FABRE MEDICAMENTS, NOVARTIS, SANOFI SYNTHELABO	consultant individuel	+ 5000 € du capital rémunération personnelle	01/1999 01/2000	
10240	JAILLON	Patrice	22/05/2006	EC-CO	PFIZER	essai clinique CASHMERE	président du conseil scientifique	01/2004	
10240	JAILLON	Patrice	22/05/2006	CF-INT	SANOFI SYNTHELABO	Symposium congrès de la société française de pharmacologie - Bordeaux (2005)	rémunération personnelle		
10240	JAILLON	Patrice	22/05/2006	CF-INT	MERCK	Symposium - congrès de la société française de pharmacologie - Montpellier (2006)	rémunération personnelle		
10240	JAILLON	Patrice	22/05/2006	VB	SANOFI SYNTHELABO, IRIS, SERVIER, PIERRE FABRE MEDICAMENTS	subvention pour la réunion annuelle de l'association (2005)	Association pour le Développement de la Pharmacologie Clinique - ADPC		
10240	JAILLON	Patrice	22/05/2006	VB	BIOPHARMA, ALTANA, ABBOTT, PIERRE FABRE MEDICAMENT, ...	taxe d'apprentissage (2005)	Université Pierre et Marie Curie Paris 6		
10240	JAILLON	Patrice	04/02/2000	IF	GLAXO WELLCOME	Actions			
10240	JAILLON	Patrice	04/02/2000	IF	SANOFI-SYNTHELABO	Actions			
10240	JAILLON	Patrice	04/02/2000	LD	Institut de recherche internationale SERVIER	Contrat consultant-expert			
10240	JAILLON	Patrice	04/02/2000	LD	ROCHE	Expertise pharmacologique			
10240	JAILLON	Patrice	04/02/2000	LD	PFIZER International	Expertise pharmacologique			
10240	JAILLON	Patrice	04/02/2000	LD	3M SANTE	Expertise pharmacologique			
10240	JAILLON	Patrice	04/02/2000	IP-EC	E. MERCK DARMSTADT	Essai clinique ESCAMI			
10240	JAILLON	Patrice	04/02/2000	IP-RE	3M SANTE	Fléca ne CR			
10240	JAILLON	Patrice	04/02/2000	IP-AC	3M SANTE	Board Rythmologie			
10240	JAILLON	Patrice	04/02/2000	IP-CF	LILLY France	Conseil scientifique			
10240	JAILLON	Patrice	04/02/2000	IP-CF	WYETH	Séminaire formation			
10240	JAILLON	Patrice	04/02/2000	IP-CF	PFIZER INTERNATIONAL	Séminaire formation			
10240	JAILLON	Patrice	04/02/2000	VB		Taxe d'apprentissage : Université Paris 6			
10240	JAILLON	Patrice	01/01/2000	IF	SANOFI				
10240	JAILLON	Patrice	01/01/2000	IF	SYNTHELABO				
10240	JAILLON	Patrice	01/01/2000	IF	HYBRIDON				
10240	JAILLON	Patrice	01/01/2000	LD	ROCHE	Contrats d'expertise en pharmacologie clinique et préclinique			
10240	JAILLON	Patrice	01/01/2000	LD	EISAI				
10240	JAILLON	Patrice	01/01/2000	LD	SERVIER				
10240	JAILLON	Patrice	01/01/2000	IP-AUT	EDIMARK	Conseiller scientifique de la Rédaction			
10240	JAILLON	Patrice	01/01/2000	IP-EC	ROCHE	Coordinateur d'essais cliniques			
10240	JAILLON	Patrice	01/01/2000	IP-EC	SERVIER				
10240	JAILLON	Patrice	01/01/2000	IP-EC	KNOLL				
10240	JAILLON	Patrice	01/01/2000	IP-RE	ROCHE	A la demande du laboratoire			
10240	JAILLON	Patrice	01/01/2000	IP-RE	EISAI				
10240	JAILLON	Patrice	01/01/2000	IP-RE	SERVIER				
10240	JAILLON	Patrice	01/01/2000	IP-RE	3M SANTE				
10240	JAILLON	Patrice	01/01/2000	IP-RE	KNOLL				
10240	JAILLON	Patrice	01/01/2000	IP-CF	ROCHE				
10240	JAILLON	Patrice	01/01/2000	IP-CF	PFIZER International				
10240	JAILLON	Patrice	01/01/2000	IP-CF	Institut LILLY				
10240	JAILLON	Patrice	01/01/2000	IP-CF	IFIP				
10240	JAILLON	Patrice	01/01/2000	(Autre)	BOZ-STRATSANTE	Conférences			
10240	JAILLON	Patrice	01/01/1999	IF	SANOFI				
10240	JAILLON	Patrice	01/01/1999	IF	SYNTHELABO				
10240	JAILLON	Patrice	01/01/1999	IF	HYBRIDON				
10240	JAILLON	Patrice	01/01/1999	LD	ROCHE	Contrats d'expertise en pharmacologie clinique et préclinique			
10240	JAILLON	Patrice	01/01/1999	LD	EISAI				
10240	JAILLON	Patrice	01/01/1999	LD	SERVIER				
10240	JAILLON	Patrice	01/01/1999	LD	BAYER				
10240	JAILLON	Patrice	01/01/1999	IP-EC	ROCHE	Coordinateur d'essais cliniques			
10240	JAILLON	Patrice	01/01/1999	IP-EC	SERVIER				
10240	JAILLON	Patrice	01/01/1999	IP-EC	KNOLL				
10240	JAILLON	Patrice	01/01/1999	IP-EC	IPSEN-BEAUFOUR				
10240	JAILLON	Patrice	01/01/1999	IP-EC	BAYER				
10240	JAILLON	Patrice	01/01/1999	IP-RE	ROCHE	A la demande du laboratoire			
10240	JAILLON	Patrice	01/01/1999	IP-RE	EISAI				
10240	JAILLON	Patrice	01/01/1999	IP-RE	SERVIER				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10240	JAILLON	Patrice	01/01/1999	IP-RE	IPSEN-BEAUFOUR				
10240	JAILLON	Patrice	01/01/1999	IP-RE	BAYER				
10240	JAILLON	Patrice	01/01/1999	IP-CF	ROCHE				
10240	JAILLON	Patrice	01/01/1999	IP-CF	PFIZER International				
10240	JAILLON	Patrice	01/01/1999	IP-CF	André REY Consultants				
10240	JAILLON	Patrice	01/01/1999	IP-CF	Sciences Po Formation				
10240	JAILLON	Patrice	01/01/1999	IP-CF	SANOFI WINTHROP				
10240	JAILLON	Patrice	01/01/1999	IP-CF	Institut LILLY				
10240	JAILLON	Patrice	01/01/1999	IP-CF	MERCK-LIPHA				
10240	JAILLON	Patrice	01/01/1999	IP-CF	DROITet PHARMACIE				
10240	JAILLON	Patrice	01/01/1999	IP-CF	IFIP				
10240	JAILLON	Patrice	01/01/1999	IP-AUT	EDIMARK	Conseiller scientifique de la rédaction			
10240	JAILLON	Patrice	01/01/1998	IF	RPR				
10240	JAILLON	Patrice	01/01/1998	IF	Sanofi				
10240	JAILLON	Patrice	01/01/1998	IF	Synthélabo				
10240	JAILLON	Patrice	01/01/1998	IF	Hybridon				
10240	JAILLON	Patrice	01/01/1998	LD	Roche				
10240	JAILLON	Patrice	01/01/1998	LD	Servier				
10240	JAILLON	Patrice	01/01/1998	LD	Essai				
10240	JAILLON	Patrice	01/01/1998	IP-AUT	Roche				
10240	JAILLON	Patrice	01/01/1998	IP-AUT	Servier				
10240	JAILLON	Patrice	01/01/1998	IP-AUT	Knoll				
10240	JAILLON	Patrice	01/01/1998	IP-AUT	Essai				
10240	JAILLON	Patrice	01/01/1998		conseiller scientifique de la rédaction de la Société				
10240	JAILLON	Patrice	01/01/1998	IP-AUT	EDIMARK				
10240	JAILLON	Patrice	01/01/1998	PAR	fils salarié RPR				
65766	JAMET	Aurélie	12/05/2010	CF-AUD	B BRAUN	Congrès Eurupharmat - Strasbourg		10/2009	10/2009
65766	JAMET	Aurélie	20/01/2010	CF-AUD	B BRAUN	Journées Europharmat, Strasbourg		10/2009	
65766	JAMET	Aurélie	20/01/2010	CF-AUD	SERVIER	Journées Européennes de cardiologie		01/2009	
63991	JAVIER-MODER	Rose-Marie	03/05/2007	EC-INV	ELI LILLY	Etude Teripantide	investigateur (non-principal)		12/2005
63991	JAVIER-MODER	Rose-Marie	03/05/2007	EC-INV	SERVIER	RANELATE DE STRONTIUM	investigateur (non-principal)		12/2006
63991	JAVIER-MODER	Rose-Marie	03/05/2007	IP-CF	ABBOTT	Rencontre d'experts	Rémunération personnelle	11/2006	11/2006
63991	JAVIER-MODER	Rose-Marie	03/05/2007	IP-CF	GRUNENTHAL	Formation douleur	Rémunération personnelle	11/2006	11/2006
63991	JAVIER-MODER	Rose-Marie	03/05/2007	CF-AUD	ROCHE	ASBMR 2006 - PHILADELPHIE		09/2006	09/2006
63991	JAVIER-MODER	Rose-Marie	03/05/2007	CF-AUD	AVENTIS et PROCTER	Congrès SFR 2006 - Paris		12/2006	12/2006
63991	JAVIER-MODER	Rose-Marie	03/05/2007	CF-AUD	NOVARTIS	Journées GEMO - Paris		04/2007	04/2007
63991	JAVIER-MODER	Rose-Marie	24/01/2006	EC-CO	IRIS	Ranclate de Strontium (1997)	co-investigateur		
63991	JAVIER-MODER	Rose-Marie	24/01/2006	CF-AUD	ROCHE	Congrès de l'American Society of Bone and Mineral research - Nashville		09/2005	
63991	JAVIER-MODER	Rose-Marie	24/01/2006	CF-AUD	NOVARTIS	Congrès de la Société Française de Rhumatologie - Paris		12/2005	
55583	JONDEAU	Guillaume	10/07/2009	CF-AUD	IRIS	Société Francaise de Cardiologie, Paris,			
55583	JONDEAU	Guillaume	10/07/2009	CF-AUD	IRIS	Société Francaise de CArdiologie, Nancy			
55583	JONDEAU	Guillaume	10/07/2009	EC-INV	IRIS	ivabradine	investigateur coordonnateur		
55583	JONDEAU	Guillaume	10/07/2009	EC-INV	MERCK	rolofylline, investigateur	investigateur coordonnateur		
55583	JONDEAU	Guillaume	22/02/2005	LD-AR	IRIS	3 dernières années			
55583	JONDEAU	Guillaume	22/02/2005	LD	SERVIER	3 dernières années			
55583	JONDEAU	Guillaume	22/02/2005	IP-AC	PFIZER	Comité consultatif : INSPRA	Aucune rémunération		
55583	JONDEAU	Guillaume	22/02/2005	IP-AC	ASTRA ZENECA	Atacand	Aucune rémunération		
55583	JONDEAU	Guillaume	22/02/2005	IP-EC	ASTRA ZENECA	Charm, investigateur			
55583	JONDEAU	Guillaume	22/02/2005	IP-EC	MENARINI	Seniors, investigateur			
55583	JONDEAU	Guillaume	22/02/2005	IP-EC	ACTELION	VERITAS, coordonateur national, investigateur			
55583	JONDEAU	Guillaume	22/02/2005	CF-INT	IRIS	Ivabradine, orateur lors d'un symposium au congrès du groupe Heart Failure de l'Esc à Strasbourg, en qualit			
55583	JONDEAU	Guillaume	22/02/2005	CF-AUD	ASTRA ZENECA	En qualité d'auditeur			
55583	JONDEAU	Guillaume	22/02/2005	CF-AUD	PFIZER	En qualité d'auditeur			
55583	JONDEAU	Guillaume	22/02/2005	CF-AUD	SERVIER	En qualité d'auditeur			
55583	JONDEAU	Guillaume	22/02/2005	CF-AUD	TAKEDA	En qualité d'auditeur			
55583	JONDEAU	Guillaume	22/09/2003	LD	SERVIER ISIS	Conseil			
55583	JONDEAU	Guillaume	22/09/2003	IP-AC	ASTRA ZENECA	Communication Caudesartan			
55583	JONDEAU	Guillaume	22/09/2003	IP-AC	NOVARTIS	Communication Valsartan			
55583	JONDEAU	Guillaume	22/09/2003	IP-CF	ASTRA ZENECA, NOVARTIS	Post IDM : prise en charge blocage ATP			
55583	JONDEAU	Guillaume	22/09/2003	IP-CF	BR:STOL MYERS SQUIBB	Dysfonction diastolique			
55583	JONDEAU	Guillaume	22/09/2003	IP-CF	ISIS	Ivabravine			
55583	JONDEAU	Guillaume	22/09/2003	VB	ASTRA ZENECA	Investigateur CHARM			
55583	JONDEAU	Guillaume	22/09/2003	VB	ACTELION	Investigateur VERITAS, SURVIVE, SENIOR			
55583	JONDEAU	Guillaume	30/07/2000	IP-AC	ADIR	Conseil en développement			
55583	JONDEAU	Guillaume	30/07/2000	IP-CF	ASTRA ZENECA	Insuffisance cardiaque (pour cardiologues et MG)			
55583	JONDEAU	Guillaume	30/07/2000	IP-CF	ROCHE	Insuffisance cardiaque (pour cardiologues et MG)			
55583	JONDEAU	Guillaume	30/07/2000	VB	BRISTOL MYERS SQUIBB	Investigateur - Association			
55583	JONDEAU	Guillaume	30/07/2000	VB	ASTRA-ZENECA	Investigateur - Association			
55583	JONDEAU	Guillaume	30/07/2000	VB	HERPERION	Investigateur - Association			
55583	JONDEAU	Guillaume	11/01/2000	VB	ASTRA ZENECA	Etude CHARM			
55583	JONDEAU	Guillaume	11/01/2000	VB	MESPERION	Etude Tezozentan			
55583	JONDEAU	Guillaume	11/01/2000	VB	BMS	Etude Overture			
55583	JONDEAU	Guillaume	11/01/2000	IP-AC	SERVIER	Conseil sur Ivabradine			
55583	JONDEAU	Guillaume	11/01/2000	IP-CF	3 M	NO et Angor, 1999			
55583	JONDEAU	Guillaume	11/01/2000	IP-CF	ASTRA	Antagonisle ATII et insuffisance cardiaque, 2000			
55583	JONDEAU	Guillaume	11/01/2000	IP-CF	ROCHE	Be dans l'insuffisance cardiaque			
55583	JONDEAU	Guillaume	01/01/1999	LD	Traduction en français de texte anglais : SERVIER				
55583	JONDEAU	Guillaume	01/01/1999	IP-EC	3M				
62127	JUDE	Brigitte	26/10/2002	IP-CF	AVENTIS	Etats généraux de la thrombose, 2002			
62127	JUDE	Brigitte	26/10/2002	IP-CF	LFB	Relecture d'ouvrage, 2002			
62127	JUDE	Brigitte	15/05/2002	IP-EC	SERVIER	Evaluation inhibiteur récept TXA 2			
62127	JUDE	Brigitte	15/05/2002	IP-CF	BAYER	Universités été (juin 2001) - (arthérosclérose)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62127	JUDE	Brigitte	15/05/2002	IP-CF	AVENTIS	Etats généraux thrombose - 2002			
62127	JUDE	Brigitte	15/05/2002	IP-CF	LFB	Correction plaquette conduite à tenir hémistase - 2002			
61813	JUILLIERE	Yves	08/03/2010	CF-INT	ASTRAZENECA	Congrès et conférences	Rémunération personnelle	01/2003	
61813	JUILLIERE	Yves	08/03/2010	EC-INV	ASTRAZENECA	Projet I-CARE de la SFC financé par le laboratoire	Coordinateur France	01/2003	
61813	JUILLIERE	Yves	08/03/2010	CF-INT	TAKEDA	Participation à la rédaction d'un livre sur l'IC subventionné par le laboratoire	Rémunération personnelle	10/2009	
61813	JUILLIERE	Yves	08/03/2010	CF-INT	SANOFI-AVENTIS	Congrès et conférences	Rémunération personnelle	01/2001	
61813	JUILLIERE	Yves	08/03/2010	EC-INV	NOVARTIS	Etude ATMOSPHERE avec aliskiren	Coordinateur France	03/2009	
61813	JUILLIERE	Yves	08/03/2010	CF-INT	NOVARTIS	Participation à un livre sur l'insuffisance cardiaque financé par Novartis	Rémunération personnelle	11/2009	01/2010
61813	JUILLIERE	Yves	12/03/2009	CF-INT	BMS	Participation Board IC-FSP	Rémunération personnelle	01/2001	
61813	JUILLIERE	Yves	12/03/2009	EC-INV	ASTRAZENECA	Président Board I-CARE	Président	01/2003	
61813	JUILLIERE	Yves	12/03/2009	CF-INT	SANOFI-AVENTIS	Participation Board IC-FSP	Rémunération personnelle	01/2001	
61813	JUILLIERE	Yves	12/03/2009	CF-INT	MSD-SCHERING PLOUGH	Intervention national Congrès ACP Marseille	Rémunération personnelle	03/2009	03/2009
61813	JUILLIERE	Yves	12/03/2009	EC-INV	NOVARTIS	Coordinateur France étude ATMOSPHERE	Coordinateur national - investigateur	02/2009	
61813	JUILLIERE	Yves	06/10/2008	CF-INT	ROCHE DIAGNOSTICS	Intervention nationale Congrès SFC	Rémunération personnelle	01/2008	01/2008
61813	JUILLIERE	Yves	01/10/2007	CF-AUD	ASTRAZENECA	Congrès européen Heart Failure		06/2007	06/2007
61813	JUILLIERE	Yves	01/10/2007	CF-AUD	NOVARTIS	Congrès ESC		09/2007	09/2007
61813	JUILLIERE	Yves	01/10/2007	IP-AC	SCHERING-PLOUGH	Formation des délégués régionaux	Rémunération personnelle	10/2006	
61813	JUILLIERE	Yves	01/10/2007	CF-INT	PFIZER	Une réunionrégionale	Rémunération personnelle	06/2007	06/2007
61813	JUILLIERE	Yves	01/10/2007	IP-AC	MENARINI	Conseil pour réunions de FMC	Rémunération personnelle	09/2007	
61813	JUILLIERE	Yves	01/10/2007	CF-INT	MENARINI	Interventions loco-régionales sur l'insuffisance cardiaque	Rémunération personnelle	09/2007	
61813	JUILLIERE	Yves	01/10/2007	CF-INT	BMS-SANOFI	Nombreuses interventions en France	Rémunération personnelle	01/2002	
61813	JUILLIERE	Yves	01/10/2007	CF-INT	ASTRA-ZENECA	Nombreuses interventions en France	Rémunération personnelle	01/2004	
61813	JUILLIERE	Yves	01/10/2007	IP-AC	BMS-SANOFI	Board TACTIC	Rémunération personnelle	02/2004	
61813	JUILLIERE	Yves	01/10/2007	IP-AC	ABBOTT	Board post-infactus	Rémunération personnelle	03/2006	
61813	JUILLIERE	Yves	01/10/2007	EC-INV	BMS-SANOFI	Etude I-PRESERVE	Investigateur-coordonateur	01/2002	
61813	JUILLIERE	Yves	01/10/2007	EC-INV	AMGEN	Etude RED-HF	Investigateur principal	03/2007	
61813	JUILLIERE	Yves	01/10/2007	IP-AC	MEDTRONIC	Board insuffisance cardiaque	Rémunération personnelle	09/2007	
61813	JUILLIERE	Yves	29/05/2006	EC-INV	MEDTRONIC	étude CARE HF (resynchronisation)	investigateur principal		12/2005
61813	JUILLIERE	Yves	29/05/2006	EC-INV	ASTRA ZENECA	étude CHARM (candesartan)	investigateur principal		12/2003
61813	JUILLIERE	Yves	29/05/2006	EC-INV	AMGEN	anémie et IC (darbopoietine)	investigateur principal		12/2005
61813	JUILLIERE	Yves	29/05/2006	EC-INV	AMGEN	étude RED-HF (darbopoietine)	investigateur principal	01/2006	
61813	JUILLIERE	Yves	29/05/2006	EC-INV	ROCHE	étude Comet (carvedilol)	investigateur principal		12/2003
61813	JUILLIERE	Yves	29/05/2006	EC-INV	BMS	étude overture (omapatrilat)	investigateur principal		12/2002
61813	JUILLIERE	Yves	29/05/2006	EC-INV	BMS	étude CV154-008 (BMS 207940)	investigateur principal		12/2000
61813	JUILLIERE	Yves	29/05/2006	EC-INV	BMS	étude PROVE-IT (paraplatine)	investigateur principal		12/2003
61813	JUILLIERE	Yves	29/05/2006	EC-INV	BMS	étude CV137-018 (omapatrilat)	investigateur principal		12/2003
61813	JUILLIERE	Yves	29/05/2006	EC-INV	BMS SANOFI	étude I.Preserve (irbesartan)	investigateur principal	01/2004	
61813	JUILLIERE	Yves	29/05/2006	EC-INV	ASTRA ZENECA	projet I.CARE (educ. Thérapeutique)	initiateur projet	01/2004	
61813	JUILLIERE	Yves	29/05/2006	EC-INV	SERVIER	étude Improvement (Epidémio)	investigateur principal		12/2002
61813	JUILLIERE	Yves	29/05/2006	EC-CO	ORION	étude EFICA (épidémio)	co-investigateur		12/2004
61813	JUILLIERE	Yves	29/05/2006	IP-AC	BMS SANOFI	Board TACTIC	rémunération personnelle	01/2003	
61813	JUILLIERE	Yves	29/05/2006	IP-AC	ABBOTT	board post PDM	rémunération personnelle	01/2006	
61813	JUILLIERE	Yves	29/05/2006	CF-INT	ASTRA ZENECA	nombreuses interventions Nationales Régionales (candesartan, metoprolol)	rémunération personnelle		
61813	JUILLIERE	Yves	29/05/2006	CF-INT	BMS SANOFI	nombreuses interventions Nationales Régionales (irbesartan, pravastatin)	rémunération personnelle		
61813	JUILLIERE	Yves	29/05/2006	CF-INT	ABBOTT	intervention nationale	rémunération personnelle		
61813	JUILLIERE	Yves	29/05/2006	CF-INT	MERCK	intervention nationale (bisoprolol)	rémunération personnelle		
61813	JUILLIERE	Yves	29/05/2006	CF-AUD	ASTRA ZENECA	plusieurs réunions, nationales et internationales			
61813	JUILLIERE	Yves	29/05/2006	CF-AUD	BMS SANOFI	plusieurs réunions, nationales et internationales			
61813	JUILLIERE	Yves	29/05/2006	(Autre)	ASTRA ZENECA-BMS SANOFI	aide à la diffusion d'un livre sur l'insuffisance cardiaque destiné aux patients		01/2005	12/2007
61813	JUILLIERE	Yves	17/11/2005	EC-INV	MEDTRONIC	Etude CARE- HF (Resynchronisation)	Investigateur principal		12/2005
61813	JUILLIERE	Yves	17/11/2005	EC-INV	ASTRA ZENECA	Etude CHARM (candesartan)	Investigateur principal		12/2003
61813	JUILLIERE	Yves	17/11/2005	EC-INV	AMGEN	Anémie et IC (darbepoietine)	Investigateur principal		12/2005
61813	JUILLIERE	Yves	17/11/2005	EC-INV	BMS	Etude OVERTURE (Omapatrilat)	Investigateur principal		12/2002
61813	JUILLIERE	Yves	17/11/2005	EC-INV	ROCHE	Etude COMET (Carvédilol)	Investigateur principal		12/2003
61813	JUILLIERE	Yves	17/11/2005	EC-INV	BMS	Etude CV154-008 (BMS 207940)	Investigateur coordonnateur		12/2000
61813	JUILLIERE	Yves	17/11/2005	EC-INV	BMS	Etude PROVE IT (paraplatine)	Investigateur principal		12/2003
61813	JUILLIERE	Yves	17/11/2005	EC-INV	BMS	Etude CV137-018 (Omapatrilat)	Investigateur coordonnateur		12/2003
61813	JUILLIERE	Yves	17/11/2005	EC-INV	BMS-SANOFI	Etude I-PRESERVE (irbesartan) étude en cours	Investigateur Coordonnateur		
61813	JUILLIERE	Yves	17/11/2005	EC-INV	ASTRA-ZENECA	Projet I-CARE (éducation thérapeutique et IC (insuffisance cardiaque) (en cours)	Initiateur du projet		
61813	JUILLIERE	Yves	17/11/2005	EC-INV	SERVIER	Etude Improvement (épidémiologie de l'IC)	Investigateur principal		12/2002
61813	JUILLIERE	Yves	17/11/2005	EC-CO	ORION	Etude EFICA (Epidémiologie de l'IC aigue en France)	Co-investigateur		12/2004
61813	JUILLIERE	Yves	17/11/2005	IP-AC	BMS-SANOFI	Board IC à fonction systolique préservée (board TACTIC) - en cours	Rémunération personnelle	01/2003	
61813	JUILLIERE	Yves	17/11/2005	CF-INT	ASTRA-ZENECA	Nombreusos réunions nationales et locorégionales (produits : candesartan, metoprolol)	Rémunération personnelle		
61813	JUILLIERE	Yves	17/11/2005	CF-INT	BMS-SANOFI	Nombreuses réunions nationales et internationales et locorégionales (produits : Irbesartan, Pravastatin)	Rémunération personnelle		
61813	JUILLIERE	Yves	17/11/2005	CF-AUD	ASTRA-ZENECA	Plusieurs réunions nationales et internationales			
61813	JUILLIERE	Yves	17/11/2005	CF-AUD	BMS-SANOFI	plusieurs réunions nationales et internationales			
61813	JUILLIERE	Yves	17/11/2005	(Autre)	ASTRA-ZENECA, BMS-SANOFI	Aide à la diffusion d'un livre sur l'insuffisance cardiaque destiné aux patients		01/2005	12/2006
10250	KAHAN	André	08/06/2006	LD-AR	ACTELION	comité scientifique sclérodermie	rémunération personnelle	01/2003	
10250	KAHAN	André	08/06/2006	EC-INV	GENEVRIER	étude clinique / Chondrosulf	investigateur coordonateur	01/1999	
10250	KAHAN	André	08/06/2006	EC-INV	EXPANSCIENCE	étude clinique / Piasclédine	investigateur coordonateur	01/2003	
10250	KAHAN	André	08/06/2006	EC-INV	ROCHE	étude clinique / MABTHERA	investigateur coordonateur	01/2006	
10250	KAHAN	André	08/06/2006	EC-INV	AB SCIENCE	étude clinique / AB 1010	investigateur coordonateur	01/2005	
10250	KAHAN	André	08/06/2006	EC-CO	ROCHE	étude clinique / MRA	co-investigateur	01/2005	
10250	KAHAN	André	08/06/2006	EC-CO	ABBOTT	étude clinique / HUMIRA	co-investigateur	01/2005	
10250	KAHAN	André	08/06/2006	EC-CO	SERVIER	étude clinique / Ranélate Strontium	co-investigateur	01/2002	12/2005
10250	KAHAN	André	08/06/2006	EC-CO	LILLY	étude clinique / PTH	co-investigateur	01/2005	
10250	KAHAN	André	08/06/2006	RE-DE	NEGMA	evaluation dossier / DIACERHEINE (réponse à des questions)	rémunération personnelle	01/2002	
10250	KAHAN	André	08/06/2006	CF-INT	GENEVRIER- IBSA	congrès EULAR - congrès Suisse - étude Chondrosulf	rémunération personnelle	01/2006	01/2006
10250	KAHAN	André	08/06/2006	VB	ABBOTT, WYETH, ACTELION, ROCHE, MERCK	subvention : prix de recherche à l'INSERM	Association CERMOSA	01/2005	12/2005
10250	KAHAN	André	08/06/2006	VB	LUNAR	subvention : remboursement frais d'enseignement d'ostéodensitométrie	Association CERMOSA	01/2005	
10250	KAHAN	André	23/08/2005	LD-AR	GENEVRIER/IBSA	Membre du conseil scientifique : étude chondrosulf	rémunération personnelle	01/2005	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10250	KAHAN	André	23/08/2005	LD-AR	ACTELION	Membre du conseil scientifique : développement Bosentan	rémunération personnelle	01/2003	12/2006
10250	KAHAN	André	23/08/2005	EC-INV	ROCHE	Etude clinique Mabthera	coordonateur national	01/2005	12/2006
10250	KAHAN	André	23/08/2005	EC-INV	EXPANSCIENCE	Etude clinique Piascledine	coordonateur	01/2000	12/2002
10250	KAHAN	André	23/08/2005	EC-CO	ROCHE	Etude clinique : MRA	investigateur	01/2005	12/2006
10250	KAHAN	André	23/08/2005	EC-CO	ARBOTT	Etude clinique : Humira	investigateur	01/2004	12/2006
10250	KAHAN	André	23/08/2005	EC-CO	SERVIER	Etude clinique : Ranelate Strontium	investigateur	01/2003	12/2005
10250	KAHAN	André	23/08/2005	IP-RE	NEGMA	Dossier AMM - étude Echodiah - Diacérhéine		01/2000	12/2001
10250	KAHAN	André	23/02/2005	IP-AC	GENEVRIER - IBSA	2004			
10250	KAHAN	André	23/02/2005	IP-EC	GENEVRIER-IBSA	Chondrosulf			
10250	KAHAN	André	23/02/2005	IP-EC	AB	AB 1010			
10250	KAHAN	André	23/02/2005	IP-EC	SERVIER	Ranelate strontium			
10250	KAHAN	André	23/02/2005	IP-EC	PROCTER	Risédronate			
10250	KAHAN	André	23/02/2005	IP-EC	CENTOCOR	Infliximab			
10250	KAHAN	André	23/02/2005	IP-RE	NEGMA	Diacerheine			
10250	KAHAN	André	23/02/2005	IP-CF	BOEHRINGER	Meloxicam - congrès internationaux			
10250	KAHAN	André	23/02/2005	IP-CF		Congrès EULAR, ACR			
10250	KAHAN	André	23/02/2005	VB	MERCK, SERVIER				
10250	KAHAN	André	01/07/2000	IP-EC	GENEVRIER	Coordination essais cliniques			
10250	KAHAN	André	01/07/2000	IP-EC	PHARMASCIENCES	Coordination essais cliniques			
10250	KAHAN	André	01/07/2000	IP-EC	PROCTER & GAMBLE	Coordination essais cliniques			
10250	KAHAN	André	01/07/2000	IP-EC	MERCK SHARP DOHME	Coordination essais cliniques			
10250	KAHAN	André	01/07/2000	IP-RE	NEGMA	Etude Echodiah			
10250	KAHAN	André	01/07/2000	IP-RE	GRANIONS	Etude arthrose			
10250	KAHAN	André	01/07/2000	IP-CF	MERCK SHARP DOHME	Symposium Rofecoxib - Paris 2000			
10250	KAHAN	André	01/01/1999	IP-EC	BOEHRINGER				
10250	KAHAN	André	01/01/1999	IP-EC	CIS BIO				
10250	KAHAN	André	01/01/1999	IP-EC	SEARLE				
10250	KAHAN	André	01/01/1998	IP-AUT	Boehringer France				
10250	KAHAN	André	01/01/1998	IP-AUT	Hoffman la Roche				
10250	KAHAN	André	01/01/1998	IP-AUT	CIS-BIO				
10250	KAHAN	André	01/01/1998	IP-AUT	Jouveinal				
10250	KAHAN	André	01/01/1998	IP-AUT	Elan				
10250	KAHAN	André	01/01/1998	IP-AUT	Roche				
10250	KAHAN	André	01/01/1998	IP-AUT	ACR				
10251	KAHN	Jean-Claude	23/06/2004	IP-EC	SANOFI SYNTHELABO	Etude multicentrique, étude 1 préservé			
10251	KAHN	Jean-Claude	06/12/2001	LD	Revue ABSTRACT-CARDIO (Groupe Impact-Médecin)	Rédacteur en Chef			
10251	KAHN	Jean-Claude	06/12/2001	IP-EC	SCHERING-PLOUGH	Investigateur principal - Etude Practice			
10251	KAHN	Jean-Claude	06/12/2001	IP-EC	MENARINI RECHERCHE	Investigateur principal - Etude Séniors			
10251	KAHN	Jean-Claude	06/12/2001	IP-EC	NOVARTIS	Investigateur principal - Etude Valiant			
10251	KAHN	Jean-Claude	06/12/2001	IP-EC	ASTRA ZENECA	Coordinateur régional - Etude Stralacand			
10251	KAHN	Jean-Claude	22/06/2000	IP-EC	BAYER	Essai sur la Célivostatine (PRINCESS)			
10251	KAHN	Jean-Claude	22/06/2000	IP-EC	SMITH KLINE BEECHAM	Essai sur le Lotrohbon (BRAVO)			
10251	KAHN	Jean-Claude	22/06/2000	IP-EC	BMS SANOFI SYNTHELABO	Essai sur le Clopidogrel (CURE)			
10251	KAHN	Jean-Claude	22/06/2000	IP-EC	ASTRA ZENECA	Essai sur le Candesartan (CHARM)			
10251	KAHN	Jean-Claude	22/06/2000	IP-EC	NOVARTIS	Essai sur le Valsaiton (VALIANT)			
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	PRODUITS ROCHE	Coordonnateur national pour un essai			
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	BOEHRINGER INGELHEIM	Investigateur principal			
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	SEARLE				
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	ASTRA				
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	TAKEDA				
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	SEARLE				
10251	KAHN	Jean-Claude	01/01/1999	IP-EC	SERVIER				
10251	KAHN	Jean-Claude	01/01/1998	IP-AUT	Roche				
64390	KALOUSTIAN	Edgar	17/09/2010	CF-INT	TAKEDA	pourquoi le diabétique est-il difficile à prendre en charge?□□Place des glitazones dans le diabète de type 2	Rémunération personnelle	09/2010	09/2010
64390	KALOUSTIAN	Edgar	25/08/2010	CF-AUD	SANOFI	EASD Stockolm		09/2010	09/2010
64390	KALOUSTIAN	Edgar	25/08/2010	CF-AUD	SANOFI	EASD Stockolm		09/2010	09/2010
64390	KALOUSTIAN	Edgar	23/08/2010	CF-INT	NOVO NORDISK	analogue GLP1	Rémunération personnelle	11/2010	
64390	KALOUSTIAN	Edgar	20/06/2010	CF-INT	ASTRA ZENECA	Facteurs de risque cardiovasculaires	Rémunération personnelle	06/2010	
64390	KALOUSTIAN	Edgar	20/06/2010	CF-AUD	NOVO NORDISK	ADA Orlando		06/2010	06/2010
64390	KALOUSTIAN	Edgar	20/03/2010	CF-AUD	LILLY	congres 2010 Alfediam-SFD		03/2010	03/2010
64390	KALOUSTIAN	Edgar	20/03/2010	CF-INT	SANOFI AVENTIS	traitement du diabète de type 2	Rémunération personnelle	02/2010	
64390	KALOUSTIAN	Edgar	20/03/2010	CF-INT	SANOFI AVENTIS	traitement du diabète de type 2	Rémunération personnelle	02/2010	
64390	KALOUSTIAN	Edgar	20/03/2010	CF-INT	NOVO NORDISK	Amiens Animation d'une réunion sur les recommandations du TT du diabète de type 2-Liraglutide	Rémunération personnelle	01/2010	01/2010
64390	KALOUSTIAN	Edgar	29/01/2010	CF-INT	NOVO NORDISK	Amiens Novotel	Rémunération personnelle	01/2010	01/2010
64390	KALOUSTIAN	Edgar	25/06/2009	CF-AUD	NOVARTIS	Congrès ADA Nlle Orléans		06/2009	06/2009
64390	KALOUSTIAN	Edgar	25/06/2009	CF-AUD	LILLY	Invitation congrès société française d'endocrinologie Octobre 2009 Nice		10/2009	10/2009
64390	KALOUSTIAN	Edgar	01/04/2009	CF-AUD	NOVO NORDISK	Congrès EASD Vienne	Victoza	09/2009	10/2009
64390	KALOUSTIAN	Edgar	01/04/2009	CF-AUD	NOVARTIS	Congrès de l'ADA Nouvelle-Orléans	Galvus	06/2009	06/2009
64390	KALOUSTIAN	Edgar	01/04/2009	CF-AUD	ROCHE DIAGNOSTIC	Congrès de l'ALFEDIAM à Strasbourg	Lecteur de glycémie	03/2009	03/2009
64390	KALOUSTIAN	Edgar	01/04/2009	EC-INV	NOVARTIS	Organisation d'une réunion de spécialistes au niveau régional sur la vildagliptine en mai 2009			
64390	KALOUSTIAN	Edgar	01/04/2009	EC-INV	NOVO NORDISK	Organisation de réunions d'information sur le liraglutide. J'ai déclaré ce conflit avant la discussion sur le proc		12/2008	12/2009
64390	KALOUSTIAN	Edgar	26/09/2008	EC-INV	NOVO NORDISK	Etude 3L - abandon avant inclusion			
64390	KALOUSTIAN	Edgar	26/09/2008	EC-CO	SANOFI AVENTIS	Origin abandon avant inclusion			
64390	KALOUSTIAN	Edgar	26/09/2008	CF-INT	TAKEDA et Quotidien du Médecin	Glitazones dans le traitement du diabète de type 2 - Compiègne-Noyon - Auvers sur Oise/ Aclos	rémunération personnelle	01/2007	12/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-INT	SANOFI AVENTIS	Les recommandations de prise en charge du diabète de type 2 / ACOMPLIA / Noyon Beauvais	rémunération personnelle	01/2007	12/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-INT	LILLY	GLP1 (implication dans la prise en charge du diabète de type 2)	rémunération personnelle	01/2007	12/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-INT	MERCK	DPP4 et diabète / Sitagliptine	rémunération personnelle	01/2007	12/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-INT	GSK	Animation d'une réunion sur la place des glitazones dans le traitement du diabète de type 2	aucune rémunération	01/2006	12/2006
64390	KALOUSTIAN	Edgar	26/09/2008	CF-AUD	TAKEDA	Congrès de l'ADA - San Francisco		06/2008	06/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-AUD	SERVIER	Congrès EASD - Rome		09/2008	09/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-AUD	SERVIER	Congrès Alfediam		03/2008	03/2008
64390	KALOUSTIAN	Edgar	26/09/2008	CF-AUD	SERVIER	Congrès EASD Amsterdam		09/2007	09/2007

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64390	KALOUSTIAN	Edgar	26/09/2008	{Autre}	NOVARTIS	Forte probabilité dans les semaines qui viennent d'un engagement pour l'information régionale auprès des m			
64390	KALOUSTIAN	Edgar	21/06/2006	LD	NOVO NORDISK	Mise en place d'un essai clinique sur l'insuline Lévémir chez le sujet âgé		06/2006	
64390	KALOUSTIAN	Edgar	21/06/2006	LD-AR	TAKEDA	Enseignement post universitaire	Rémunération à une institution		
64390	KALOUSTIAN	Edgar	21/06/2006	LD-AR	GSK	Enseignement post universitaire	Rémunération à une institution		
64390	KALOUSTIAN	Edgar	21/06/2006	LD-AR	NOVO NORDISK	EPU	Aucune rémunération		
64390	KALOUSTIAN	Edgar	21/06/2006	IP-AC	NOVO NORDISK	Protocole Lévémir sujet âgé	Aucune rémunération	06/2006	
64390	KALOUSTIAN	Edgar	21/06/2006	CF-AUD	TAKEDA	ADA - Washington		06/2006	06/2006
64390	KALOUSTIAN	Edgar	21/06/2006	IF	EDF	Valeurs boursières	> 5000 € ou >5% du capital		
64390	KALOUSTIAN	Edgar	21/06/2006	IF	AEROPORTS DE PARIS	Valeurs bousières	<5000 € OU <5% du capital		
64390	KALOUSTIAN	Edgar	21/06/2006	IF	CAP GEMINI	Valeurs bousières	<5000 € ou <5% du capital		
64390	KALOUSTIAN	Edgar	21/06/2006	CF-INT	TAKEDA	Enseignement post universitaire - Actos			
64390	KALOUSTIAN	Edgar	21/06/2006	CF-INT	GSK	Enseignement post universitaire - Avandia ®	Rémunération personnelle		
64390	KALOUSTIAN	Edgar	21/06/2006	CF-INT	NOVO NORDISK	EPU restaurant - Novonorm ®	Sans rémunération		
61003	KANTELIP	Jean-Pierre	24/03/2010	Néant					
61003	KANTELIP	Jean-Pierre	24/03/2010	EC-CO		Etude dans le cadre des travaux de recherche de l' IFR 133			
61003	KANTELIP	Jean-Pierre	24/03/2010	CF-INT	URCAM Bourgogne franche Comté	Besançon : Journée du médicament : prévention du risque iatrogénique lié au médicament	Rémunération personnelle	10/2009	
61003	KANTELIP	Jean-Pierre	24/03/2010	EC-INV		Etudes dans le cadre des travaux de recherche de l'IFR 133			
61003	KANTELIP	Jean-Pierre	24/03/2010	CF-INT	URCAM BOURGOGNE-FRANCHE COMTE	Besançon : Journées du médicament : prévention du risque iatrogénique lié aux médicaments	rémunération personnelle	10/2009	10/2009
61003	KANTELIP	Jean-Pierre	13/03/2009	EC-CO		études dans le cadre des travaux de recherche de l'IFR 133			
61003	KANTELIP	Jean-Pierre	13/03/2009	CF-INT	NAMORMEC FMC	Besançon : EPU "optimiser la prescription"	rémunération personnelle	05/2007	05/2007
61003	KANTELIP	Jean-Pierre	13/03/2009	CF-INT	GROUPE L'ENCEPHALE	Besançon : relais d'expert "actualités de la prise en charge ai long court des schizophrénies"	rémunération personnelle	09/2007	09/2007
61003	KANTELIP	Jean-Pierre	13/03/2009	EC-CO		Etudes dans le cadre des travaux de recherche de l'IFR 133			
61003	KANTELIP	Jean-Pierre	13/03/2009	CF-INT	MAMORMEC FMC	Besancon : EPU "optimiser la prescription	Rémunération personnelle	05/2007	
61003	KANTELIP	Jean-Pierre	13/03/2009	CF-INT	GROUPE " L'ENCEPHALE"	Besancon : Relais d'expert "actualitésde la prise en charge au long court des schizophrénies"	Rémunération personnelle	09/2007	
61003	KANTELIP	Jean-Pierre	13/03/2008	EC-CO		Etudes dans le cadre des travaux de recherche de l'IFR 133			
61003	KANTELIP	Jean-Pierre	13/03/2008	CF-INT	NAMORMEC FMC	EPU "optimiser la prescription" - Besançon	rémunération personnelle	05/2007	05/2007
61003	KANTELIP	Jean-Pierre	13/03/2008	CF-INT	Groupe "l'encéphale"	Relais d'expert "actualités de la prise en charge au long court des schizophrénies - Besançon	rémunération personnelle	09/2007	09/2007
61003	KANTELIP	Jean-Pierre	26/03/2007	EC-INV	CHU BESANCON HAS	Evitabilité des effets indésirables médicamenteux dans un centre de long séjour - Projet EPP	coordonnateur	01/2006	12/2007
61003	KANTELIP	Jean-Pierre	26/03/2007	EC-INV	CHU BESANCON (financement INSERM PHRC)	Apport de la pharmaco-génétique dans la stratégie thérapeutique en gériatrie - □□Evaluation des bénéfices	investigateur	01/2005	12/2010
61003	KANTELIP	Jean-Pierre	29/01/2007	CF-INT	DEVELOPEMENT INSTITUTE INTERNATIONAL	Forum 2005 - Pharmacovigilance	Aucune rémunération	04/2006	
61003	KANTELIP	Jean-Pierre	30/05/2006	EC-CO		Etudes réalisées dans le cadre de travaux de notre équipe labellisée			
61003	KANTELIP	Jean-Pierre	16/02/2006	EC-CO		Dans le cadre d'équipes labellisées			
61003	KANTELIP	Jean-Pierre	16/02/2005	CF-INT	DEVELOPEMENT INSTITUT INTERNATIONAL	Forum 2005 - Pharmacovigilance	Aucune rémunération	04/2006	
61003	KANTELIP	Jean-Pierre	24/08/2004	IP-EC		Dans le cadre d'équipes contractualisées			
61003	KANTELIP	Jean-Pierre	25/01/2001	VB		Essai préclinique : Contrat Université de Franche Comté			
61003	KANTELIP	Jean-Pierre	27/09/1999	VB	VIRSOL	Essai préclinique en cours : Contrat Université de Franche Comté			
61003	KANTELIP	Jean-Pierre	27/09/1999	IP-EC	SERVIER, ADIR	Essai Phase III, 1998-1999 ; Association ADRM			
61003	KANTELIP	Jean-Pierre	27/08/1999	IP-EC	BOEHRINGER INGELHEIM	Phase III, 1998-1999 ; Association INTERUMEC			
61003	KANTELIP	Jean-Pierre	27/09/1999	IP-CF		F.M.C. Franche Comté - Bourgogne : Pharmacologie cardio-vasculaire ; Troubles du sommeil			
64381	KHAYAT	David	12/12/2007	LD-AR	ROCHE	conseil	Rémunération personnelle		
64381	KHAYAT	David	12/12/2007	LD-AR	PANACEA	conseil	Rémunération personnelle		
64381	KHAYAT	David	12/12/2007	LD-AR	ANTIGENICS	conseil	Rémunération personnelle		
64381	KHAYAT	David	12/12/2007	EC-CO	PFIZER	axitinib phase 2	co investigateur		
64381	KHAYAT	David	12/12/2007	EC-INV	SANOFI AVENTIS	aflibercept phase 2	principal investigateur		
64381	KHAYAT	David	12/12/2007	LD-AR	LILLY	conseil	Rémunération personnelle		
64381	KHAYAT	David	12/12/2007	LD-AR	SERVIER	conseil	Rémunération personnelle		
64381	KHAYAT	David	12/12/2007	LD-AR	ASTRAZENECA	conseil	Rémunération personnelle		
64381	KHAYAT	David	12/12/2007	EC-INV	PIERRE FABRE	Vinflunine phase 3	principal investigateur		
64381	KHAYAT	David	10/06/2006	IF	TCO	Capitaux propres (conjoint)□□date de début: <2000□□date de fin: en cours	5000€ ou 5% du capital		
64381	KHAYAT	David	10/06/2006	IF	ISOSANTE	capitaux propres (conjoint)	5000€ ou 5% du capital	01/2002	03/2005
64381	KHAYAT	David	10/06/2006	LD-AR	SANOFI-AVENTIS-SERVIER-ROCHE-ASTRA ZENECA-ORTHO BIOTECH-BMS-MERCK KGAA	Conseiller scientifique	Rémunératrion personnelle	01/2000	04/2004
64381	KHAYAT	David	10/06/2006	IP-AC	MILC (Mission Interministerielle de Lutte Contre le Cancer)	Conseiller permanent	Aucune rémunération	03/2003	07/2004
64381	KHAYAT	David	10/06/2006	IP-AC	Human Genome Science (Barcelone)	Conseil	Rémunération personnelle	06/2003	06/2003
64381	KHAYAT	David	10/06/2006	IP-AC	BMS Fondation (Utah)	Cancer award selection committee meeting	Rémunération personnelle	01/2004	01/2004
64381	KHAYAT	David	10/06/2006	CF-INT	EIH	Barcelone : european institute of Health (astra zeneca fondation)	rémunération personnelle	03/2004	03/2004
64381	KHAYAT	David	10/06/2006	CF-INT	ORTHO BIOTECH	Brescia/ chairman conseil scientifique	rémunération personnelle	06/2004	06/2004
64381	KHAYAT	David	10/06/2006	CF-INT	MERCK KGAA	Copenhagen : new directives in the treatment of colorectal cancer (ECCO)	rémunération personnelle	09/2003	09/2003
64381	KHAYAT	David	10/06/2006	CF-INT	ORTHO BIOTECH	Tialle (Modena) : fatigue et quality of life	rémunération personnelle	09/2003	09/2003
64381	KHAYAT	David	10/06/2006	CF-INT	INTALFARMACO	Forence / Padova : nouvelles apports d'unités dans le traitement des métastases cérébrales	rémunération personnelle	11/2003	11/2003
60408	KOROBELNIK	Jean-François	16/04/2010	EC-INV	PHRC	Etude GEFAL	Investigateur principal	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	EC-INV	LAB BAYER	Etude Galileo	Investigateur coordonnateur	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	EC-INV	LAB ALCON	Etude GATE	Investigateur principal	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	EC-INV	LAB BAYER	Etude VIEW2	Investigateur principal	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	LD-AR	LAB THEA	Consultant	Rémunération personnelle	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	LD-AR	LAB NOVARTIS	Consultant	Rémunération personnelle	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	LD-AR	LAB BAYER	Consultant et membre du steering comitee de View2 et Galileo	Rémunération personnelle	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	LD-AR	LAB ALLERGAN	Consultant	Rémunération personnelle	01/2010	12/2010
60408	KOROBELNIK	Jean-François	16/04/2010	LD-AR	LAB ALCON	Consultant	Rémunération personnelle	01/2010	12/2010
60408	KOROBELNIK	Jean-François	07/04/2009	EC-CO	LAB NOVARTIS	Lucentis étude MontBlanc	Co-investigateur	08/2008	12/2009
60408	KOROBELNIK	Jean-François	07/04/2009	LD-AR	LABORATOIRES BAUSH ET LOMB	Consultant Micronutrition	Rémunération personnelle	04/2009	12/2009
60408	KOROBELNIK	Jean-François	07/04/2009	LD-AR	LABORATOIRES NOVARTIS	Consultant DMLA	Rémunération personnelle	01/2009	12/2009
60408	KOROBELNIK	Jean-François	07/04/2009	LD-AR	LABORATOIRES ALCON	Consultant pour la chirurgie rétinovitréenne	Rémunération personnelle	01/2009	12/2009
60408	KOROBELNIK	Jean-François	07/04/2009	LD-AR	LABORATOIRES BAYER SCHERING	Membre du steering committee de l'étude VIEW2	Rémunération personnelle	12/2007	12/2012
60408	KOROBELNIK	Jean-François	21/03/2008	LD-AR	LABORATOIRES NOVARTIS	Membre de l'AMD faculty group	Rémunération personnelle	03/2007	12/2008
60408	KOROBELNIK	Jean-François	21/03/2008	LD-AR	LABORATOIRES BAYER SCHERING	Membre du steering committee de l'étude VIEW2	Rémunération personnelle	12/2007	12/2012
60408	KOROBELNIK	Jean-François	21/03/2008	LD-AR	LABORATOIRES ALCON	Consultant chirurgie	Rémunération personnelle	03/2008	12/2008
60408	KOROBELNIK	Jean-François	27/11/2007	LD-AR	LABORATOIRES PFIZER	Consultant DMLA	Rémunération personnelle	12/2007	11/2008
60408	KOROBELNIK	Jean-François	06/01/2007	LD-AR	LABORATOIRE NOVARTIS	Consultant	Rémunération personnelle	08/2006	08/2007

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60408	KOROBELNIK	Jean-François	28/12/2006	LD-AR	LABORATOIRE PFIZER	Consultant pour la DMLA	Rémunération personnelle	12/2006	11/2007
60408	KOROBELNIK	Jean-François	12/06/2006	EC-CO	LILLY	essai clinique multicentrique randomisé (Etude FOCAL B7AMC-MBDL) sur la rubauxistaurine (ARXXANT) d	Co-Investigateur	04/2004	12/2009
60408	KOROBELNIK	Jean-François	12/06/2006	EC-CO	NOVARTIS	Essai clinique multicentrique ransomisé (Etude EXCITE) sur le Lucentis dans la DMLA	Investigateur principal à Bordeaux	05/2006	12/2007
60408	KOROBELNIK	Jean-François	12/06/2006	EC-INV	PFIZER	Essai clinique multicentrique (étude 1016) sur le Macugen dans la DMLA (lésions précoces)	Investigateur coordonnateur	05/2006	12/2007
60408	KOROBELNIK	Jean-François	26/10/2005	LD-AR	PFIZER	Consultant Macugen	rémunération personnelle	10/2004	12/2006
60408	KOROBELNIK	Jean-François	11/04/2005	IP-AC	EURODHEA	Consultant	Vous	10/2004	05/2005
60408	KOROBELNIK	Jean-François	11/04/2005	IP-EC	IOLTECH	Co-investigateur : Mydriasert (il y a plus de 3 ans)		02/2003	06/2003
60408	KOROBELNIK	Jean-François	11/04/2005	IP-RE	IOLTECH	Mydriasert		09/2003	10/2003
60408	KOROBELNIK	Jean-François	11/04/2005	CF-INT	ALCON	AAO		10/2005	10/2005
60408	KOROBELNIK	Jean-François	11/04/2005	CF-AUD	PFIZER	ARVO		05/2005	05/2005
60408	KOROBELNIK	Jean-François	28/02/2005	LD	PFIZER	Macugen	Consultant	05/2004	
60408	KOROBELNIK	Jean-François	28/02/2005	EC-CO	ALCON	Co-Investigateur : Retaane		10/2003	12/2009
60408	KOROBELNIK	Jean-François	28/02/2005	EC-CO	PFIZER	Etude multicentrique randomisée 1003 comparant le pegaptanid (Macugen) au placebo dans la DMLA exsud		05/2002	10/2004
60408	KOROBELNIK	Jean-François	28/02/2005	EC-CO	SERVIER	Etude multicentrique randomisée France DMLA2 comparant Vastarel et placebo dans la prévention de la DM		05/2001	09/2005
60408	KOROBELNIK	Jean-François	14/06/2004	IP-EC	ALCON	Développement ANECORTAVE			
60408	KOROBELNIK	Jean-François	14/06/2004	IP-EC	PFIZER	Développement MACUGEN			
60408	KOROBELNIK	Jean-François	01/09/2003	IP-EC	EYETECH - PFIZER	Macugen pour le DMLA			
60408	KOROBELNIK	Jean-François	01/09/2003	IP-EC	ALCON	Arucortane pour le DMLA			
60408	KOROBELNIK	Jean-François	01/09/2003	IP-EC	SERVIER	Vastarel pour le DMLA			
60408	KOROBELNIK	Jean-François	01/09/2003	IP-EC	BAUSCH & LOMB	Traitement de l'uvéite			
60408	KOROBELNIK	Jean-François	01/09/2003	IP-EC	NOVARTIS	Visudyne pour la DMLA			
60408	KOROBELNIK	Jean-François	18/10/2002	IP-EC	ALCON	Essais cliniques ANECORTAVE			
60408	KOROBELNIK	Jean-François	18/10/2002	IP-EC	EYETECH	Essai clinique MALUCTEN			
60408	KOROBELNIK	Jean-François	18/10/2002	IP-EC	SERVIER	Essais clinique VASTAREL- France DMLA2			
60408	KOROBELNIK	Jean-François	05/08/2002	IP-EC	EYETECH	VEGF dans le DMLA			
60408	KOROBELNIK	Jean-François	05/08/2002	IP-EC	ALCON	Anecortave dans le DMLA			
60408	KOROBELNIK	Jean-François	05/08/2002	IP-AC	NOVARTIS	Visudyne et DMLA			
60408	KOROBELNIK	Jean-François	11/09/2000	Néant					
60408	KOROBELNIK	Jean-François	15/02/2000	IP-RE	ALCON				
10253	KREFT-JAIS	Carmen	08/01/2009	Néant					
10253	KREFT-JAIS	Carmen	08/01/2009	Néant					
10253	KREFT-JAIS	Carmen	06/01/2009	Néant					
10253	KREFT-JAIS	Carmen	09/10/2007	Néant					
10253	KREFT-JAIS	Carmen	30/10/2005	IP-AC	Prism Event Management	Mitocondrial collaborative Committee, participation au groupe en qualité de rapporteur auprès de l'EMEA - M	Aucune rémunération	05/2005	05/2005
10253	KREFT-JAIS	Carmen	30/10/2005	CF-INT	DIA	Modérateur et conférencier - Medical Approach in Diagnosis and Management of ADRs (sept. 2003)	Aucune rémunération		
10253	KREFT-JAIS	Carmen	30/10/2005	CF-INT	DIA	Modérateur et conférencier - Medical Approach in Diagnosis and Management of ADRs (sept. 2004)	Rémunération personnelle		
10253	KREFT-JAIS	Carmen	30/10/2005	CF-INT	DII	Forum 2005 Pharmacovigilance	Aucune rémunération	04/2005	04/2005
10253	KREFT-JAIS	Carmen	30/10/2005	CF-INT	IFIS	Forum Pharmacovigilance	Aucune rémunération	04/2003	04/2003
10253	KREFT-JAIS	Carmen	30/10/2005	PAR	UCB	Beau-frère			
10253	KREFT-JAIS	Carmen	25/05/2004	(Autre)		Membre du comité de Safety pour Protelos, Oxocor (ranelate de strontium) jusqu'en juin 1999 à titre gratuit			
10253	KREFT-JAIS	Carmen	23/04/2004	IP-CF	DIA	Medical Approach and Managment of ADR's - 2003			
10253	KREFT-JAIS	Carmen	01/01/1999	PAR	FIRST, SOTI, TROPOS, SERVIER	Protocoles			
10253	KREFT-JAIS	Carmen	01/01/1998	PAR	Comité de Safety				
10253	KREFT-JAIS	Carmen	01/01/1998	PAR	Protocoles First				
10253	KREFT-JAIS	Carmen	01/01/1998	PAR	Soti				
10253	KREFT-JAIS	Carmen	01/01/1998	PAR	Tropos				
10255	KUTTENN	Frédérique	30/05/2010	IP-AC	ORGANON	Certificat sur l'Utilité du Progestatif Orgametril (épisodique en cours)	Aucune Rémunération	01/2005	
10255	KUTTENN	Frédérique	30/05/2010	IP-AC	Jury GALIEN	Membre du jury	Aucune Rémunération	01/2003	
10255	KUTTENN	Frédérique	30/05/2010	CF-AUD	SANOFI PASTEUR	Congrès Européen de la Société Française de Gynécologie Maison de la Chimie Paris		10/2008	10/2008
10255	KUTTENN	Frédérique	30/05/2010	VB	CODEPHARMA	Budget d'un EPU 28/10/2007 (Cocktail - mailing)	Bénéficiaire : AEPPG	10/2007	10/2007
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	BESINS	Maintenance d'un ostéodensitomètre	Maintenant assurée depuis et appareil remplacé par l'AP-HP	01/2006	12/2007
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	FERRING	Soirée de Gynécologie du groupe Pitié Salpêtrière EPU		03/2007	03/2007
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	CODEPHARMA	Soirée de gynécologie du groupe Pitié Salpêtrière EPU		10/2007	10/2007
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	IPSEN	Soirée de gynécologie du groupe Pitié Salpêtrière EPU		11/2007	11/2007
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	FERRING	Soirée de gynécologie du groupe Pitié Salpêtrière EPU		05/2009	05/2009
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	IPSEN	Soirée de gynécologie du groupe Pitié Salpêtrière EPU		03/2010	03/2010
10255	KUTTENN	Frédérique	30/05/2010	(Autre)	BESINS	Soirée de gynécologie du groupe Pitié Salpêtrière EPU		06/2010	06/2010
10255	KUTTENN	Frédérique	26/03/2009	LD-AR	ORGANON - SCHERING PLOUGH	Certificat sur le caractère indispensable (absence d'alternative) du Lynestrenol (Orgametril)	Aucune rémunération	01/2007	12/2009
10255	KUTTENN	Frédérique	26/03/2009	RE-AUT	PRIX GALIEN	Jury du prix Galien	Aucune rémunération	01/2003	
10255	KUTTENN	Frédérique	26/03/2009	CF-AUD	PFIZER	Congrès Européen de la Société Française de Gynécologie - Maison de la Chimie - Paris		10/2008	10/2008
10255	KUTTENN	Frédérique	26/03/2009	(Autre)	CODEPHARMA	Mailing + Cocktail : soirée de gynécologie de la Pitié Salpêtrière - 80 participants "Les contraceptions difficiles"		10/2007	10/2007
10255	KUTTENN	Frédérique	26/03/2009	(Autre)	BEZINS ISCOVESCO	Mailing + Cocktail : "Progestatifs et seins"		03/2008	03/2008
10255	KUTTENN	Frédérique	26/03/2009	(Autre)	PFIZER, DAYER	Mailing + Cocktail : "Prolactine et Pathologies mammaires"		03/2009	03/2009
10255	KUTTENN	Frédérique	22/06/2006	VB	BESINS INTERNATIONAL	Matériel : mise à disposition d'un ostéodensitomètre pour mesure de la DMO des patients.	AP-HP	01/1993	12/2006
10255	KUTTENN	Frédérique	22/06/2006	CF-INT	HRA PHARMA, FOURNIER, ROTTAFARM, EFFIK, AVENTIS, ORGANON, LILLY, THERAMEX, WYETH, PFIZER, SOLVAY PHARMA, PIERRE FABRE, SERVIER, NOVARTIS, IPSEN, BESINS, SCHERING	Faculté Necker : "THS tous coupables ?",Organisation Congres pour INSERM + Société Française d'Endocr	Aucune rémunération	01/2004	12/2004
10255	KUTTENN	Frédérique	22/06/2006	RE-AUT	JURY PRIX GALIEN	Membre	Aucune rémunération	01/2003	12/2006
10255	KUTTENN	Frédérique	22/06/2006	RE-AUT	ORGANON	Intervention ponctuelle□□--> utilité Orgamétril	Aucune rémunération	01/2005	12/2005
10255	KUTTENN	Frédérique	22/06/2006	RE-DE	BESINS INTERNATIONAL	Demande d'AMM France - Europe□□ANDROGEL	Rémunération versée à une institution	01/2001	12/2002
10255	KUTTENN	Frédérique	22/06/2006	RE-DE	BESINS INTERNATIONAL	Demande d'AMM France et Europe□□ANDROGEL	Rémunération institution	01/2001	12/2002
10255	KUTTENN	Frédérique	23/10/2000	IP-EC	BESINS-ISCOVESCO	Convention avec Université René Descartes - Travaux scientifiques : Effets cellulaires Progestérone sur pro			
10255	KUTTENN	Frédérique	23/10/2000	IP-RE	BESINS-ISCOVESCO	Androgel : demande d'AMM			
10255	KUTTENN	Frédérique	23/10/2000	VB	ZENECA PHARMA	Séminaire / Association loi 1901			
10255	KUTTENN	Frédérique	23/10/2000	PAR		Jury Bourse IPSEN			
10255	KUTTENN	Frédérique	01/01/1999	VB	CASSENNE	Activité ponctuelle de conseils : Association Loi 1901 AEPPG.			
10255	KUTTENN	Frédérique	01/01/1999	VB	THERABEL	Association Loi 1901 AEPPG.			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10255	KUTTENN	Frédérique	01/01/1999	VB	SERVIER	Association Loi 1901 AEPPG.			
10255	KUTTENN	Frédérique	01/01/1999	VB	SOLVAY	Association Loi 1901 AEPPG.			
10255	KUTTENN	Frédérique	01/01/1999	VB	SCHERING	Une conférence : Association Loi 1901 AEPPG.			
10255	KUTTENN	Frédérique	01/01/1998	VB	Cassenne		pour l'association de Recherche sur la physiologie et la pathologie Gonadique		
10255	KUTTENN	Frédérique	01/01/1998	VB	Servier		pour l'association de Recherche sur la physiologie et la pathologie Gonadique		
10255	KUTTENN	Frédérique	01/01/1998	VB	Merck-Clévenot		pour l'association de Recherche sur la physiologie et la pathologie Gonadique		
60761	LABLANCHE	Jean-Marc	02/04/2007	EC-INV	ASTRAZENECA	Rosuvastatine	investigateur principal (en cours)		
60761	LABLANCHE	Jean-Marc	02/04/2007	EC-CO	BOSTON	TAXUS II et VI (en cours)	investigateur		
60761	LABLANCHE	Jean-Marc	02/04/2007	EC-CO	PFIZER	ILLUMINATE Torcetrapib Endpoint committee (en cours)	investigateur		09/2007
60761	LABLANCHE	Jean-Marc	02/04/2007	IP-AC	PFIZER	Statines (en cours)	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	IP-AC	ASTRAZENECA	statines (en cours)	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	IP-AC	MSD-SP	statines Ezétimibe (en cours)	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	PFIZER	Statines	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	ASTRAZENECA	statines	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	MSD-SP	Statines Ezétimibe	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	SERVIER	congrès commentaires	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	NOVARTIS	Statines	Rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-AUD	ASTRAZENECA	Congrès de l'ESC		09/2006	09/2006
60761	LABLANCHE	Jean-Marc	02/04/2007	EC-CO	ABBOTT	Zomaxx	investigateur		
60761	LABLANCHE	Jean-Marc	02/04/2007	EC-CO	CORDIS	Cypher	investigateur		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	LILLY	Réopro	rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	SCHERING PLOUGH	Integrilin - syndromes coronaires aigus	rémunération personnelle		
60761	LABLANCHE	Jean-Marc	02/04/2007	CF-INT	NYCOMED	Angiox	rémunération personnelle		11/2007
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-EC	BOSTON SCIENTIFIQUE	Etudes TAXUS II et VI terminées			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-EC	MEDTRONIC	Etude emerald terminée			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-EC	PFIZER, ASTRA, NOVARTIS, AVENTIS	Etudes cliniques de médicaments			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-AC		Aucun des dispositifs médicaux			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-AC	ASTRA, PFIZER, MSD/SP	Board hypolipidémiants			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-CF	BOSTON	Stents actifs			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-CF	NYCOMED, GSK	Thrombose			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-CF	PFIZER, ASTRAT, MSD/SP	Hypolipidemiants			
60761	LABLANCHE	Jean-Marc	30/09/2005	IP-CF	CORDIS, BOSTON, MEDTRONIC, PFIZER, ASTRA, SERVIER, MSD	Congrés			
60761	LABLANCHE	Jean-Marc	28/10/2004	IP-EC	BOSTON SCIENTIFIQUE	Taxus II, VI, Filler wire			
60761	LABLANCHE	Jean-Marc	28/10/2004	IP-EC	CORDIS	Bridge (stent cypher)			
60761	LABLANCHE	Jean-Marc	28/10/2004	IP-EC	MEDTRONIC	Emerald (protection myocardique)			
60761	LABLANCHE	Jean-Marc	28/10/2004	IP-AC	BOSTON SCIENTIFIQUE	Quelques réunions d'experts			
60761	LABLANCHE	Jean-Marc	28/10/2004	IP-CF	BOSTON SCIENTIFIQUE	Présentation des études Taxus			
60761	LABLANCHE	Jean-Marc	28/10/2004	VB	CHU	ID essais cliniques			
60761	LABLANCHE	Jean-Marc	17/03/2004	IP-EC	CORDIS J&J	Registre BRIDGE Stent Cypher			
60761	LABLANCHE	Jean-Marc	17/03/2004	IP-EC	BOSTON	Etudes Taxus II et VI			
60761	LABLANCHE	Jean-Marc	17/03/2004	IP-EC	MEDTRONIC	EMERALD Protection myocardique			
60761	LABLANCHE	Jean-Marc	17/03/2004	IP-EC	GUIDANT	DELIVER Registre Stent			
60761	LABLANCHE	Jean-Marc	17/03/2004	IP-CF	BOSTON	Stents pharmacoactifs			
60761	LABLANCHE	Jean-Marc	17/03/2004	IP-CF	CORDIS	Stents pharmacoactifs			
60761	LABLANCHE	Jean-Marc	10/01/2001	IP-EC	Toutes les entreprises travaillant dans le domaine de la pathologie coronaire				
60761	LABLANCHE	Jean-Marc	10/01/2001	IP-RE	Idem				
60761	LABLANCHE	Jean-Marc	10/01/2001	IP-AC	Idem				
60761	LABLANCHE	Jean-Marc	10/01/2001	IP-CF	Idem				
60761	LABLANCHE	Jean-Marc	10/01/2001	VB	Idem				
55591	LACOMBLEZ	Lucette	21/05/2010	CF-AUD	TEVA	9th international symposium on MS		05/2010	05/2010
55591	LACOMBLEZ	Lucette	21/05/2010	CF-AUD	EISAI	JNLF (journées neurologie langue francaise) lyon avril 2010		04/2009	04/2010
55591	LACOMBLEZ	Lucette	25/05/2009	IP-AC	EISAI	board démence	Rémunération personnelle	06/2009	
55591	LACOMBLEZ	Lucette	25/05/2009	IP-AC	NOVARTIS	advisory board demence (alzheimer/parkinson)	Rémunération personnelle	01/2009	
55591	LACOMBLEZ	Lucette	25/05/2009	EC-CO	TROPHOS/EUROPE	phase II/III ALS / TRO 19622	investigateur	05/2009	
55591	LACOMBLEZ	Lucette	25/05/2009	EC-CO	GSK	phase II biopsie SLA anti nogo	investigateur	05/2009	
55591	LACOMBLEZ	Lucette	25/05/2009	EC-INV	APHP	essai clinique SLA DOSERALS	investigateur coordinateur	07/2009	
55591	LACOMBLEZ	Lucette	25/05/2009	EC-INV	APHP	essai clinique lithium ALS	investigateur coordinateur	03/2009	
55591	LACOMBLEZ	Lucette	03/10/2008	CF-AUD	EISAI	AAN chicago	April 13, and Thursday, April 17□	04/2008	04/2008
55591	LACOMBLEZ	Lucette	03/10/2008	EC-CO	GSK	phase O biopsie SLA nogo	investigateur	06/2008	
55591	LACOMBLEZ	Lucette	03/10/2008	EC-CO	TEVA	phase II/III SLA Talampanel	investigateur	10/2008	
55591	LACOMBLEZ	Lucette	09/08/2007	EC-INV	NOVARTIS	comparaison patch/ gélules Rivastigmine maladie Alzheimer	investigateur	09/2007	
55591	LACOMBLEZ	Lucette	09/08/2007	EC-INV	FAUST	phase II/FP0011 maladie de Parkinson	investigateur principal/ membre du comité de pilotage	09/2007	01/2008
55591	LACOMBLEZ	Lucette	09/08/2007	EC-INV	NOVARTIS	étude observationnelle démence Parkinson	Investigateur principal / membre comité	09/2007	09/2008
55591	LACOMBLEZ	Lucette	09/08/2007	EC-CO	NOVARTIS	comparaison MA patch vs gélules Rivastigmine	investigateur	09/2007	
55591	LACOMBLEZ	Lucette	09/08/2007	CF-AUD	NOVARTIS	Réunion investigateur - Genève		09/2007	09/2007
55591	LACOMBLEZ	Lucette	09/08/2007	CF-AUD	NOVARTIS	Congrès Parkinson - Amsterdam		12/2007	12/2007
55591	LACOMBLEZ	Lucette	09/08/2007	EC-INV	SANOFI	phase 0/ recherche marqueurs SLA		06/2007	
55591	LACOMBLEZ	Lucette	09/08/2007	EC-CO	NOVARTIS	étude observationnelle démence parkinson	investigateur	09/2007	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
55591	LACOMBLEZ	Lucette	09/08/2007	CF-AUD	JANSSEN	San Antonio (USA)/ démences vasculaires/ galantamine		07/2007	07/2007
55591	LACOMBLEZ	Lucette	09/08/2007	EC-CO	ONO	phase II/III/SLA	investigateur	05/2007	
55591	LACOMBLEZ	Lucette	09/08/2007	LD-AR	AMERSHAM	activité conseil	rémunération institution		
55591	LACOMBLEZ	Lucette	09/08/2007	IP-AC	AMERSHAM	conseil scientifique /Datscan ®	Rémunération institution	09/2005	
55591	LACOMBLEZ	Lucette	09/08/2007	EC-CO	FAUST	essai clinique	co-investigateur	01/2006	12/2006
55591	LACOMBLEZ	Lucette	09/08/2007	EC-CO	TROPHOS	essai clinique SLA	co-investigateur	01/2006	01/2007
55591	LACOMBLEZ	Lucette	09/08/2007	EC-CO	TEVA	phase II/SLA/copaxone	investigateur	07/2006	06/2008
55591	LACOMBLEZ	Lucette	09/08/2007	LD-AR	FAUST	activité conseil	rémunération personnelle	01/2005	01/2008
55591	LACOMBLEZ	Lucette	09/08/2007	LD-AR	NOVARTIS	activité conseil	rémunération personnelle	01/2005	
55591	LACOMBLEZ	Lucette	09/10/2006	IP-AC	AMERSHAM	conseil scientifique /datscan	Rémunération institution	09/2005	
55591	LACOMBLEZ	Lucette	09/10/2006	CF-AUD	NOVARTIS	10th international conference on Alzheimer disease and related disorders		07/2006	07/2006
55591	LACOMBLEZ	Lucette	09/10/2006	CF-AUD	JANSSEN	9th springfield symposium/geneve		04/2006	04/2006
55591	LACOMBLEZ	Lucette	09/10/2006	EC-CO	TEVA	phase II/SLA/copaxone	investigateur	07/2006	
55591	LACOMBLEZ	Lucette	09/10/2006	EC-CO	FAUST	phaseII parkinson/FP0011	investigateur	05/2005	07/2006
55591	LACOMBLEZ	Lucette	09/10/2006	EC-CO	NOVARTIS	phaseIIb/sla/TCH	investigateur	12/2002	01/2005
55591	LACOMBLEZ	Lucette	09/10/2006	EC-CO	FAUST	phase II/SLA/FP0011	investigateur	10/2004	01/2006
55591	LACOMBLEZ	Lucette	09/10/2006	EC-CO	TROPHOS	phase II/SLA/TRO19822	investigateur	01/2006	10/2006
55591	LACOMBLEZ	Lucette	20/04/2006	LD-AR	NOVARTIS	activité conseil	rémunération personnelle	01/2005	
55591	LACOMBLEZ	Lucette	20/04/2006	LD-AR	FAUST	activité conseil	rémunération personnelle	01/2005	
55591	LACOMBLEZ	Lucette	20/04/2006	LD-AR	AMERSHAM	activité conseil	rémunération institution		
55591	LACOMBLEZ	Lucette	20/04/2006	EC-INV	FAUST	FP 0011 - essai SLA (Sclérose Latérale Amyotrophique)	investigateur	01/2005	12/2006
55591	LACOMBLEZ	Lucette	20/04/2006	EC-CO	TROPHOS	essai clinique SLA (Sclérose Latérale Amyotrophique)	co-investigateur	01/2006	
55591	LACOMBLEZ	Lucette	20/04/2006	EC-CO	FAUST	essai clinique Parkinson	co-investigateur	01/2006	
55591	LACOMBLEZ	Lucette	20/04/2006	CF-INT	NOVARTIS	congrès Neurologies - Paris "Declin cognitif"	rémunération personnelle	10/2005	10/2005
55591	LACOMBLEZ	Lucette	20/04/2006	CF-INT	SANOFI	"Neuroprotection - Paris - Neuroprotection maladie d'Alzheimer"	rémunération personnelle	12/2005	12/2005
55591	LACOMBLEZ	Lucette	20/04/2006	CF-AUD	JANSSEN	9th international Springfield Symposium in Alzheimer Therapy - Genève		04/2006	04/2006
55591	LACOMBLEZ	Lucette	20/04/2006	CF-AUD	BOEHRINGER	5th Symposium international on Parkinson disease - Barcelona		04/2006	04/2006
55591	LACOMBLEZ	Lucette	20/03/2005	IP-AC	EXONHIT	Comité de pilotage (dans le 2 années précédentes)	Aucune rémunération		
55591	LACOMBLEZ	Lucette	20/03/2005	IP-AC	SANOFI	Xaliproden (comité de pilotage (il y a plus de 3 ans)	Aucune rémunération		
55591	LACOMBLEZ	Lucette	20/03/2005	IP-EC	EXONHIT	Co-investigateur		10/2002	10/2004
55591	LACOMBLEZ	Lucette	20/03/2005	IP-EC	NOVARTIS	Co-investigateur - Exelon		09/2002	04/2004
55591	LACOMBLEZ	Lucette	20/03/2005	IP-CF	ETSAI, NOVARTIS	invitation en qualité d'auditeur (EPU)			
55591	LACOMBLEZ	Lucette	20/03/2005	VB	EXONHIT, SANOFI (XALIPRODEN), NOVARTIS (TCH - EXELON), AMERSHAM (DUTSRAN)				
55591	LACOMBLEZ	Lucette	05/02/2004	IP-EC	EXONHIT	Participation teering committee			
55591	LACOMBLEZ	Lucette	05/02/2004	IP-EC	AVENTIS	Coordination recherches cliniques			
55591	LACOMBLEZ	Lucette	05/02/2004	IP-AC	LILLY	Développement produit			
55591	LACOMBLEZ	Lucette	05/02/2004	IP-AC	AVENTIS	Développement produits			
55591	LACOMBLEZ	Lucette	05/02/2004	IP-AC	JANSSEN	Alzheimer			
55591	LACOMBLEZ	Lucette	05/02/2004	VB	CHIESI	Association ACE (Coordination essai clinique)			
55591	LACOMBLEZ	Lucette	05/02/2004	VB	NOVARTIS	Association ACE (participation essai clinique)			
55591	LACOMBLEZ	Lucette	05/02/2004	VB	AMERSHAM	Association ACE (activité conseil)			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-EC	NOVARTIS	Parkinson, Alzheimer, HLA			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-EC	EXONHIT	HLA			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-EC	ONO	HLA			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-EC	CHIESI				
55591	LACOMBLEZ	Lucette	10/12/2003	IP-AC	LILLY	Maladie d'Alzheimer			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-AC	AVENTIS	Maladie d'Alzheimer			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-CF	PFIZER	Neuro-urologie EPU			
55591	LACOMBLEZ	Lucette	10/12/2003	IP-CF	JANSSEN	Médicaments maladie d'Alzheimer - EPU			
55591	LACOMBLEZ	Lucette	10/12/2003	VB	NOVARTIS	ACE			
55591	LACOMBLEZ	Lucette	10/12/2003	VB	EXONHIT	ACE			
55591	LACOMBLEZ	Lucette	10/12/2003	VB	ONO	ACE			
55591	LACOMBLEZ	Lucette	10/12/2003	VB	CHIESI	ACE			
55591	LACOMBLEZ	Lucette	28/02/2002	IP-AC	CHIESI	Etude dans la plainte amnésique	Courrier adressé à Ph D		
55591	LACOMBLEZ	Lucette	28/02/2002	IP-AC	EISAI	Dans le cadre étude dans la maladie de Leny			
55591	LACOMBLEZ	Lucette	19/12/2000	IP-RE	AVENTIS	SCA et ?			
55591	LACOMBLEZ	Lucette	19/12/2000	IP-AC	LILLY	Projet Olanzapine Alzheimer			
55591	LACOMBLEZ	Lucette	19/12/2000	IP-CF	LILLY	Dépression Démence			
55591	LACOMBLEZ	Lucette	19/12/2000	VB	SANOFI	Essais cliniques : Claude Bernard			
55591	LACOMBLEZ	Lucette	19/12/2000	VB	PIERRE FABRE	Essais cliniques : ACE			
55591	LACOMBLEZ	Lucette	19/12/2000	VB	NOVARTIS	Essais cliniques : ACE			
55591	LACOMBLEZ	Lucette	19/12/2000	VB	AMGEN	Essais cliniques : ACE			
55591	LACOMBLEZ	Lucette	19/12/2000	VB	AVENTIS	Essais cliniques : ACE			
55591	LACOMBLEZ	Lucette	19/12/2000	IP-AUT	NYCOMED	Essais cliniques : ACE			
55591	LACOMBLEZ	Lucette	11/01/2000	IP-RE	RHONE POULENC RORER				
55591	LACOMBLEZ	Lucette	11/01/2000	IP-CF	LILLY, NOVARTIS, AVENTIS				
55591	LACOMBLEZ	Lucette	11/01/2000	IP-AC	NOVARTIS, SERVIER				
55591	LACOMBLEZ	Lucette	11/01/2000	VB	NOVARTIS, SANOFI SYNTHELABO, RHONE POULENC RORER, AMGEN				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	SANOFI Recherche				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	RHONE POULENC RORER				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	AMGEN				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	ROCHE				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	SANOFI WINTHROP				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	BAYER				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-EC	EISAI				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-RE	PARKE DAVIS				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-RE	IRIS				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-RE	NOVARTIS				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-RE	LILLY				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-AC	IRIS				

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
55591	LACOMBLEZ	Lucette	01/01/1999	IP-AC	NOVARTIS				
55591	LACOMBLEZ	Lucette	01/01/1999	IP-AC	LILLY				
61121	LACROIX	Dominique	10/07/2006	LD-AR	MEDTRONIC EUROPE	COMITE D'ANALYSE D'EFFETS INDESIRABLES PACEMAKER OU DEFIBRILLATEURS	Rémunération personnelle	01/2000	12/2006
61121	LACROIX	Dominique	10/07/2006	CF-AUD	SERVIER MEDICAL	Congrès Européen de cardiologie (ESC)		09/2006	
61121	LACROIX	Dominique	10/07/2006	CF-INT	SERVIER MEDICAL	Rencontres de Cardiologie	Rémunération personnelle	06/2006	
61121	LACROIX	Dominique	10/07/2006	CF-INT	VITATRON	Symposium Fibrillation atriale	Rémunération personnelle	03/2006	
61121	LACROIX	Dominique	07/04/2006	LD-AR	MEDTRONIC SA,BAKKEN RESEARCH,CENTER (PAYS BAS)	Adverse event - Advisory Committee (membre permanent)	rémunération personnelle	01/1999	
61121	LACROIX	Dominique	07/04/2006	CF-INT	VITATRON	Barcelona AF sympoisum	rémunération personnelle	03/2006	03/2006
61121	LACROIX	Dominique	07/04/2006	CF-INT	SERVIER	rencontres de Cardiologie Montroyal	rémunération personnelle	06/2006	06/2006
61121	LACROIX	Dominique	07/04/2006	CF-AUD	SERVIER	American Freant association Dallas USA		11/2005	11/2005
61121	LACROIX	Dominique	07/04/2006	CF-AUD	BIOTRONIK	Cardiostim - Nice 2006		06/2006	06/2006
61121	LACROIX	Dominique	30/09/2004	LD-AR	MEDTRONIC EUROPE	Comité consultatif effets indésirables dans les études pacemaker ou défibrillateurs		01/2000	
61121	LACROIX	Dominique	30/09/2004	CF-INT	BIOSENSE WEBSTER	Séminaires ou colloques sur les méthodes ablasives en cardiologie			
61121	LACROIX	Dominique	30/09/2004	VB	BIOSENSE WEBSTER	Etudes sur les méthodes ablasives en cardiologie			
61121	LACROIX	Dominique	17/09/2003	IP-AC	MEDTRONIC Europe	Board européen effets indésirables pace makers et défibrillateurs			
61121	LACROIX	Dominique	17/09/2003	IP-CF	BIOSENCE WEBSTER	Colloque troubles du rythme, cartographie, méthodes ablasives			
61121	LACROIX	Dominique	17/09/2003	VB	BIOSENSE WEBSTER	Etudes cliniques - CHU de Lilol, délégation à la recherche			
61121	LACROIX	Dominique	14/10/2002	IP-AC	MEDTRONIC EUROPE (Bakken Research Center, Maastricht - Pays Bas)	Adverse events advisory committee			
61121	LACROIX	Dominique	14/10/2002	VB	CORDIS BIOSENSE, WEBTER EUROPE	Essais thérapeutiques ; CHU de Lille			
61121	LACROIX	Dominique	24/07/2000	IP-EC	MEDTRONIC SA	Essais matériels			
61121	LACROIX	Dominique	24/07/2000	IP-EC	GUIDANT France SA	Essais matériels			
61121	LACROIX	Dominique	24/07/2000	IP-EC	ST JUDE MEDICAL SA	Essais matériels			
61121	LACROIX	Dominique	24/07/2000	IP-AC	MEDTRONIC EUROPE	Board européen, analyse effets indésirables			
61121	LACROIX	Dominique	24/07/2000	IP-AC	DIVISION TACHY	Board européen, analyse effets indésirables			
61121	LACROIX	Dominique	24/07/2000	IP-CF	KNOLL France	Formation visiteurs médicaux			
61007	LAGARCE	Laurence	11/03/2010	Néant					
61007	LAGARCE	Laurence	06/10/2008	CF-AUD	LABORATOIRE SERVIER	réunion annuelle des pharmacologues de l'ouest		06/2008	06/2008
61007	LAGARCE	Laurence	06/10/2008	CF-AUD	SERVIER	réunion annuelle des pharmacologues de l'Ouest		06/2008	06/2008
61007	LAGARCE	Laurence	16/11/2007	Néant					
61007	LAGARCE	Laurence	23/02/2007	Néant					
61007	LAGARCE	Laurence	12/03/2004	PAR	ETHYPHARM	Expertise			
61007	LAGARCE	Laurence	16/01/2001	Néant					
61007	LAGARCE	Laurence	27/09/1999	Néant					
55663	LAINÉ-CESSAC	Pascale	19/02/2010	Néant					
55663	LAINÉ-CESSAC	Pascale	09/02/2009	CF-AUD	SERVIER	Pharmacologues de l'Ouest Tours		06/2008	06/2008
55663	LAINÉ-CESSAC	Pascale	07/02/2008	PAR	LABORATOIRE MARC LAINE	PDG (entreprise de distribution de produits de santé)	Belle-soeur		
55663	LAINÉ-CESSAC	Pascale	12/07/2007	CF-AUD	SERVIER	Fontevraud /réunion des pharmacologues du grand ouest	06/2006	06/2007	
55663	LAINÉ-CESSAC	Pascale	15/12/2006	CF-AUD	ROCHE	3èmes Echanges sur la recherche clinique	Paris	12/2006	12/2006
55663	LAINÉ-CESSAC	Pascale	25/09/2006	PAR	LABORATOIRE MARC LAINE	PDG de cette entreprise de distribution de médicaments	Belle soeur	01/1977	
55663	LAINÉ-CESSAC	Pascale	25/09/2006	CF-AUD	ROCHE	Recherche clinique en France : Perspectives d'avenir et nouvelles organisations pour les promoteurs institut	ROCHE 52 Bd du Parc 92521 Neuilly/Seine	12/2005	12/2005
55663	LAINÉ-CESSAC	Pascale	01/06/2006	PAR	LABORATOIRE MARC LAINE	PDG	Belle - sœur		
55663	LAINÉ-CESSAC	Pascale	28/06/2005	PAR	LABORATOIRE MARC-LAINE (entreprise de distribution de médicaments)	belle-sœur			
55663	LAINÉ-CESSAC	Pascale	15/03/2004	PAR	LABORATOIRE MARC LAINE (Distribution de produits de santé)	Belle-famille			
55663	LAINÉ-CESSAC	Pascale	08/09/2003	PAR	LABORATOIRE MARC LAINE (Entreprise de distribution de médicaments)	Belle famille			
55663	LAINÉ-CESSAC	Pascale	28/09/2001	Néant					
55663	LAINÉ-CESSAC	Pascale	16/01/2001	Néant					
55663	LAINÉ-CESSAC	Pascale	27/09/1999	Néant					
55663	LAINÉ-CESSAC	Pascale	07/05/1999	Néant					
63874	LAIRY	Gérard	13/04/2010	PAR	LABORATOIRES SERVIER	RESPONSABLE QUALITE SERVICE INFORMATIQUE	GENDRE	01/2001	
63874	LAIRY	Gérard	13/04/2010	PAR	LABORATOIRES SERVIER	PHARMACIEN RESPONSABLE PHARMACOVIGILANCE	FILLE	01/2001	
63874	LAIRY	Gérard	07/04/2009	(Autre)	EXPERT MÉDICAL PONCTUEL CABINET BON USAGE	Rédactionnel, conseil, accompagnement d'établissements de santé		04/2009	
63874	LAIRY	Gérard	20/03/2008	(Autre)	HAS	Correspondant régional		07/2007	06/2008
63874	LAIRY	Gérard	20/03/2008	(Autre)	ISCMM	Formateur pour l'EPP		12/2007	
63874	LAIRY	Gérard	20/03/2008	PAR	SERVIER	Responsable pharmacovigilance	fille	09/2007	
63874	LAIRY	Gérard	20/03/2008	(Autre)	HAS	correspondant régional HAS - expertise chef de projet	audits cliniques - Ateliers de production	01/1992	07/2007
63874	LAIRY	Gérard	20/03/2008	PAR	SERVIER	Informaticien	gendre	01/2000	
63874	LAIRY	Gérard	20/03/2008	PAR	SERVIER	Responsable données médicales de recherche clinique	fille	01/2000	09/2007
63874	LAIRY	Gérard	13/01/2007	CF-INT	ASSOCIATION VIETNAM EUROPE SANTé / TEDIS SA NAMVIET	Ho Chi Minh Ville. Gestion de la pharmacie hospitalière. Molécules onéreuses, T2A et financement des hopi	Rémunération personnelle	12/2006	12/2006
63874	LAIRY	Gérard	13/01/2007	IP-AC	NUKLEUS / LABORATOIRES ROCHE	Reflexions sur les molécules onéreuses et innovation au travers de la T2A	Rémunération personnelle	11/2005	11/2005
63874	LAIRY	Gérard	09/01/2007	IP-AC	NUKLEUS/ LABORATOIRES ROCHE	Reflexion sur le financement des produits onéreux au travers de la T2A	rémunération personnelle	12/2005	12/2005
63874	LAIRY	Gérard	09/01/2007	CF-INT	ASSOCIATION VIETNAM EUROPE SANTé / TEDIS VIETNAM	Programme Tedis Vietnam - Ho Chi Minh Ville - colloque de pharmaciens hospitaliers, intervention sur molé	rémunération personnelle	12/2006	12/2006
63874	LAIRY	Gérard	09/01/2007	PAR	SERVIER	Responsable données médicales de recherche clinique	fille	01/2000	
63874	LAIRY	Gérard	09/01/2007	PAR	SERVIER	Informaticien	gendre	01/2000	
63874	LAIRY	Gérard	09/01/2007	(Autre)	HAS	correspondant régional HAS - expertise chef de projet	audits cliniques - Ateliers de production	01/1992	
63874	LAIRY	Gérard	21/09/2005	PAR	SERVIER	responsable des données médicales (fille - pharmacien) 2000 - en cours			
63874	LAIRY	Gérard	21/09/2005	PAR	SERVIER	informatique (gendre)			
63874	LAIRY	Gérard	21/09/2005	(Autre)	ANDEM - HAS	Chef de projet puis correspondant - groupe de travail sur guides d'audit - avis sur référentiels traitement des			
10261	LAMARCHE	Jean	14/12/2010	(Autre)		membre du jury des prix éditoriaux 2010 de la presse médicale et des professions de santé	aucune rémunération		
10261	LAMARCHE	Jean	14/12/2010	(Autre)		membre de l'UTIP (enseignement post universitaire)	aucune rémunération		
10261	LAMARCHE	Jean	14/12/2010	(Autre)		cours ponctuels dans les facultés de pharmacie paris,chatenay,amiens	aucune rémunération		
10261	LAMARCHE	Jean	28/04/2009	LD-AR	PHARMACIE VANEAU BABYLONE	Pharmacien des investigateurs	Aucune rémunération	04/1999	
10261	LAMARCHE	Jean	28/04/2009	CF-INT		Association Croix Verte et Ruban Rouge AFC (Association Française contraception) revue prescrire	Aucune rémunération		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10261	LAMARCHE	Jean	28/04/2009	CF-AUD		Rien de prévu			
10261	LAMARCHE	Jean	06/10/2008	CF-INT	SCHERING PLOUGH	Montpellier - projet Suboxone	rémunération personnelle	01/2006	
10261	LAMARCHE	Jean	06/10/2008	CF-INT	HRA PHARMA	Paris - projet nouvelle contraception d'urgence 2009	rémunération personnelle	07/2008	
10261	LAMARCHE	Jean	06/10/2008	VB	ORDRE NATIONAL DES PHARMACIENS	Soutien et action de l'Association	- Association Sida / Toxicomanie□ - Croix verte et Ruban Rouge	01/2008	12/2008
10261	LAMARCHE	Jean	26/04/2007	LD-AR	PHARMACIE VANEAU BABYLONE-PARIS	Pharmacien remplacant	Aucune rémunération	07/2005	
10261	LAMARCHE	Jean	26/04/2007	IP-CF	SCHERING PLOUGH	Intervention sur le SUBOXONE - Montpellier (1 fois)	Association Croix Verte et Ruban Rouge - Rémunération partagée personnelle / institution	10/2006	10/2006
10261	LAMARCHE	Jean	26/04/2007	(Autre)	UTIP	Membre : exposé		01/2006	
10261	LAMARCHE	Jean	26/04/2007	(Autre)	CESPHARM	Vice-président - exposé	CESPHARM : Comité d'Education Sanitaire et Sociai de la Pharmacie Française	01/2005	
10261	LAMARCHE	Jean	21/09/2005	Néant					
10261	LAMARCHE	Jean	25/08/2004	(Autre)		Je représente l'Ordre ou une association (Croix Verte et Ruban Rouge) lorsque je suis sollicité			
10261	LAMARCHE	Jean	10/05/1999	IP-CF		Conférences, colloques, actions de formation : tout sujet sur la pharmacie d'officine			
10261	LAMARCHE	Jean	10/05/1999	VB	BOUCHARA	Association Croix Verte et Ruban Rouge (Président) (subvention annuelle de la DGS)			
10261	LAMARCHE	Jean	10/05/1999	VB	Laboratoires fabricants les médicaments contre le SIDA	Association Croix Verte et Ruban Rouge (Président) (subvention annuelle de la DGS)			
10261	LAMARCHE	Jean	13/01/1999	IP-AUT	BOUCHARA	Association Croix Verte et Ruban Rouge (Président) (subventionnée par la DGS)			
10261	LAMARCHE	Jean	13/01/1999	(Autre)		Membre du Conseil National de l'Ordre des Pharmaciens			
10261	LAMARCHE	Jean	01/01/1999	VB		Membre du Conseil National de l'Ordre des Pharmaciens			
10261	LAMARCHE	Jean	01/01/1999	VB	BOUCHARA	Travaux non rémunérés			
10261	LAMARCHE	Jean	01/01/1999	VB		Président de Croix verte et Ruban Rouge (Association fondée par la DGS)			
10261	LAMARCHE	Jean	01/01/1999	VB	SERVIER, BOUCHARA, BMS, MAYOLI SPINDLER	Président bénévole de l'association Croix Verte et Ruban Rouge, subventionnée par la DGS et aidée par différents laboratoires dont le principal est BOUCHARA			
10261	LAMARCHE	Jean	01/01/1998	VB	Président de Croix Verte et Ruban Rouge				
10261	LAMARCHE	Jean	01/01/1998	PAR	SCHERING PLOUGH		Travaux non rémunérés		
10261	LAMARCHE	Jean	01/01/1998	PAR	MAYOLI-QPINDLER		Travaux non rémunérés		
10261	LAMARCHE	Jean	01/01/1998	PAR	AP-HP		Travaux non rémunérés		
65421	LAMBROZO	Jacques	01/11/2009	LD-AR	LABORATOIRE SERVIER	Consultant	Rémunération personnelle	01/1990	
65421	LAMBROZO	Jacques	01/11/2009	LD-AR	BOUYGUES TELECOM	Conseil scientifique	Rémunération personnelle	01/2002	
65421	LAMBROZO	Jacques	13/09/2008	IF	EDF	Actions	< 5000 € ou < 5% du capital	01/2006	
65421	LAMBROZO	Jacques	13/09/2008	LD-ODE	EDF	Directeur services des études médicales	CDI	01/1983	
65421	LAMBROZO	Jacques	13/09/2008	LD-AR	SERVIER	Consultant	rémunération personnelle	01/1980	
65421	LAMBROZO	Jacques	13/09/2008	(Autre)	BOUYGUES TELECOM	Membre du conseil scientifique		01/2002	
61009	LAPEYRE-MESTRE	Maryse	05/10/2010	Néant					
61009	LAPEYRE-MESTRE	Maryse	08/04/2010	Néant					
61009	LAPEYRE-MESTRE	Maryse	27/01/2010	Néant					
61009	LAPEYRE-MESTRE	Maryse	09/02/2009	(Autre)	LABORATOIRE SERVIER	Prix Paul Mirouze	Prix décerné par l'Académie Nationale de Médecine (sur présentation de projet de recherche sur médicaments antidiabétiques et cancer colo-rectal) financé par le laboratoire Servier	12/2007	12/2007
61009	LAPEYRE-MESTRE	Maryse	08/02/2008	VB	CENTRE DU RECHERCHE SUR LA PEAU – INSTITUT DE RECHERCHE PIERRE FABRE	Etude clinique (projet CERPER)	CHU de Toulouse, Université Paul Sabatier	09/2007	08/2009
61009	LAPEYRE-MESTRE	Maryse	08/02/2008	EC-INV	CENTRE DE RECHERCHE SUR LA PEAU – INSTITUT DE RECHERCHE PIERRE FABRE	Etude clinique : biologie cutanée et corticothérapie	investigateur principal	09/2007	08/2009
61009	LAPEYRE-MESTRE	Maryse	08/02/2008	EC-INV	HELSINN HEALTHCARE SA	Evaluation pharmacoepidemiologique des risques hépatiques, gastro-intestinaux et autres du Nimesulide et	Investigateur principal	06/2007	09/2007
61009	LAPEYRE-MESTRE	Maryse	08/02/2008	VB	THERABEL LUCIEN PHARMA	Rapport d'étude : "Evaluation pharmacoepidemiologique des risques hépatiques, gastro-intestinaux et autres	Institut d'Hydrologie Médicale de Toulouse et des Pyrénées	06/2007	09/2007
61009	LAPEYRE-MESTRE	Maryse	08/02/2008	EC-INV	THERABEL LUCIEN PHARMA	Evaluation pharmacoepidemiologique des risques hépatiques, gastro-intestinaux et autres du Nimesulide et	Investigateur principal	06/2007	09/2007
61009	LAPEYRE-MESTRE	Maryse	07/05/2007	Néant					
61009	LAPEYRE-MESTRE	Maryse	02/01/2006	EC-CO	THERABEL	Evaluation du risque hépatotoxique/ nimésulide	co-investigateur	06/2002	12/2002
61009	LAPEYRE-MESTRE	Maryse	18/04/2005	LD	THERABEL	Nimésulide (évaluation hypotonicité), juin 2002		06/2002	12/2002
61009	LAPEYRE-MESTRE	Maryse	18/04/2005	IP-AC	GLAXO	Déplacement et participation financé par Glaxo	Aucune rémunération	06/2002	06/2002
61009	LAPEYRE-MESTRE	Maryse	18/04/2005	IP-AC	COLLEGE ON PROBLEMS ON DRUG DEPENDENCE (CPDD)	Participation au Congrès (juin 2002)	Aucune rémunération	06/2002	06/2002
61009	LAPEYRE-MESTRE	Maryse	19/10/2004	IP-RE	THERABEL LUCIEN PHARMA	Effets Hépatique du Nimésulide			
61009	LAPEYRE-MESTRE	Maryse	19/10/2004	IP-CF	GSK	College on problem on drug dependence			
61009	LAPEYRE-MESTRE	Maryse	13/02/2003	VB	THERABEL LUCIEN PHARMA	Etude pharmacoépidémiologique des effets hépatiques de AINS et du minésulide en particulier - centre Midi-Pyrenées de pharmacovigilance, CHU de Toulouse			
61009	LAPEYRE-MESTRE	Maryse	28/01/2000	Néant					
61009	LAPEYRE-MESTRE	Maryse	22/01/1999	Néant					
10265	LAQUEILLE	Xavier	10/12/2010	CF-INT	LILLY	Conférence FMC□□Tabac et troubles psychiatriques	Rémunération personnelle	03/2011	03/2011
10265	LAQUEILLE	Xavier	10/12/2010	CF-INT	NYCOMED	Invitation en tant qu'intervenant□□FENTANYL par voie nasale	Rémunération personnelle	03/2011	03/2011
10265	LAQUEILLE	Xavier	01/02/2010	EC-INV	SCHERING PLOUGH	Etude du potentiel d'injectabilité de la suboxone VS buprenorphine	investigateur principal du service	11/2009	12/2010
10265	LAQUEILLE	Xavier	24/03/2009	EC-INV	AGEPS/APHP- BOUCHARA RECORDATI	Etude pharmacocinétique méthadone gélule versus méthadone sirop	coordonnateur	01/2005	12/2005
10265	LAQUEILLE	Xavier	24/03/2009	EC-INV	SCHERING PLOUGH	Etude d'induction Suboxone chez le sujet dépendant aux opiacés	investigateur principal France	01/2007	12/2009
10265	LAQUEILLE	Xavier	24/03/2009	RE-DE	AGEPS	Méthadone gélule - Rapport d'expertise commission d'AMM	rémunération personnelle	01/2005	12/2005
10265	LAQUEILLE	Xavier	24/03/2009	CF-INT	JANSSEN CILAG	Cannabis et troubles schizophrènes - Risperdal ®- Marseille / Trouville	rémunération institution	01/2008	12/2008
10265	LAQUEILLE	Xavier	24/03/2009	CF-AUD	OTSUKA /BMS	Congrès de l'encéphale - Abilify ®		01/2007	01/2007
10265	LAQUEILLE	Xavier	24/03/2009	CF-AUD	OTSUKA/BMS	Congrès de l'encéphale - Abilify®		01/2008	12/2008
10265	LAQUEILLE	Xavier	16/12/2008	CF-INT	JANSSEN OTSUKA LILLY	CONFERENCES ET CONGRES	Aucune rémunération	01/2008	12/2008
10265	LAQUEILLE	Xavier	14/11/2005	CF-AUD	OTSUKA-BMS	European College on Neuropsychopharmacology.□□AMSTERDAM		11/2005	11/2005
10265	LAQUEILLE	Xavier	14/11/2005	CF-AUD	LUNDBECK	European College on Neuropsychopharmacology. □□PRAGUE		09/2003	09/2003
10265	LAQUEILLE	Xavier	14/11/2005	CF-INT	JANSSEN	Cannabis	Vous	01/2002	12/2002
10265	LAQUEILLE	Xavier	14/11/2005	CF-INT	LILLY	Psychose et addiction	Vous	01/2005	12/2005
10265	LAQUEILLE	Xavier	14/11/2005	EC-CO	SERVIER	AGOMELATINE□□VS□□VENLAFAXINE	Investigateur	09/2002	12/2003

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10265	LAQUEILLE	Xavier	14/11/2005	RE-DE	AGEPS/APHP	Rapport d'AMM□□METHADONE Gelule	rémunération personnelle	06/2005	09/2005
10265	LAQUEILLE	Xavier	14/11/2005	CF-INT	SANOFI AVENTIS	Psychose et addiction□□	Vous	01/2005	12/2005
10265	LAQUEILLE	Xavier	14/11/2005	EC-INV	AGEPS/APHP	METHADONE Gélule vs METHADONE Sirop	coordonnateur	06/2004	03/2005
10265	LAQUEILLE	Xavier	25/02/2001	IP-EC	IRIS	Asomélaline uxfimoxéline		01/2002	12/2002
10265	LAQUEILLE	Xavier	18/07/1999	IP-EC	IRIS (Courbevoie)				
10265	LAQUEILLE	Xavier	18/07/1999	IP-EC	IBAH (Le Kremlin-Bicêtre)				
10265	LAQUEILLE	Xavier	18/07/1999	IP-EC	SKB (Nanterre)				
10265	LAQUEILLE	Xavier	18/07/1999	IP-CF	LILLY (Saint-Cloud)	EPU			
10265	LAQUEILLE	Xavier	01/01/1999	IP-EC	IRIS (92400 Courbevoie)	Anxiolytique et Antidépresseur, expérimentation clinique			
10265	LAQUEILLE	Xavier	01/01/1999	VB		Association de recherche hospitalière : pas d'honoraires personnels			
10265	LAQUEILLE	Xavier	01/01/1998	IP-AUT	Wyeth				
10265	LAQUEILLE	Xavier	01/01/1998	IP-AUT	Servier				
10265	LAQUEILLE	Xavier	01/01/1998	VB	Schering-Plough		pour le programme hospitalier de recherche clinique		
64533	LARDOUX	Hervé	05/02/2007	CF-INT	SCHERING-PLOUGH	3 réunions (Corbeil-Essonnes) : "nouveaux Hypolipemic " Ezétimibe	rémunération personnelle	01/2005	12/2006
64533	LARDOUX	Hervé	05/02/2007	CF-INT	TOSHIBA	ESC 2006 (Barcelone - Espagne) : Symposium Imagerie Cardio vasculaire	rémunération personnelle	01/2007	12/2007
64533	LARDOUX	Hervé	05/02/2007	CF-AUD	SERVIER	ACC 2006 - rapporteur des séances d'échocardiographie - "ACC LIVE"			
63508	LAROCHE	Marie-Laure	01/03/2010	CF-AUD	SERVIER	Journée de formation de pharmacologie clinique (Alzheimer) - Vaux de Cernay (Yvelines)		12/2009	12/2009
63508	LAROCHE	Marie-Laure	20/10/2008	(Autre)	ROCHE		Remboursement de transport pendant le stage post-doc	11/2008	10/2009
63508	LAROCHE	Marie-Laure	01/02/2008	Néant					
63508	LAROCHE	Marie-Laure	21/12/2006	Néant					
63508	LAROCHE	Marie-Laure	03/05/2006	Néant					
62787	LASNE	Dominique	09/03/2010	CF-AUD	INSTRUMENTATION LABORATORY	ISTH, Boston	Frais de déplacement et hébergement	07/2009	07/2009
62787	LASNE	Dominique	09/03/2010	CF-AUD	BAYER	ASH, San Francisco	Frais de déplacement et hébergement	12/2008	12/2008
62787	LASNE	Dominique	09/03/2010	CF-INT	SIEMENS	Journée de formation en hémostase	Aucune rémunération	12/2008	12/2008
62787	LASNE	Dominique	09/03/2010	IP-AC	INSTRUMENTATION LABORATORY	Groupe de reflexion sur l'hémostase	Aucune rémunération		
62787	LASNE	Dominique	14/11/2007	EC-INV	SANOFI	Etude de phase II : Plavix chez le nouveau né	Expérimentateur non principal	01/2005	12/2006
62787	LASNE	Dominique	14/11/2007	IP-AC	LFB	Réflexion sur la protéine C en chirurgie cardiaque pédiatrique	Rémunération institution	03/2006	12/2006
62787	LASNE	Dominique	14/11/2007	CF-AUD	INSTRUMENTATION LABORATORY	Congrès de l'ISTH 2007 à Genève		07/2007	07/2007
62787	LASNE	Dominique	28/09/2006	LD-AR	BAYER	Board Aprotinine - Trasylol ®	rémunération institution	01/2004	12/2005
62787	LASNE	Dominique	28/09/2006	EC-CO	SANOFI	étude du Clopidogrel chez l'enfant	collaborateur à l'étude	01/2003	12/2008
62787	LASNE	Dominique	28/09/2006	IP-AC	INSTRUMENTATION LABORATORY (IL)	groupe de réflexion en hémostase	aucune rémunération	01/2005	
62787	LASNE	Dominique	28/09/2006	CF-AUD	PHARMION	GEHT Marrakech - mai 2005		05/2005	05/2005
62787	LASNE	Dominique	28/09/2006	CF-AUD	SANOFI	GEHT Grenoble		10/2005	10/2005
62787	LASNE	Dominique	28/09/2006	CF-AUD	IL	GEHT St Etienne		10/2006	10/2006
62787	LASNE	Dominique	12/05/2005	VB	BAYER	Groupe de réflexion sur le Trasylol	ARHNEM		
62787	LASNE	Dominique	12/04/2005	IP-RE	SERVIER	Membre du Safety comité pour une étude de phase d'un autre agrément (2000-2001)			
62787	LASNE	Dominique	12/04/2005	IP-AC	BAYER	Trasylol (année 2005)			
62787	LASNE	Dominique	18/08/2003	IP-AC	PHARMON	Groupe de travail sur l'utilisation du Refludan (HIT School)			
64391	LASSMANN-VAGUE	Véronique	12/11/2010	CF-AUD	SERVIER	Stockolm, EASD,		09/2010	09/2010
64391	LASSMANN-VAGUE	Véronique	12/11/2010	CF-AUD	SANOFI-AVENTIS	Paris,Coeur et diabète		02/2010	02/2010
64391	LASSMANN-VAGUE	Véronique	12/11/2010	CF-AUD	VITALAIRE	Lille,SFD,(soc fr.de diabétologie)		03/2010	03/2010
64391	LASSMANN-VAGUE	Véronique	12/11/2010	CF-AUD	NOVONORDISK	Vienne,EASD(assoc. europ.de diabétologie)		09/2009	10/2009
64391	LASSMANN-VAGUE	Véronique	25/06/2009	Néant					
64391	LASSMANN-VAGUE	Véronique	25/06/2009	CF-AUD	ROCHE DIAGNOSTICS	Paris congrès DELF (Diabete Education Langue Française)		02/2009	02/2009
64391	LASSMANN-VAGUE	Véronique	25/06/2009	CF-AUD	SERVIER	Rome congrès EASD (European association for the study of diabetes)		09/2008	09/2008
64391	LASSMANN-VAGUE	Véronique	25/06/2009	CF-AUD	SERVIER	STRASBOURG-congrèsALFEDIAM		03/2009	03/2009
64391	LASSMANN-VAGUE	Véronique	25/06/2009	CF-AUD	VITALAIRE	EASD - Amsterdam - étude épidémiologique sur pompes		09/2007	09/2007
64391	LASSMANN-VAGUE	Véronique	25/06/2009	CF-INT	VITALAIRE	Capetown - IDF - résultats étude épidémiologique sur pompe à insuline	aucune rémunération	12/2006	12/2006
64391	LASSMANN-VAGUE	Véronique	25/06/2009	EC-INV	VITALAIRE	Etude épidémiologique sur les pompes à insuline en France	co-investigateur	01/2004	12/2007
64391	LASSMANN-VAGUE	Véronique	25/06/2009	IP-AC	NOVO NORDISK	Consultant pour l'étude LEVEMIR chez le sujet âgé	rémunération personnelle	01/2006	01/2008
64391	LASSMANN-VAGUE	Véronique	04/10/2007	EC-INV	VITALAIRE	Etude épidémiologique sur les pompes à insuline en France	co-investigateur	01/2004	
64391	LASSMANN-VAGUE	Véronique	04/10/2007	IP-AC	NOVO NORDISK	Consultant pour l'étude LEVEMIR chez le sujet âgé	rémunération personnelle	01/2006	
64391	LASSMANN-VAGUE	Véronique	04/10/2007	CF-INT	VITALAIRE	Capetown - IDF - résultats étude épidémiologique sur pompe à insuline	aucune rémunération	12/2006	
64391	LASSMANN-VAGUE	Véronique	04/10/2007	CF-AUD	VITALAIRE	EASD - Amsterdam - étude épidémiologique sur pompes		09/2007	
64391	LASSMANN-VAGUE	Véronique	15/06/2006	IF	L'OREAL	Titres	< 5000 Euros ou <5% du capital	01/1999	
64391	LASSMANN-VAGUE	Véronique	15/06/2006	EC-CO	NOVO NORDISK	Etude Multicentrique Européenne sur insuline NOVORAPID dans la grossesse	Co-investigateur	01/2002	12/2005
64391	LASSMANN-VAGUE	Véronique	15/06/2006	EC-CO	MEDTRONIC - MINIMED	Etude Multicentrique sur pompes à insuline implantées	Co-investigateur	01/1991	12/2006
64391	LASSMANN-VAGUE	Véronique	15/06/2006	IP-AC	VITALAIRE	(Prestataire de service pour pompes à insuline) - Mise en place d'un protocole :Observatoire transversal de	Rémunération personnelle	01/2004	
64391	LASSMANN-VAGUE	Véronique	15/06/2006	CF-AUD	LILLY	Journées Lilly - Paris Janvier 2006		01/2006	01/2006
64391	LASSMANN-VAGUE	Véronique	15/06/2006	CF-INT	VITALAIRE	ALFEDIAM - Présentation des résultats du protocole "Observatoire transversal de l'initiation du traitement pa	Aucune rémunération	03/2006	03/2006
62291	LAVILLE	Maurice	15/04/2010	VB	ROCHE	Subvention de recherche: étude RESODIAL	Université Lyon 1 - EZUS	09/2008	07/2010
62291	LAVILLE	Maurice	15/04/2010	CF-INT	AMGEN	Néphrologie translationnelle (Paris)	Rémunération personnelle	12/2009	12/2009
62291	LAVILLE	Maurice	15/04/2010	CF-INT	JANSSEN-CILAG	Journées de Néphrologie (Nice)	Rémunération personnelle	03/2010	03/2010
62291	LAVILLE	Maurice	15/04/2010	IP-AC	SERVIER	Conseil pédagogique	Rémunération personnelle	01/2009	12/2010
62291	LAVILLE	Maurice	15/04/2010	EC-CO	OTSUKA	Etude TEMPO	investigateur	01/2008	12/2010
62291	LAVILLE	Maurice	15/04/2010	LD-AR	HOSPAL/GAMBRO	Board Evodial	Rémunération personnelle	01/2009	12/2010
62291	LAVILLE	Maurice	15/04/2010	LD-AR	OTSUKA	Comité d'experts - Samsca	Rémunération personnelle	01/2009	12/2010
62291	LAVILLE	Maurice	16/11/2007	CF-INT	SHIRE	Conférence hyperphosphorémie et IRC (La Ptié)	Rémunération personnelle	01/2007	01/2007
62291	LAVILLE	Maurice	16/11/2007	CF-INT	SERVIER	Conférence hypertension et rein	Rémunération personnelle	01/2007	12/2007
62291	LAVILLE	Maurice	16/11/2007	CF-INT	CHIESI	Conférence hypertension et rein	Rémunération personnelle	01/2007	12/2007
62291	LAVILLE	Maurice	16/11/2007	CF-INT	ROCHE	Ateliers de néphrologie	Rémunération personnelle	01/2006	12/2007
62291	LAVILLE	Maurice	16/11/2007	IP-AC	BOEHRINGER	Board Micardis	Rémunération personnelle	01/2007	12/2007
62291	LAVILLE	Maurice	16/11/2007	EC-INV	ROCHE	Essai NH20052	coordonateur France	06/2007	12/2009
62291	LAVILLE	Maurice	16/11/2007	EC-INV	ASPREVA	Etude ALMS	coordonateur France	01/2005	12/2009
62291	LAVILLE	Maurice	16/11/2007	EC-CO	KERYX	Essai Sulodexide	co-investigateur	01/2006	12/2008
62291	LAVILLE	Maurice	16/11/2007	EC-INV	AMGEN	Essai EVOLVE	investigateur	01/2007	12/2010
62291	LAVILLE	Maurice	16/11/2007	CF-AUD	JANSSEN-CILAG	American Society of Nephrology - San Diego nov. 2006		11/2006	11/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62291	LAVILLE	Maurice	16/11/2007	LD-AR	SHIRE	Advisory Board - Fosrénol	rémunération personnelle / institution	01/2005	12/2009
62291	LAVILLE	Maurice	04/12/2006	LD-AR	SHIRE	Advisory Board - Fosrénol	rémunération personnelle / institution	01/2005	
62291	LAVILLE	Maurice	04/12/2006	EC-INV	AMGEN	essai clinique / MIMPARA	investigateur	01/2003	12/2005
62291	LAVILLE	Maurice	04/12/2006	EC-INV	ROCHE	essai clinique / CERA	coordonnateur	01/2004	12/2006
62291	LAVILLE	Maurice	04/12/2006	EC-INV	SHIRE	essai clinique / FOSRENOL	coordonnateur	01/2003	12/2005
62291	LAVILLE	Maurice	04/12/2006	RE-DE	AMERSHAM	AMM - Iodixanol	rémunération personnelle / institution	01/2004	12/2004
62291	LAVILLE	Maurice	04/12/2006	RE-DE	SHIRE	Fosrénol	rémunération personnelle / institution	01/2005	12/2005
62291	LAVILLE	Maurice	04/12/2006	IP-AC	BMS-SANOFI	Néphropathie diabète type 2	rémunération personnelle / institution	01/2002	12/2006
62291	LAVILLE	Maurice	04/12/2006	CF-INT	AMERSHAM	Néphrotoxicité des produits de contraste	rémunération personnelle	01/2005	12/2006
62291	LAVILLE	Maurice	04/12/2006	CF-INT	BMS-SANOFI	rein et hypertension artérielle	rémunération personnelle	01/2003	12/2005
62291	LAVILLE	Maurice	04/12/2006	CF-INT	SERVIER	microcirculation rénale et HTA	rémunération personnelle / institution	01/2003	12/2008
62291	LAVILLE	Maurice	04/12/2006	CF-AUD	JANSSEN-CILAG	American Society of Nephrology - San Diego nov. 2006			
62291	LAVILLE	Maurice	04/12/2006	VB	ROCHE,AMGEN,ASTRA-ZENECA,BAXTER	contrats de recherche	Université 1 (UMR-MA-103)	01/2004	12/2006
62291	LAVILLE	Maurice	07/01/2003	IP-EC	MERCK LIPHA	Etude Posidiol (clinique)			
62291	LAVILLE	Maurice	07/01/2003	IP-EC	ROCHE	Etude CREATE (clinique)			
62291	LAVILLE	Maurice	07/01/2003	IP-EC	PFIZER	Etude replira (clinique)			
62291	LAVILLE	Maurice	07/01/2003	IP-EC	ASTRA ZENECA	Etude shomcaud (clinique)			
62291	LAVILLE	Maurice	07/01/2003	IP-EC	AMGEN	Etudes expérimentales			
62291	LAVILLE	Maurice	07/01/2003	IP-RE	AVENTIS	Ramipril et insuffisance rénale			
62291	LAVILLE	Maurice	07/01/2003	IP-AC	MERCK LIPHA	Stratégie de tout antihypertenseur			
62291	LAVILLE	Maurice	07/01/2003	IP-AC	BMS, SANIFI-SYNTHELABO	Groupe convergences			
62291	LAVILLE	Maurice	07/01/2003	IP-AC	BELLCO	Méthodes de dialyse			
62291	LAVILLE	Maurice	07/01/2003	IP-CF	SERVIER	Conférence Hypocrate			
62291	LAVILLE	Maurice	07/01/2003	IP-CF	GENZYME	Formation d'équipe			
62291	LAVILLE	Maurice	07/01/2003	IP-CF	BAXTER	Insuffisance rénale chronique			
62291	LAVILLE	Maurice	07/01/2003	IP-CF	HOSPAL	Méthode de dialyse			
63036	LAVILLE	Martine							
10230	LE HEUZEY	Jean-Yves	15/10/2010	Néant					
10230	LE HEUZEY	Jean-Yves	31/10/2008	EC-INV	BOEHRINGER INGELHEIM	Dabigatran	coordinateur RELY	10/2008	
10230	LE HEUZEY	Jean-Yves	31/10/2008	EC-INV	SERVIER	Ivabradine	Membre DSMD étude SHIFT	04/2008	
10230	LE HEUZEY	Jean-Yves	14/10/2007	EC-INV	SANOFI	Dronedarone	coordinateur DIONYSOS	09/2007	
10230	LE HEUZEY	Jean-Yves	28/05/2006	EC-INV	SANOFI	Clopidogrel	coordonnateur ACTIVE	01/2004	
10230	LE HEUZEY	Jean-Yves	28/05/2006	EC-INV	SANOFI	Celivarone	coordonnateur CORYFEE	01/2006	06/2007
10230	LE HEUZEY	Jean-Yves	28/05/2006	EC-INV	BOEHRINGER INGELHEIM	Dabigatran	coordonnateur REZY	01/2006	
10230	LE HEUZEY	Jean-Yves	28/05/2006	EC-CO	3M	Flecaine	Etude observation	01/2005	12/2006
10230	LE HEUZEY	Jean-Yves	28/05/2006	IP-AC	MEDTRONIC	Board conseil	rémunération personnelle	01/2003	
10230	LE HEUZEY	Jean-Yves	28/05/2006	IP-AC	GUIDANT	Board conseil	rémunération personnelle	01/2003	12/2005
10230	LE HEUZEY	Jean-Yves	28/05/2006	IP-AC	SERVIER	Ivabradine Safety Committee	rémunération personnelle	04/2004	12/2006
10230	LE HEUZEY	Jean-Yves	28/05/2006	IP-AC	PROCTER GAMBLE	Loginet AVK	réminération personnelle	01/2005	12/2006
10230	LE HEUZEY	Jean-Yves	28/05/2006	IP-AC	SANOFI PASTEUR	Vaccin Variole / safety	rémunération personnelle	01/2005	09/2007
10230	LE HEUZEY	Jean-Yves	28/05/2006	IP-AC	CARDIOME	DSMB RSD 1235	rémunération personnelle	01/2004	12/2006
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	TAKEDA	Journées européennes SFC - Kenzen	rémunération personnelle	01/2005	01/2005
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	ASTRA ZENECA	Journées européennes SFC - Atacand	rémunération personnelle	01/2006	01/2006
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	3M SANTE	Atelier d 'expertise rythmologiques	rémunération personnelle	01/2003	12/2003
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	3M SANTE	Atelier d' expertise rythmologiques	rémunération personnelle	01/2004	12/2004
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	3M SANTE	Atelier d' expertise rythmologiques	rémunération personnelle	01/2005	12/2005
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	VITATRON	AF Barcelone Symposium	rémunération personnelle	01/2005	12/2005
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	VITATRON	AF Barcelone Symposium	rémunération personnelle	01/2006	12/2006
10230	LE HEUZEY	Jean-Yves	28/05/2006	CF-INT	3M SANTE	Atelier d'expertise rythmologiques	rémunération personnelle	01/2006	12/2006
10230	LE HEUZEY	Jean-Yves	20/09/2005	IP-EC	MEDTRONIC	Borad/ EAF			
10230	LE HEUZEY	Jean-Yves	20/09/2005	IP-EC	GUIDANT	Etude ?? de vitality			
10230	LE HEUZEY	Jean-Yves	18/10/2004	IP-EC	SERVIER	Safety committee sur Ivabradine			
10230	LE HEUZEY	Jean-Yves	18/10/2004	IP-AC	SANOFI	Advisory board Dromedine			
10230	LE HEUZEY	Jean-Yves	18/10/2004	VB	SANOFI	Essai clinique ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events			
10230	LE HEUZEY	Jean-Yves	29/05/2004	IP-EC	MEDTRONIC	Etude LEAF			
10230	LE HEUZEY	Jean-Yves	29/05/2004	IP-AC	GUIDANT	K.O.L			
10230	LE HEUZEY	Jean-Yves	05/05/2004	IP-EC	MEDTRONIC	Etude LEAF			
10230	LE HEUZEY	Jean-Yves	05/05/2004	IP-AC	GUIDANT	K.O.L.			
10230	LE HEUZEY	Jean-Yves	22/10/2003	IP-EC	MEDTRONIK	Etude LEAF pour l'ATSOO			
10230	LE HEUZEY	Jean-Yves	22/10/2003	IP-EC	BIOTRONIK	Etude Valid actuellement terminée			
10230	LE HEUZEY	Jean-Yves	22/10/2003	IP-AC	GUIDANT	Participation au Key opinion Leaders Board			
10230	LE HEUZEY	Jean-Yves	22/10/2001	IP-EC	BIOTRONIK	Investigateur - Etude VALID			
10230	LE HEUZEY	Jean-Yves	22/10/2001	IP-EC	MEDTRONIC	Investigateur - Etude INAF			
10230	LE HEUZEY	Jean-Yves	22/10/2001	IP-AC	GUIDANT	Board K.O.L			
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-EC	PFIZER				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-EC	KNOLL				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-EC	SEARLE				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-RE	ROCHE				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AC	SYNTHELABO				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AC	BOEHRINGER-MANNHEIM				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AC	MENARINI				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AC	HOECHST				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AC	PAREXEL				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	PIERRE FABRE				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	SANOFI				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	3M				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	SERVIER				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	MERCK CLEVENOT				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	WYETH-LEDERLE				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	ZENECA				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	PFIZER	Congrès à l'étranger			
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	3M				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	KNOLL				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	ROCHE				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	MERCK CLEVENOT				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	CARETEAM				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AUT	SPECIA				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	HOUDE				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	UPSA				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-CF	KNOLL				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-AC	BOEHRINGER INGELHEIM				
10230	LE HEUZEY	Jean-Yves	01/01/1999	IP-EC	3M				
10230	LE HEUZEY	Jean-Yves	01/01/1999	VB	PROCTER & GAMBLE	Investigateur dans des essais cliniques pour l'Association Claude Bernard AP-HP			
10230	LE HEUZEY	Jean-Yves	01/01/1999	VB	3M	Association Claude Bernard AP-HP			
10230	LE HEUZEY	Jean-Yves	01/01/1999	VB	SANDOZ	Association Claude Bernard AP-HP			
10230	LE HEUZEY	Jean-Yves	01/01/1999	VB	MERCK CLEVENOT	Association Claude Bernard AP-HP			
10230	LE HEUZEY	Jean-Yves	01/01/1999	VB	CARETEAM	Association Claude Bernard AP-HP			
64848	LE PAPE	Alain	12/11/2009	IF	BIOPHARMA CONSULTING	1 action < 5,000 Euros		01/2002	
64848	LE PAPE	Alain	12/11/2009	LD-AR	MDS PHARMA SERVICES	Consulting en imagerie in vivo pour le développement pharmaceutique	Rémunération personnelle/institution	01/1997	12/2005
64848	LE PAPE	Alain	12/11/2009	LD-AR	GUERBET	Consulting en imagerie in vivo pour le développement pharmaceutique	Rémunération personnelle/institution	01/2009	12/2010
64848	LE PAPE	Alain	12/11/2009	EC-CO	SERVIER	Technologie Orléans - Toxicologie Gidy : imagerie pour le développement pharmaceutique et la toxicologie	Direction scientifique, contrat CNRS - En cours	01/2007	
64848	LE PAPE	Alain	12/11/2009	EC-CO	CERB Baugy	Développement de nouvelles stratégies d'imagerie en cancérologie, inflammation, infection	Direction scientifique, contrat CNRS - En cours	01/2000	
64848	LE PAPE	Alain	12/11/2009	RE-AUT	PIERRE FABRE Médicament Toulouse	Etude par imagerie de l'activité pharmacologique du TOPAAL comprimé	Rémunération personnelle/institution	01/2007	12/2007
64848	LE PAPE	Alain	12/11/2009	IP-AC	SANOFI AVENTIS	Oncologie expérimentale - Vitry sur Seine	Conseil en imagerie in vivo pour le développement de nouveaux anti-cancéreux - tous produits - Rémunération institution - En cours	01/2005	
64848	LE PAPE	Alain	12/11/2009	IP-AC	PIERRE FABRE	Oncologie expérimentale - Toulouse	Conseil en imagerie in vivo pour le développement de nouveaux anti-cancéreux - tous produits - Rémunération institution - En cours	01/2004	
64848	LE PAPE	Alain	12/11/2009	CF-INT	MDS	Pharmacologie de sécurité - Conférence imagerie en recherche préclinique aux colloques de Lyon - En 200	Aucune rémunération		
64848	LE PAPE	Alain	12/11/2009	CF-INT	Groupe Métabolisme et Pharmacocinétique GMP	2007 - Conférence sur l'imagerie des biomarqueurs de l'inflammation et du cancer - Gien	Aucune rémunération		
64848	LE PAPE	Alain	12/11/2009	CF-INT	Société Française de Toxicologie	2008 - L'imagerie pour la biodistribution et la toxicologie des nanoparticules - Paris	Aucune rémunération		
64848	LE PAPE	Alain	12/11/2009	CF-INT	Société Française de Pathologie Toxicologique	2009 - Imagerie des biomarqueurs pour l'évaluation de l'efficacité et la sécurité des médicaments - Paris	Aucune rémunération		
64848	LE PAPE	Alain	12/11/2009	CF-INT	ORION CONCEPT	2009 - Application de l'imagerie à la R&D en dermocosmétologie - Orléans	Aucune rémunération		
64848	LE PAPE	Alain	12/11/2009	VB	PIERRE FAFBRE MEDICAMENT	Toulouse - Contrat de collaboration ou de prestation	Bénéficiaire : CNRS	01/2004	12/2011
64848	LE PAPE	Alain	12/11/2009	VB	SERVIER	Orléans - Contrat de collaboration ou de prestation	Bénéficiaire : CNRS	01/2007	12/2011
64848	LE PAPE	Alain	12/11/2009	VB	MDS PHARMA SERVICES	L'Arbresle - Contrat équipe conseil	Bénéficiaire : CNRS	01/1995	12/1997
64848	LE PAPE	Alain	12/11/2009	VB	CERB	Contrat de collaboration ou de prestation	Bénéficiaire : CNRS	01/2009	12/2010
64848	LE PAPE	Alain	12/11/2009	PAR	BIOPHARM CONSULTING	Tours - Actionnaire - Epouse - En cours		01/2002	
64848	LE PAPE	Alain	12/11/2009	(Autre)		Conseils Régionaux et Organismes Scientifiques	Expertise de projet - En cours	01/2002	
64848	LE PAPE	Alain	11/02/2008	LD-AR	MDS PHARMA SERVICE L'ARBRESLES	Consulting en imagerie in vivo pour le développement pharmaceutique		01/1997	12/2005
64848	LE PAPE	Alain	11/02/2008	EC-CO	SERVIER TECHNOLOGIE (Orléans)	Imagerie de la distribution, ciblage vectorisation de médicaments (en cours)	direction scientifique contrat CNRS	01/2007	
64848	LE PAPE	Alain	11/02/2008	EC-CO	SERVIER CENTRE DE TOXICOLOGIE (Gidy)	Développement de stratégies d'imagerie pour la toxicologie (en cours)	direction scientifique contrat CNRS	01/2007	
64848	LE PAPE	Alain	11/02/2008	RE-AUT	PIERRE FABRE MEDICAMENT (Toulouse)	Etude par imagerie de l'activité pharmaceutique du TOPAAL comprimé		01/2007	12/2007
64848	LE PAPE	Alain	11/02/2008	IF	BIOPHARM CONSULTING (Tours)	1 action : <5000 € ou <5% du capital		01/2002	
64848	LE PAPE	Alain	11/02/2008	IP-AC	SANOFI AVENTIS	Conseil imagerie in vivo pour le développement de nouveaux anti-cancéreux (oncologie expérimentale - Vitry Sur Seine) : en cours		01/2005	
64848	LE PAPE	Alain	11/02/2008	IP-AC	PIERRE FABRE	Conseil imagerie in vivo pour le développement de nouveaux anti-cancéreux (oncologie expérimentale - Toulouse) : en cours		01/2004	
64848	LE PAPE	Alain	11/02/2008	IP-CF	COLLOQUE MDS PHARMACOLOGIE DE SECURITE	Conférence imagerie en recherche préclinique aux colloques de Lyon		01/2005	12/2005
64848	LE PAPE	Alain	11/02/2008	IP-CF	COLLOQUE MDS PHARMACOLOGIE DE SECURITE	Conférence imagerie en recherche préclinique aux colloques de Lyon		01/2008	12/2008
64848	LE PAPE	Alain	11/02/2008	IP-CF	GROUPE METABOLISME ET PHARMACEUTIQUE GMP	Conférence sur l'imagerie des licomarqueurs de l'inflammation et du cancer		01/2007	12/2007
64848	LE PAPE	Alain	11/02/2008	IP-AUT	PIERRE FABRE MEDICAMENTS	4 brevets Pierre Fabre - CNRS sur le ciblage in vivo des macrophages		01/1991	12/1995
64848	LE PAPE	Alain	11/02/2008	VB	PIERRE FABRE MEDICAMENT (Toulouse)	Contrat de collaboration ou de prestation - CNRS		01/2004	12/2011
64848	LE PAPE	Alain	11/02/2008	VB	SERVIER (ORLEANS)	Contrat de collaboration ou de prestation - CNRS		01/2007	12/2011
64848	LE PAPE	Alain	11/02/2008	VB	MDS PHARMA SERVICES (Lyon)	contrat d'équipe-conseil - CNRS		01/1995	12/1997
64848	LE PAPE	Alain	11/02/2008	PAR	BIOPHARM CONSULTING (Tours)	Epouse (actionnaire) : en cours		01/2002	
64848	LE PAPE	Alain	11/02/2008	(Autre)	CONSEILS RÉGIONAUX ET ORGANISMES SCIENTIFIQUES	expertise de sujets : en cours		01/2002	
64848	LE PAPE	Alain	11/02/2008	LD	BIOPHARM CONSULTING				
61906	LEBBE	Céleste	13/04/2010	EC-CO	GENTA	Genasense (en cours)	Co-investy	01/2008	
61906	LEBBE	Céleste	13/04/2010	EC-CO	BMS	Ipilimumab (en cours)	Co-investy	01/2007	
61906	LEBBE	Céleste	13/04/2010	EC-CO	GSK	Mage 3 (en cours)	Co-investy	01/2009	
61906	LEBBE	Céleste	13/04/2010	EC-CO	Plexiton ROCHE	Braf inhibiteur (en cours)	Co-investy	01/2010	
61906	LEBBE	Céleste	13/04/2010	IP-AC	BMS	3 boards en 2 ans	Rémunération personnelle	01/2008	
61906	LEBBE	Céleste	13/04/2010	CF-AUD	AMGEN	AACR 2009/ 2010		04/2010	
61906	LEBBE	Céleste	13/04/2010	CF-AUD	BMS	ASCO 2009		06/2009	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61906	LEBBE	Céleste	13/04/2010	CF-AUD	BMS	ASCO 2010		06/2010	
61906	LEBBE	Céleste	27/03/2009	IP-AC	BMS	participation a un board en novembre 2008	Rémunération personnelle	11/2008	11/2008
61906	LEBBE	Céleste	27/03/2009	EC-INV	VICAL	allovectin melanome	investigateur coordonateur France	09/2008	
61905	LEBBE	Céleste	27/03/2009	IP-AC	CELLGENE	participation a un board	Aucune rémunération	12/2008	12/2008
61905	LEBBE	Céleste	27/03/2009	EC-INV	SYNTA	elesclomol	coinvestigateur	03/2008	
61906	LEBBE	Céleste	27/03/2009	EC-INV	SYNTA	elesclomol melanome	co investigateur	03/2008	03/2009
61906	LEBBE	Céleste	27/03/2009	EC-INV	NOVARTIS/INSERM	rad kaposi	investigateur principal	07/2008	
61905	LEBBE	Céleste	27/03/2009	EC-INV	GENTA	genasense essai mélanome phase III	co-investigateur	02/2007	
61906	LEBBE	Céleste	27/03/2009	EC-INV	BMS	ipilimumab essai melanome metastatique	co-investigateur	01/2006	
61905	LEBBE	Céleste	27/03/2009	EC-INV	BMS	ipilimumab essai melanome adjuvant	co-investigateur	04/2009	
61906	LEBBE	Céleste	27/03/2009	EC-INV	BMS	agoniste CD137	co-investigateur	05/2008	
61906	LEBBE	Céleste	22/05/2006	EC-INV	NOVARTIS	GLIVEC dermatofibrosarcome promotion INSERM	Investigateur principal, coordonateur	01/2004	12/2006
61906	LEBBE	Céleste	22/05/2006	EC-INV	BMS	Anti CTLA4 mélanome	investigateur	01/2005	
61906	LEBBE	Céleste	22/05/2006	EC-INV	GENTA	Genasense mélanome	investigateur principal	01/2006	05/2007
61905	LEBBE	Céleste	22/05/2006	EC-CO	APHP	Coordination d'un PHRC sur la morbidité du virus HHV8 en transplantation d'organe	investigateur principal	01/2004	12/2007
61906	LEBBE	Céleste	22/05/2006	RE-AUT	MERCK	APSOR - commission de transparence	aucune rémunération		
61906	LEBBE	Céleste	22/05/2006	CF-AUD	NOVARTIS	AACR 2005, 2006 ;ASCO 2006			
61906	LEBBE	Céleste	28/02/2006	LD-AR	AFSSAPS	Membre du GTD (depuis 3 ans)	Aucune rémunération		
61906	LEBBE	Céleste	28/02/2006	EC-INV	NOVARTIS	Essai Glivec néoadjuvant Dermatofibrosarcome	coordonateur principal	07/2004	01/2007
61906	LEBBE	Céleste	28/02/2006	EC-CO	GENTA	Etude de PK Genasense DMC	investigateur principal	04/2006	
61906	LEBBE	Céleste	28/02/2006	EC-CO	MEDAREX	Anti CTLA4 - 3 études dans Mélanome Métastatique (en cours ou à venir)	co-investigateur		
61906	LEBBE	Céleste	28/02/2006	CF-INT	AACR	Participations à l'AACR - les 2 années précédentes	aucune rémunération		
61906	LEBBE	Céleste	28/02/2006	CF-INT	ASCO	participations (ASCO : American Society of Clinical Oncology)	aucune rémunération	01/2005	12/2005
61906	LEBBE	Céleste	25/08/2003	IP-EC	BRISTOL MYERS SQUIBB	Evaluation d'un inhibiteur de metalloprotéose (Kaposi HIV ganpluside (vaccin) dans mélanome)			
61906	LEBBE	Céleste	25/08/2003	IP-EC	EORTC, SCHERING-PLOUGH	Interferon adjuvant/mélanome			
61906	LEBBE	Céleste	25/08/2003	IP-CF	Institutions publiques (AP-HP, INSERM)	Maladie Kaposi, mélanome)			
61906	LEBBE	Céleste	25/08/2003	IP-AUT	SERVIER	Prise en charge de frais de congrès - Juin 2003 - Congrès de l'ASCO			
61906	LEBBE	Céleste	29/11/2002	VB		La rémunération des essais cliniques est versée sur un compte INSERM ou Naturalia et Biologia et sert à financer des attachés de recherche clinique			
61906	LEBBE	Céleste	29/11/2002	PAR		Soeur à l'Afssaps			
60252	LECHAT	Philippe	14/06/2006	EC-INV	MERCK KGA	Essai CIBIS III Bisoprolol	Président du Comité Exécutif	01/2000	12/2005
60252	LECHAT	Philippe	14/06/2006	EC-INV	MENARINI	Essai SENIORS Nebivolol	Membre du Comité Exécutif	01/2000	12/2004
60252	LECHAT	Philippe	14/06/2006	(Autre)	ASTRA ZENECA		Versement de royalties d'un brevet sur héminenrine à Paul Lechat (Père de Philippe Lechat) puis à Mme Paul Lechat (mère de Philippe Lechat)	01/1975	
60252	LECHAT	Philippe	14/06/2006	CF-INT	MERCK KGA	Japanese Heart Failure meeting Septembre 2005	Rémunération personnelle		
60252	LECHAT	Philippe	14/06/2006	VB	SERVIER	Conseil sur le développement de l'ivabradine dans l'insuffisance cardiaque	Naturalia et Biologia	01/2004	12/2004
60252	LECHAT	Philippe	14/06/2006	VB	SANOFI	Etude EPOX	Université Pierre et Marie Curie	01/2003	12/2004
60252	LECHAT	Philippe	14/06/2006	VB	SANOFI	Etude Valide	Naturalia et Biologia	01/2005	12/2007
60252	LECHAT	Philippe	14/06/2006	CF-INT	ASTRA ZENECA	IUPHAR / Pékin Juillet 2006	Aucune rémunération		
60252	LECHAT	Philippe	14/06/2006	CF-INT	SERVIER	Séminaires SERVIER - SFP - Novembre 2003-2004-2005	Aucune rémunération		
60252	LECHAT	Philippe	14/06/2006	CF-INT	MERCK KGA	HEART FAILURE 2004-2006	Rémunération personnelle		
60252	LECHAT	Philippe	14/06/2006	CF-INT	MERCK KGA	ESC 2003-2004-2005	Rémunération personnelle		
60252	LECHAT	Philippe	14/06/2006	IP-AC	PIERRE FABRE	Conseil sur données expérimentales sur un inhibiteur échangeur Na-H	Rémunération personnelle	01/2004	12/2004
60252	LECHAT	Philippe	14/06/2006	EC-INV	MENARINI	Essai SENIORS Nebivolol	Membre du Comité exécutif	01/2000	12/2004
60252	LECHAT	Philippe	14/06/2006	EC-INV	MERCK KGA	Essai CIBIS III Bisoprolol	Président du Comité exécutif	01/2000	12/2005
60252	LECHAT	Philippe	08/09/2005	Néant					12/2003
60252	LECHAT	Philippe	02/04/2005	LD	SERVIER	Il y a plus de 3 ans	Aucune rémunération		12/2005
60252	LECHAT	Philippe	02/04/2005	IP-AC	MERCK	Bisoprolol			
60252	LECHAT	Philippe	02/04/2005	IP-EC	MENARINI	Investigateur étude pivot Nativolol			
60252	LECHAT	Philippe	02/04/2005	IP-EC	MERCK	Investigateur principal Bisoprolol			
60252	LECHAT	Philippe	02/04/2005	IP-RE	ORION	Levosimendan			
60252	LECHAT	Philippe	02/04/2005	IP-CF		Intervenant congrès ESC, Bisoprolol, Nativolol			
60252	LECHAT	Philippe	27/08/2003	IP-EC	MERCK	Coordination de l'étude CIBIS III - Promoteur : E. MERCK Kg A			
60252	LECHAT	Philippe	27/08/2003	IP-RE	UCB PHARMA	Analyse du dossier Piracutam			
60252	LECHAT	Philippe	27/08/2003	VB	SERVIER	Conseil pour le développement de l'ivabradine			
10276	LEENHARDT	Antoine	17/06/2009	VB	MEDTRONIC	Don	Naturalia et Biologia	11/2008	
10276	LEENHARDT	Antoine	17/06/2009	VB	BOSTON	Don	Naturalia et biologia	11/2008	
10276	LEENHARDT	Antoine	17/06/2009	CF-AUD	PIERRE FABRE	ESC Barcelone	aucune	08/2009	09/2009
10276	LEENHARDT	Antoine	17/06/2009	IP-AC	SANOFI AVENTIS	Conseil développement dronédarone	Rémunération personnelle	01/2009	
10276	LEENHARDT	Antoine	17/06/2009	EC-CO	BOSTON	Etude clinique défibrillateur		01/2009	
10276	LEENHARDT	Antoine	16/11/2007	EC-CO	SORIN GROUP	Etude clinique - stimulateur	Co-investigateur	12/2007	
10276	LEENHARDT	Antoine	05/09/2007	VB	MEDTRONIC	Activités de Recherche	Naturalia et Biologia	07/2007	
10276	LEENHARDT	Antoine	05/09/2007	VB	GUIDANT	Activités de Recherche	Naturalia et Biologia	06/2007	
10276	LEENHARDT	Antoine	05/09/2007	CF-AUD	MEDTRONIC	Europace Lisbonne		06/2007	06/2007
10276	LEENHARDT	Antoine	05/09/2007	CF-AUD	SERVIER	ESC Vienne		09/2007	09/2007
10276	LEENHARDT	Antoine	05/09/2007	EC-CO	BIOTRONIK	Etude clinique - DAI (en cours)	Co-investigateur	02/2007	
10276	LEENHARDT	Antoine	16/05/2006	EC-INV	GUIDANT	Etude clinique - DAI (en cours)	Investigateur principal		
10276	LEENHARDT	Antoine	16/05/2006	EC-INV	ST JUDE MEDICAL	Etude clinique - DAI (en cours)	Investigateur principal		
10276	LEENHARDT	Antoine	16/05/2006	EC-INV	MEDTRONIC	Etude épidémiologique (en cours)	investigateur		
10276	LEENHARDT	Antoine	16/05/2006	IP-AC	SORIN FRANCE	Conseil	rémunération personnelle	01/2003	
10276	LEENHARDT	Antoine	16/05/2006	CF-INT	SANOFI	EPU	rémunération partagée personnelle / institution		
10276	LEENHARDT	Antoine	16/05/2006	CF-INT	MSD CHIBRET	EPU	rémunération partagée personnelle / institution		
10276	LEENHARDT	Antoine	16/05/2006	CF-INT	ASTRA ZENECA	EPU	rémunération partagée personnelle / institution		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10276	LEENHARDT	Antoine	09/06/2004	IP-EC	GUIDANT, MEDTRONIC, SAINT- JUDE, BROTRONIK, ELA				
10276	LEENHARDT	Antoine	09/06/2004	IP-AC	SAINT-JUDE, BROTRONIK				
10276	LEENHARDT	Antoine	09/06/2004	IP-CF	GUIDANT, SAINT-JUDE, BROTRONIK, MEDTRONIC				
10276	LEENHARDT	Antoine	09/06/2004	VB	MEDTRONIC	Association Naturalia et Biologia			
10276	LEENHARDT	Antoine	09/06/2004	VB	GUIDANT	Association Naturalia et Biologia			
10276	LEENHARDT	Antoine	23/10/2001	IP-EC	PROCTER et GAMBLE	Essais cliniques			
10276	LEENHARDT	Antoine	23/10/2001	IP-EC	SANOFI	Essais cliniques			
10276	LEENHARDT	Antoine	23/10/2001	IP-AC	GUIDANT	Conseil			
10276	LEENHARDT	Antoine	23/10/2001	IP-AC	MEDTRONIC	Conseil			
10276	LEENHARDT	Antoine	23/10/2001	IP-AC	ELA	Conseil			
10276	LEENHARDT	Antoine	23/10/2001	IP-AC	SAINT-JUDE	Conseil			
10276	LEENHARDT	Antoine	23/10/2001	IP-CF	SAINT-JUDE	Formations			
10276	LEENHARDT	Antoine	20/06/2000	IP-EC	GUIDANT	Essai clinique			
10276	LEENHARDT	Antoine	20/06/2000	IP-EC	MERTRONIC	Essai clinique			
10276	LEENHARDT	Antoine	20/06/2000	IP-EC	ST JUDE MEDICAL France	Essai clinique			
10276	LEENHARDT	Antoine	20/06/2000	IP-EC	BROTRONIK	Essai clinique			
10276	LEENHARDT	Antoine	20/06/2000	IP-EC	ELA	Essai clinique			
10276	LEENHARDT	Antoine	20/06/2000	IP-AC	MEDTRONIC	Conseil			
10276	LEENHARDT	Antoine	20/06/2000	IP-AC	ST JUDE MEDICAL France	Conseil			
10276	LEENHARDT	Antoine	20/06/2000	IP-EC	ELA	Conseil			
10276	LEENHARDT	Antoine	20/06/2000	IP-CF	GUIDANT	Défibrillateur automatique			
10276	LEENHARDT	Antoine	20/06/2000	IP-CF	MEDTRONIC	Défibrillateur automatique			
10276	LEENHARDT	Antoine	01/01/1999	LD	Agence TERRE NEUVE				
10276	LEENHARDT	Antoine	01/01/1999	IP-EC	CARETEAM				
10276	LEENHARDT	Antoine	01/01/1999	IP-EC	ROCHE				
10276	LEENHARDT	Antoine	01/01/1999	IP-RE	ROCHE				
10276	LEENHARDT	Antoine	01/01/1999	IP-AC	CARETEAM				
10276	LEENHARDT	Antoine	01/01/1999	IP-CF	3M SANTE				
10276	LEENHARDT	Antoine	01/01/1999	IP-CF	SANOFI				
10276	LEENHARDT	Antoine	01/01/1999	IP-CF	BMS				
10276	LEENHARDT	Antoine	01/01/1999	IP-CF	KNOLL				
10276	LEENHARDT	Antoine	01/01/1999	IP-AUT	ROCHE				
10276	LEENHARDT	Antoine	01/01/1998	IP-AUT	Pfizer				
10276	LEENHARDT	Antoine	01/01/1998	IP-AUT	Roche				
10276	LEENHARDT	Antoine	01/01/1998	IP-AUT	Sanofi				
10276	LEENHARDT	Antoine	01/01/1998	IP-AUT	Knoll				
10276	LEENHARDT	Antoine	01/01/1998	IP-AUT	3M Santé				
10276	LEENHARDT	Antoine	01/01/1998	IP-AUT	UPSA				
63966	LEGER	Damien	22/05/2009	EC-INV	SANOFI AVENTIS	Epivansérine M 100 907	Investigateur principal	01/2006	12/2007
63966	LEGER	Damien	22/05/2009	EC-INV	GSK	GW679679	Coordonnateur national	01/2006	12/2007
63966	LEGER	Damien	22/05/2009	EC-INV	TAKEDA	Ramalteon	Investigateur principal	01/2004	12/2005
63966	LEGER	Damien	22/05/2009	EC-INV	LUNDBECK	Gaboxadol	Investigateur principal	01/2002	12/2004
63966	LEGER	Damien	22/05/2009	EC-INV	SERVIER	M20098	Investigateur principal	01/2007	12/2008
63966	LEGER	Damien	22/05/2009	EC-INV	NARVAL	Orthèse d'avancée mandibulaire	Investigateur principal	01/2007	12/2008
63966	LEGER	Damien	22/05/2009	EC-INV	ACTELION	ACT 078573	Investigateur principal	01/2008	12/2009
63966	LEGER	Damien	22/05/2009	IP-AC	SANOFI AVENTIS	Epivansérine M 100 907		01/2006	12/2008
63966	LEGER	Damien	22/05/2009	IP-AC	GSK	GW679679 □□EsZopiclone□□Adartel		01/2006	12/2008
63966	LEGER	Damien	22/05/2009	IP-AC	TAKEDA	Ramalteon		01/2007	12/2007
63966	LEGER	Damien	22/05/2009	IP-AC	LUNDBECK	Gaboxadol□□Circadin		01/2004	12/2008
63966	LEGER	Damien	22/05/2009	IP-AC	NARVAL	Orthèse d'avancée mandibulaire		01/2007	12/2008
63966	LEGER	Damien	22/05/2009	IP-AC	PFIZER	Lyrica		01/2007	12/2008
63966	LEGER	Damien	22/05/2009	IP-AC	ACTELION	ACT 078573		01/2008	12/2009
63966	LEGER	Damien	22/05/2008	EC-INV	SANOFI AVENTIS	Epivansérine M 100 907	investigateur principal	01/2006	12/2007
63966	LEGER	Damien	22/05/2008	EC-INV	GSK	GW 679679	Coordonnateur principal	01/2006	12/2007
63966	LEGER	Damien	22/05/2008	EC-INV	TAKEDA	Ramalteon	investigateur principal	01/2004	12/2005
63966	LEGER	Damien	22/05/2008	EC-INV	LUNDBECK	Gaboxadol	investigateur principal	01/2002	12/2004
63966	LEGER	Damien	22/05/2008	EC-INV	SERVIER	M20098	investigateur principal	01/2007	12/2008
63966	LEGER	Damien	22/05/2008	EC-INV	NARVAL	Orthèse d'avancée mandibulaire	investigateur principal	01/2007	12/2008
63966	LEGER	Damien	22/05/2008	EC-INV	ACTELION	ACT 078573	investigateur principal	01/2008	12/2009
63966	LEGER	Damien	22/05/2008	IP-AC	SANOFI AVENTIS	Epivansérine M 100 907		01/2006	12/2008
63966	LEGER	Damien	22/05/2008	IP-AC	GSK	GW 679679 EsZopiclone Adartel		01/2006	12/2008
63966	LEGER	Damien	22/05/2008	IP-AC	TAKEDA	Ramalteon		01/2007	
63966	LEGER	Damien	22/05/2008	IP-AC	LUNDBECK	Gaboxadol / Circadin		01/2004	12/2008
63966	LEGER	Damien	22/05/2008	IP-AC	NARVAL	Orthèse d'avancée mandibulaire		01/2007	12/2008
63966	LEGER	Damien	22/05/2008	IP-AC	PFIZER	Lyrica		01/2007	12/2008
63966	LEGER	Damien	22/05/2008	IP-AC	ACTELION	ACT 078573		01/2008	12/2009
63966	LEGER	Damien	22/04/2008	EC-INV	SANOFI AVENTIS	EPIVANSERINE - M 100 907	investigateur principal -	01/2006	12/2007
63966	LEGER	Damien	22/04/2008	EC-INV	GSK	GW679679	coordonnateur national	01/2006	12/2007
63966	LEGER	Damien	22/04/2008	EC-INV	TAKEDA	RAMALTEON	investigateur principal	01/2004	12/2005
63966	LEGER	Damien	22/04/2008	EC-INV	LUNDBECK	GABOXADOL	investigateur principal	01/2002	12/2004
63966	LEGER	Damien	22/04/2008	EC-INV	SERVIER	M20098	investigateur principal	01/2007	12/2008
63966	LEGER	Damien	22/04/2008	IP-AC	SANOFI AVENTIS	EPIVANSERINE - M 100 907	rémunération personnelle	01/2006	12/2008
63966	LEGER	Damien	22/04/2008	IP-AC	GSK	GW679679 - ESZOPICLONE - ADARTEL	rémunération personnelle	01/2006	12/2008
63966	LEGER	Damien	22/04/2008	IP-AC	TAKEDA	RAMALTEON	rémunération personnelle	01/2007	
63966	LEGER	Damien	22/04/2008	IP-AC	LUNDBECK	GABOXADOL - CIRCADIN	rémunération personnelle	01/2004	12/2008
63966	LEGER	Damien	22/04/2008	IP-AC	PFIZER	LYRICA	rémunération personnelle	01/2007	12/2008
63966	LEGER	Damien	22/04/2008	CF-AUD	GSK	congrès français du sommeil - Nantes (Adartrel)		01/2007	12/2007
63309	LEGRAND	Erick	25/07/2006	EC-CO	NOVARTIS	Zo Pedronate	Co-investigateur	01/2005	01/2006
63309	LEGRAND	Erick	25/07/2006	EC-CO	P & G	Risedronate	Co-investigateur	01/2005	01/2006
63309	LEGRAND	Erick	25/07/2006	IP-AC	ROCHE	Groupe de travail (Bonnival)		01/2005	01/2007
63309	LEGRAND	Erick	25/07/2006	IP-AC	P & G et AVENTIS	Diaporama Osthéoporose		01/2005	01/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63309	LEGRAND	Erick	25/07/2006	IP-AC	AMGEN	Conseil et Développement ostéoporose		01/2005	01/2006
63309	LEGRAND	Erick	25/07/2006	IP-AC	MSD	Conseil		01/2005	
63309	LEGRAND	Erick	25/07/2006	CF-INT	LILLY	10 conférences sur le traitement de l'ostéoporose		01/2004	12/2006
63309	LEGRAND	Erick	25/07/2006	IP-CF	MSD	10 conférences de rhumatologie		01/2004	01/2006
63309	LEGRAND	Erick	25/07/2006	IP-CF	PROCTER & GAMBLE	2 conférences ostéoporose		01/2005	12/2006
63309	LEGRAND	Erick	25/07/2006	IP-CF	SERVIER	4 conférences ostéoporose		01/2005	12/2006
63309	LEGRAND	Erick	01/03/2005	IP-EC	AVENTIS - PROCTER & GAMBLE - BMS - MSD	Etudes cliniques			
63309	LEGRAND	Erick	01/03/2005	IP-AC	LILLY - ROCHE	Conseil scientifique			
63309	LEGRAND	Erick	01/03/2005	IP-AC	BMS	FMC			
63309	LEGRAND	Erick	01/03/2005	IP-CF	LILLY - AVENTIS - SERVIER - PROCTER	FMC, symposium			
63309	LEGRAND	Erick	01/03/2005	IP-CF	MSD	FMC			
63309	LEGRAND	Erick	17/05/2004	IP-EC	AVENTIS	Essai clinique			
63309	LEGRAND	Erick	17/05/2004	IP-EC	PROCTER & GAMBLE	Essai clinique			
63309	LEGRAND	Erick	17/05/2004	IP-CF	LILLY	Conférence, FMC			
63309	LEGRAND	Erick	17/05/2004	IP-CF	PROCTER & GAMBLE	Conférence, FMC			
63309	LEGRAND	Erick	17/05/2004	IP-CF	AVENTIS	Conférence, FMC			
63309	LEGRAND	Erick	17/05/2004	IP-CF	MERCK SHARP & DOHME	Conférence, FMC			
64007	LEGROUX-GEROT	Isabelle	02/02/2010	EC-CO	BONDIR (ROCHE)	Bonviva	Co-investigateur	01/2009	12/2009
64007	LEGROUX-GEROT	Isabelle	02/02/2010	EC-CO	AMGEN	Denusomab	Co-investigateur	11/2009	
64007	LEGROUX-GEROT	Isabelle	02/02/2010	CF-INT	ASTRA ZENECA	Lille Arimidex (Retnlissement osseux et articulaire cancer du sein)	Aucune rémunération	11/2009	11/2009
64007	LEGROUX-GEROT	Isabelle	02/02/2010	CF-INT	NOVARTIS	Aclasta "Epidémiologie ostéoprose masculine" ASSM Denver USA	Rémunération institution	09/2009	09/2009
64007	LEGROUX-GEROT	Isabelle	02/02/2010	CF-AUD	PROCTER GAMBLE	SFR Paris - Risedronate		11/2009	12/2009
64007	LEGROUX-GEROT	Isabelle	02/02/2010	CF-AUD	SERVIER	Séminaire qualité Paris		06/2009	06/2009
64007	LEGROUX-GEROT	Isabelle	22/12/2008	EC-CO	ROCHE	BONVIVA (en cours)	co-investigateur	06/2007	
64007	LEGROUX-GEROT	Isabelle	22/12/2008	EC-CO	NYCOMED	PTH (en cours)	co-investigateur	06/2008	
64007	LEGROUX-GEROT	Isabelle	22/12/2008	CF-INT	PROTER ET GAMBLE	Touquet : anorexie mentale	rémunération institution	03/2008	03/2008
64007	LEGROUX-GEROT	Isabelle	22/12/2008	CF-INT	MSD	Haubertin : FOSAMAX, actualités	rémunération institution	01/2008	12/2008
64007	LEGROUX-GEROT	Isabelle	25/03/2008	EC-INV	PAREXEL	IBANDRONATE (en cours)	investigateur principal	10/2007	
64007	LEGROUX-GEROT	Isabelle	25/03/2008	EC-INV	PAREXEL	PTH (1.84) : en cours	investigateur principal	02/2008	
64007	LEGROUX-GEROT	Isabelle	25/03/2008	EC-CO	AMGEN	DENOSUMAB / ALENDRONATE (en cours)	co-investigateur	02/2007	
64007	LEGROUX-GEROT	Isabelle	25/03/2008	EC-CO	ROCHE	IBANDRONATE / ALENDRONATE (en cours)	co-investigateur	11/2004	11/2005
64007	LEGROUX-GEROT	Isabelle	25/03/2008	CF-INT	PROTER ET GAMBLE	Touquet : anorexie mentale	aucune rémunération	03/2008	03/2008
64007	LEGROUX-GEROT	Isabelle	25/03/2008	CF-INT	IPSEN	Lille : calcuim VIT D	rémunération institution	12/2007	12/2007
64007	LEGROUX-GEROT	Isabelle	25/03/2008	CF-AUD	PROTER ET GAMBLE	ASBMR congrés Américain ostéoporose		09/2007	09/2007
64007	LEGROUX-GEROT	Isabelle	25/03/2008	CF-AUD	PROTER	Congrés français SFR - Paris		12/2007	12/2007
64007	LEGROUX-GEROT	Isabelle	07/06/2007	EC-INV	STAND	Denosumab	Investigateur	02/2007	
64007	LEGROUX-GEROT	Isabelle	07/06/2007	EC-INV	LILLY	PTH	Investigateur	01/2002	
64007	LEGROUX-GEROT	Isabelle	07/06/2007	EC-INV	BALTO	Bonviva	Investigateur	01/2005	12/2006
64007	LEGROUX-GEROT	Isabelle	12/02/2006	EC-INV	LILLY	Forstéo	expérimentateur principal	01/2001	12/2005
64007	LEGROUX-GEROT	Isabelle	12/02/2006	EC-INV	ROCHE PAREXEL	Ibandronate	investigateur principal	06/2005	12/2005
64007	LEGROUX-GEROT	Isabelle	12/02/2006	CF-INT	PROCTER GAMBLE	Ateliers du touquet - les traitements de l'ostéoporose	rémunération personnelle	03/2005	
64007	LEGROUX-GEROT	Isabelle	12/02/2006	CF-INT	LILLY	Le Quotidien du Médecin	rémunération personnelle	10/2005	
64007	LEGROUX-GEROT	Isabelle	12/02/2006	CF-INT	ASTRA	Ostéoporose et qualité du soin	aucune rémunération	11/2005	
64007	LEGROUX-GEROT	Isabelle	12/02/2006	CF-AUD	PROCTER GAMBLE	ASBM - Nashville		09/2005	
64007	LEGROUX-GEROT	Isabelle	12/02/2006	CF-AUD	PROCTER GAMBLE	SFR		12/2005	
60291	LEJOYEUX	Michel	22/09/2008	CF-INT	LIPHA SANTE	formation addictologie	rémunération personnelle/institution		
60291	LEJOYEUX	Michel	08/06/2007	CF-INT	MERCK LIPHA	Bibliographie Alcoologie			
60291	LEJOYEUX	Michel	08/06/2007	CF-INT	LILLY		rémunération partagée personnelle/institution	06/2007	06/2007
60291	LEJOYEUX	Michel	06/02/2005	EC-INV	ARDIX	Investigateur		01/2004	12/2005
60291	LEJOYEUX	Michel	06/02/2005	EC-INV	SERVIER	Etude Agomélatine			
60291	LEJOYEUX	Michel	06/02/2005	CF-INT	LILLY	Activité psy (2003 - en cours)	rémunération personnelle		
60291	LEJOYEUX	Michel	06/02/2005	CF-INT	MERCK,LIPHA	Bibliographie en alcoologie (2003 - en cours)	rémunération personnelle		
60291	LEJOYEUX	Michel	02/02/2004	IP-EC	SERVIER	Evaluation			
60291	LEJOYEUX	Michel	02/02/2004	IP-CF	LILLY	Formation			
60291	LEJOYEUX	Michel	28/08/2003	IP-AC	SANOFI SYNTHELABO	Journées de réflexion			
60291	LEJOYEUX	Michel	28/08/2003	IP-CF	LILLY	Animation psy			
60291	LEJOYEUX	Michel	28/08/2003	IP-CF	LIPHA	Document de formation			
60291	LEJOYEUX	Michel	22/04/2002	IP-EC	SERVIER	Protocole Agomelatine			
60291	LEJOYEUX	Michel	22/04/2002	IP-CF	LILLY	Réunions de FMC			
60291	LEJOYEUX	Michel	22/04/2002	IP-RE	ROCHE	Rapport d'expertise			
60291	LEJOYEUX	Michel	22/04/2002	IP-CF	LILLY	Formation de psychiatres			
60291	LEJOYEUX	Michel	30/06/2000	IP-EC	SERVIER	Protocole d'anti-dépresseurs			
60291	LEJOYEUX	Michel	30/06/2000	IP-RE	ROCHE	Rapport d'expertise			
60291	LEJOYEUX	Michel	30/06/2000	IP-CF	LILLY	Formation de psychiatres			
61019	LEMOINE	Patrick	18/02/2008	LD-AR	LUNDBECK	Réunion expert	rémunération institution	01/2008	12/2008
61019	LEMOINE	Patrick	18/02/2008	CF-INT	LILLY France	Réunions	aucune rémunération	01/2008	12/2008
61019	LEMOINE	Patrick	18/02/2008	CF-INT	BMS	1 réunion	aucune rémunération	01/2008	12/2008
61019	LEMOINE	Patrick	18/02/2008	CF-INT	SERVIER	1 CINP	rémunération institution	07/2008	07/2008
61019	LEMOINE	Patrick	01/03/2007	Néant					
61019	LEMOINE	Patrick	03/02/2004	VB	AVENTIS - BIOCODEX - BRISTOL MYERS - LILLY - UCB - GSK - PFIZER	ARP (études, congrès, conférences, formation), APIS (un congrès annuel)			
61019	LEMOINE	Patrick	03/02/2004	VB	JANSSEN CILAG - SANOFI SYNTHELABO - SERVIER - PIERRE FABRE	ARP (études, congrès, conférences, formation), APIS (un congrès annuel)			
61019	LEMOINE	Patrick	03/02/2004	VB	LUNDBECK - ORGANON - WYETH LEDERLE - CHIESI	ARP (études, congrès, conférences, formation), APIS (un congrès annuel)			
61019	LEMOINE	Patrick	18/11/2003	VB	AVENTIS, LILLY, UCB, GLAXO SMITHKLINE, ORGANON	Association ARP (études, conférences, congrès)			
61019	LEMOINE	Patrick	18/11/2003	VB	IRIS SERVIER, WYETH-LEDERLE, PFIZER	Association APIS (1 congrès annuel)			
61019	LEMOINE	Patrick	18/11/2003	VB	LUNDBECK, BIOCODEX, ARKO-PHARMA, PIERRE FABRE				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61019	LEMOINE	Patrick	18/11/2003	VB	JANSSEN-CILAG, SANOFI-SYNTHELABO	Association ARP (études, conférences, congrès)			
					AVENTIS, LAFON, LILLY, UCB, GSK, ORGANON, JANSSEN, SANOFI-SYNTHELABO, SERVIER, WYETH				
61019	LEMOINE	Patrick	29/11/2002	VB	LEDERLE, LUNDBECK	Association APIS (1 congrès annuel) - Association ARP (Etudes, conférences, congrès) - Organisation d'un congrès pour lequel je sollicite tous les laboratoires fabriquant des p			
61019	LEMOINE	Patrick	05/09/2001	IP-AC	SANOFI SYNTHELABO	Rédaction de news (Internet)			
61019	LEMOINE	Patrick	05/09/2001	IP-AC	NEURIM	Conseils			
61019	LEMOINE	Patrick	05/09/2001	IP-AC	AVENTIS				
61019	LEMOINE	Patrick	05/09/2001	VB	INVERESK RESEARCH				
61019	LEMOINE	Patrick	05/09/2001	VB	LUNDBECK				
61019	LEMOINE	Patrick	05/09/2001	VB	SANOFI SYNTHELABO				
61019	LEMOINE	Patrick	05/09/2001	VB	QUINTILES				
61019	LEMOINE	Patrick	05/09/2001	VB	LILLY France				
61019	LEMOINE	Patrick	05/09/2001	VB	KNOLL				
61019	LEMOINE	Patrick	05/09/2001	VB	JANSSEN				
61019	LEMOINE	Patrick	05/09/2001	VB	ADIR				
61019	LEMOINE	Patrick	05/09/2001	VB	LAFON				
61019	LEMOINE	Patrick	05/09/2001	VB	AVENTIS				
61019	LEMOINE	Patrick	05/09/2001	VB	UPSA				
61019	LEMOINE	Patrick	05/09/2001	VB	CHIESI, PIERRE FABRE				
61019	LEMOINE	Patrick	05/09/2001	VB	WYETH LEDERLE				
61019	LEMOINE	Patrick	05/09/2001	VB	ORGANON				
61019	LEMOINE	Patrick	21/06/1999	IF	SANOFI SYNTHELABO	Actions			
61019	LEMOINE	Patrick	21/06/1999	IF	RHONE POULENC RORER	Actions			
61019	LEMOINE	Patrick	21/06/1999	IP-EC	ORGANON	Antidépresseur			
61019	LEMOINE	Patrick	21/06/1999	IP-EC	MITSAHISHI	Antidépresseur			
61019	LEMOINE	Patrick	21/06/1999	IP-EC	RHONE POULENC RORER	Sevrage B2D			
61019	LEMOINE	Patrick	21/06/1999	VB	LAFON	Eveil : sommes versées au budget de l'Association pour la Recherche en Psychiatrie qui organise la recherche et l'enseignement du service			
61019	LEMOINE	Patrick	21/06/1999	VB	SYNTHELABO	Sulpride : sommes versées au budget de l'Association pour la recherche en Psychiatrie			
61019	LEMOINE	Patrick	21/06/1999	VB	UPSA	Donormyl : Association pour la recherche en Psychiatrie			
61019	LEMOINE	Patrick	21/06/1999	VB	SB	Art et sciences ; antidépresseur : Association pour la recherche en Psychiatrie			
61019	LEMOINE	Patrick	21/06/1999	VB	LILLY	Sevrages (colloque) : Association pour la recherche en Psychiatrie			
61019	LEMOINE	Patrick	21/06/1999	IP-CF	RHONE POULENC RORER	Livre sur l'insomnie : Association pour la recherche en Psychiatrie			
60279	LEPINE	Jean-Pierre	22/12/2010	CF-INT	SERVIER	Valoriser votre recherche, formation thésar et chercheurs, Chamonix	Rémunération personnelle	01/2010	01/2010
60279	LEPINE	Jean-Pierre	22/12/2010	CF-INT	PFIZER WYETH	CNS Summit Dubai	Rémunération personnelle	05/2010	05/2010
60279	LEPINE	Jean-Pierre	22/12/2010	CF-INT	SERVIER	Valoriser votre recherche, formation de thésards et chercheurs	Rémunération personnelle	01/2010	01/2010
60279	LEPINE	Jean-Pierre	22/12/2010	CF-INT	SERVIER	Valoriser votre recherche, formation de thésards et chercheurs	Rémunération personnelle	01/2010	01/2010
60279	LEPINE	Jean-Pierre	15/12/2009	IP-AUT	SERVIER	VALORISER VOTRE RECHERCHE		01/2009	01/2009
60279	LEPINE	Jean-Pierre	20/10/2008	IP-AUT	ECNP BARCELONE	SYMPOSIUM Fibromyalgie□□Academy for Education Healtcare		09/2008	09/2008
60279	LEPINE	Jean-Pierre	20/10/2008	IP-AUT	SERVIER	VALORISER VOTRE RECHERCHE		02/2008	02/2008
60279	LEPINE	Jean-Pierre	20/10/2008	CF-AUD	BMS	WASHINGTON USA □□Society of Biological Psychiatry		05/2008	05/2008
60279	LEPINE	Jean-Pierre	11/10/2007	IP-AUT	SERVIER	Ho Chi Minh Ville (Vietnam) - 11èmes Journées Médicales France-Vietnam		01/2007	02/2007
60279	LEPINE	Jean-Pierre	11/10/2007	CF-AUD	ISCTM	Bruxelles (Belgique) - ISCTM		09/2007	09/2007
60279	LEPINE	Jean-Pierre	11/10/2007	CF-AUD	PFIZER	Washington (USA) - ISCTM		02/2007	02/2007
60279	LEPINE	Jean-Pierre	11/10/2007	CF-AUD	PFIZER	Chicago (USA) - ISCTM		07/2006	07/2006
60279	LEPINE	Jean-Pierre	11/10/2007	CF-INT	WYETH	Boston (USA) - Global Depression and Anxiety Strategy Consultant Board	Aucune rémunération	06/2007	06/2007
60279	LEPINE	Jean-Pierre	11/10/2007	CF-INT	BMS	San Diego (USA) - Society of Biological Psychiatry	Aucune rémunération	05/2007	05/2007
60279	LEPINE	Jean-Pierre	02/06/2006	IP-AC	SEPRACOR	ESZOPICLONE - 1ère réunion	Rémunération personnelle	02/2006	02/2006
60279	LEPINE	Jean-Pierre	02/06/2006	IP-AC	WYETH	DESVENLAFAXINE	Rémunération personnelle	05/2006	05/2006
60279	LEPINE	Jean-Pierre	02/06/2006	IP-AC	SANOFI	BETA-3 AGONIST - 1ère réunion	Rémunération personnelle	03/2006	03/2006
60279	LEPINE	Jean-Pierre	02/06/2006	CF-INT	WYETH	CINP 2006	Rémunération personnelle	07/2006	07/2006
60279	LEPINE	Jean-Pierre	02/06/2006	CF-AUD	ELI LILLY	Society of Biological Psychiatry (Toronto)		05/2006	05/2006
60279	LEPINE	Jean-Pierre	02/06/2006	CF-AUD	WYETH	APA (Atlanta)		05/2005	05/2005
60279	LEPINE	Jean-Pierre	02/06/2006	CF-AUD	PFIZER	ISCTM (Washington)		02/2006	02/2006
60279	LEPINE	Jean-Pierre	02/06/2006	EC-CO	GSK	ESEMED		01/2000	12/2005
60279	LEPINE	Jean-Pierre	02/06/2006	EC-CO	ELI LILLY	SOHO	Collaborateur		11/2006
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AC	QUINTILES	Conseil méthodologique (2003/2004)	Aucune rémunération		
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AC	ORION	Déramriclane (2003)	Aucune rémunération		
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AC	PREVERS	Récurrences sertraline	Aucune rémunération		
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AC	PFIZER	Récurrences sertraline	Aucune rémunération		
60279	LEPINE	Jean-Pierre	08/04/2005	IP-CF	PIERRE FABRE	CINP Paris 2004			
60279	LEPINE	Jean-Pierre	08/04/2005	IP-CF	WYETH	CINP Paris 2004			
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AC	GSK	Anxiété généralisée (2003)	Aucune rémunération		
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AC	PIERRE FABRE - WYETH		Aucune rémunération		
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AUT	WYETH	APA (American Psychiatric Association)			
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AUT	GSK	ECNP			
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AUT	PFIZER	ISCTCNS (Montréal)			
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AUT	GSK	Etudes épidemiologiques (Enquête ESEMED)			
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AUT	LABORATOIRES EISAI				
60279	LEPINE	Jean-Pierre	08/04/2005	IP-AUT	SOHO	Schizophrénie			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	IRIS SERVIER	Coordination d'études cliniques : azapirone et anxiété généralisée, tianeptine vs paroxétine dans les épisodes dépressifs majeurs			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	PFIZER	Coordination d'études cliniques : sertraline et prévention des récurrences - sertraline, dépressions et troubles de la personnalité			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	QUINTILES	Coordination d'études cliniques : trouble panique et venlafaxine, deramciclane et anxiété généralisée, fluvoxamine et phobies sociales			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	MERCK US	Coordination d'études épidémiologiques : Impact familial de la dépression sévère			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	PIERRE FABRE	Coordination d'études épidémiologiques : Etude médico-économique de la dépression en population générale			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	LILLY	Coordination d'études épidémiologiques : Schizophrénie et précarité (SAMU social)			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	SMITHKLINE BEECHAM	Coordination d'études épidémiologiques : Etudes épidémiologiques de la dépression en Europe (DEPRES) et ESEMed			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-AC	SMITHKLINE BEECHAM	Troubles anxieux			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-AC	PIERRE FABRE	Milnacipran et dépression			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-EC	BOEHRINGER	Dépressions résistantes			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-AC	PARKE DAVIS	Pagocione et anxiété			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-AC	ORION PHARMA	Deramciclane et anxiété généralisée			
60279	LEPINE	Jean-Pierre	12/07/2000	IP-AC	QUINTILES	Formation d'investigateurs à l'évaluation des troubles anxieux			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	SMITHKLINE BEECHAM				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	SERVIER				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	PFIZER				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	WYETH LEDERLE				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	ROCHE				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	SANOFI				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	LUNDBECK				
60279	LEPINE	Jean-Pierre	12/07/2000	IP-CF	AVENTIS				
64846	LERONDEL	Stéphanie	12/11/2009	IF	BIOPHARM CONSULTING TOURS	1 action	<5000e ou 5% du capital	01/2002	
64846	LERONDEL	Stéphanie	12/11/2009	LD-AR	LABORATOIRES GUERBET	Consulting en imagerie in viVo pour le développement pharmaceutique	rémunération personnelle et institution	01/2009	12/2010
64846	LERONDEL	Stéphanie	12/11/2009	EC-CO	SERVIER	Imagerie pour le développement pharmaceutique et la toxicologie - techologie Orléans, toxicologie Gidy (en	co-direction scientifique, contrat CNRS	01/2007	
64846	LERONDEL	Stéphanie	12/11/2009	EC-CO	CERB BAUGY	Développement de nouvelles stratégies d'imagerie en cancérologie, inflammation, infection (en cours)	co-direction scientifique, contrat CNRS	01/2009	
64846	LERONDEL	Stéphanie	12/11/2009	RE-AUT	PIERRE FABRE	Evaluation par imagerie chez l'animal de l'activité du TOPAAL comprimé (Médicaments -Toulouse)	rémunération institution	01/2007	12/2007
64846	LERONDEL	Stéphanie	12/11/2009	IP-AC	SANOFI AVENTIS	Conseil en imagerie in vivo et développement pharmaceutique oncologique ; tous produits - Oncologie expé	rémunération institution	01/2005	
64846	LERONDEL	Stéphanie	12/11/2009	IP-AC	PIERRE FABRE	Conseil en imagerie et développement pharmaceutique oncologique - tous produits - Oncologie Toulouse (e	rémunération institution	01/2004	
64846	LERONDEL	Stéphanie	12/11/2009	CF-INT	SOCIETE FRANCAISE DE PATHOLOGIE TOXICOLOGIQUE	Imagerie des biomarqueurs pour l'évaluation de l'efficacité et de la sécurité des médicaments Paris	aucune rémunération	01/2009	12/2009
64846	LERONDEL	Stéphanie	12/11/2009	VB	PIERRE FABRE	Contrat de collaboration ou de prestation (Médicaments Toulouse)	CNRS	01/2004	12/2011
64846	LERONDEL	Stéphanie	12/11/2009	VB	SERVIER ORLEANS	Contrat de collaboration ou de prestation	CNRS	01/2007	12/2011
64846	LERONDEL	Stéphanie	12/11/2009	PAR	BIOPHARM CONSULTING TOURS	Actionnaire (en cours)	Père	01/2002	
64846	LERONDEL	Stéphanie	11/02/2008	EC-CO	SERVIER TECHNOLOGIE (ORLEANS)	Imagerie de la distribution, du ciblage et de la vectorisation d'agents ant-cancéreux	Direction scientifique : contrat collaboration : CNRS - SERVIER	01/2007	12/2007
64846	LERONDEL	Stéphanie	11/02/2008	EC-CO	SERVIER CENTRE DE TOXICOLOGIE (GIDY)	Développementde stratégies d'imagerie pour la toxicologie	Direction scientifique : CNRS - SERVIER	01/2007	12/2007
64846	LERONDEL	Stéphanie	11/02/2008	RE-AUT	PIERRE FABRE MEDICAMENT (TOULOUSE)	Evaluation par imagerie chez l'animal de l'activité du TOPAAL comprimé		01/2007	12/2007
64846	LERONDEL	Stéphanie	11/02/2008	IP-AC	SANOFI AVENTIS	Conseil en imagerie et développement pharmaceutique oncologie : tous produits 'oncologie expérimentale - vitry sus seine)		01/2005	12/2005
64846	LERONDEL	Stéphanie	11/02/2008	IP-AC	PIERRE FABRE	Conseil en imagerie et développemem pharmaceutique oncologie : tous produits (oncologie - Toulouse)		01/2004	12/2004
64846	LERONDEL	Stéphanie	11/02/2008	VB	PIERRE FABRE MEDICAMENT (Toulouse)	Contrat de collaboration ou de prestation (CNRS)		01/2004	12/2011
64846	LERONDEL	Stéphanie	11/02/2008	VB	SERVIER (Orléans)	Contrat de collaboration ou de prestation (CNRS)		01/2007	12/2011
64846	LERONDEL	Stéphanie	11/02/2008	VB	MDS PHARMA SERVICES (Lyon)	Contrat équipe-conseil		01/1995	12/1997
64846	LERONDEL	Stéphanie	11/02/2008	IF	BIOPHARM CONSULTING (Tours)	1 action : <5000 € ou <5% du capital		01/2002	
64846	LERONDEL	Stéphanie	11/02/2008	LD	BIOPHARM CONSULTING		Rémunération : Institution	01/2003	
64706	LESIMPLE	Thierry	25/07/2007	LD-AR	DIVISION ONCOLOGIE BIOTRIAL	Head of the Oncology Division (en cours)	Investigateur - Coordonnateur France	03/2002	09/2002
64706	LESIMPLE	Thierry	25/07/2007	EC-INV	SCHERING PLOUGH	Essai thérapeutique Phase I / sch66336 (Sarasar) + Carboplatine + Paclitaxel	Investigateur - Coordonnateur	11/2002	10/2004
64706	LESIMPLE	Thierry	25/07/2007	EC-INV	BEAUFOUR IPSEN	Essai thérapeutique Industriel Phase I / BN80915 (Diflomotecan)	Investigateur - Coordinateur	01/2003	
64706	LESIMPLE	Thierry	25/07/2007	EC-INV	CENTRE EUGENE MARQUIS	Essai thérapeutique académique Phase II / Capecitabine + Gemcitabine + Acetate de Megestrol (en cours)	Investigateur principal	12/2003	12/2006
64706	LESIMPLE	Thierry	25/07/2007	EC-INV	CHU RENNES	Essai thérapeutique académique Phase II thérapie cellulaire	Investigateur - Coordinateur	12/2006	
64706	LESIMPLE	Thierry	25/07/2007	EC-INV	LILLY	Essai thérapeutique industriel Phase I / Enzastaurine + Digoxine (en cours)	Investigateur - Coordinateur	01/2007	
64706	LESIMPLE	Thierry	25/07/2007	EC-INV	LILLY	Essai thérapeutique industriel Phase I / Enzastaurine (en cours)	Co-investigateur	12/1999	12/2004
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	CENTRE LEON BERARD	Essai thérapeutique académique Phse III / Interleukine-2 + Interferon-alpha	Co-investigateur	12/1999	07/2004
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	CENTRE LEON BERARD	Essai thérapeutique académique Phase III / Interleukine-2 + Interferon-alpha	Co-investigateur	05/2002	11/2005
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	EORTC	Essai thérapeutique académique Phase III / GM2-KLH/QS-21	Co-investigateur	04/2003	03/2007
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	CENTRE RENE GAUDUCHEAU	Essai thérapeutique académique Phase II / Carboplatine + Etoposide	Co-investigateur	04/2003	
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	INSTITUT GUSTAVE ROUSSY	Essai thérapeutique académique Phase III / Cisplatine + Gemcitabine (en cours)	Co-investigateur	09/2003	01/2005
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	PHARMACIA UPJOHN	Essai thérapeutique industriel Phase III / Edotecarine + Temozolomide + Lomustine	Co-investigateur	03/2004	02/2006
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	SIGMA TAU	Essai thérapeutique industriel Phase III / Thymosine-alpha + Deticene + Interferon-alpha	Co-investigateur	09/2004	03/2007
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	IPSEN BEAUFOUR	Essai thérapeutique industriel Phse I / BN 80927 (Elomotecan)	Co-investigateur	09/2006	
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	EORTC	Essai thérapeutique académique Phase III / Temozolomide (en cours)	Co-investigateur	10/2006	
64706	LESIMPLE	Thierry	25/07/2007	EC-CO	CENTRE LEON BERARD	Essai thérapeutique académique Phase III / Temozolomide (en cours)	Aucune rémunération	05/2007	06/2007
64706	LESIMPLE	Thierry	25/07/2007	RE-DE	NERVIANO MEDICAL SCIENCES	Expertise AFSSAPS dans le cadre du régime d'autorisation d'août 2006 - Essai thérapeutique industriel Pha	Aucune rémunération	06/2005	06/2005
64706	LESIMPLE	Thierry	25/07/2007	RE-AUT	CHU PITIE-SAPETRIERE	PHRC 2005 - Essai thérapeutique académique Phase II / Temozolomide	Aucune rémunération	03/2006	05/2006
64706	LESIMPLE	Thierry	25/07/2007	RE-AUT	CHU PITIE SAPETRIERE	PHRC 2006 - Essai thérapeutique académique Phase I / CpG-ODN	rémunération personnelle	01/2004	12/2004
64706	LESIMPLE	Thierry	25/07/2007	IP-AC	SCHERING PLOUGH	Réunion d'experts européens et américains Interferon-alpha	Aucune rémunération	10/2005	10/2005
64706	LESIMPLE	Thierry	25/07/2007	IP-AC	SERVIER	Conseil scientifique en Recherche et Développement : Pipe-line en oncologie	Aucune rémunération	11/2006	01/2007
64706	LESIMPLE	Thierry	25/07/2007	IP-AC	IMMUTEP	Conseil scientifique en Recherche et Développement : IMP321	Aucune rémunération	01/2007	01/2007
64706	LESIMPLE	Thierry	25/07/2007	IP-AC	PFIZER	Conseil scientifique en Recherche et Développement : Pipe-line en oncologie	rémunération personnelle	02/2006	02/2006
64706	LESIMPLE	Thierry	25/07/2007	CF-INT	TNS HEALTHCARE	Centre Eugène Marquis : Mélanome - Anticorps anti-CTLA4		03/2007	03/2007
64706	LESIMPLE	Thierry	25/07/2007	CF-INT	LAB PHARMACEUTIQUES	CHU Rennes : Thérapie Ciblées en oncologie	rémunération personnelle	03/2007	03/2007
64706	LESIMPLE	Thierry	25/07/2007	CF-INT	EASTON	Centre Eugène Marquis : Inhibiteurs de mTOR : Temsirolimus		05/2005	05/2005
64706	LESIMPLE	Thierry	25/07/2007	CF-AUD	SCHERING PLOUGH	Edinburgh : European Association of NeuroOncology : Temozolomide		10/2005	10/2005
64706	LESIMPLE	Thierry	25/07/2007	CF-AUD	SCHERING PLOUGH	Pau : Association des Neurooncologues d'Expression Française - Temozolomide		06/2006	06/2006
64706	LESIMPLE	Thierry	25/07/2007	CF-AUD	SCHERING PLOUGH	Stockholm : World Congress of Neurooncology - Temozolomide		11/2006	11/2006
64706	LESIMPLE	Thierry	25/07/2007	CF-AUD	SCHERING PLOUGH	PRAGUE : EORTC-NCI-AACR International Conference - cibles moléculeires et thérapeutiques cancéreuses		11/2006	11/2006
64706	LESIMPLE	Thierry	25/07/2007	CF-AUD	SCHERING PLOUGH	Paris : Association de NeuroOncologie d'Expression Francaise - Temozolomide		01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	MDS PHARMA	46 245 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	PHARMACYCLICS	30 882 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	PAREXEL	30 042 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	STIFTUNG	22 758 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	BEAUFOUR IPSEN	16 745 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	WYETH PHARMA	15 546 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	THERAPHARM	12 268 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2007	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	CAC SA	11 473 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2005	12/2005
64706	LESIMPLE	Thierry	25/07/2007	VB	DIVERS	115 814 euros (< 10 000 euros par entreprise) - (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	COVANCE	103 648 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	MDS PHARMA	58 877 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	BEAUFOUR IPSEN	46 073 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	PRA INTERNATIONAL	37 829 euros (Essais thérapeutiques - honoraires et surcoûts)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64706	LESIMPLE	Thierry	25/07/2007	VB	PAREXEL	37 285 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	PRA INTERNATIONAL	37 829 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	PFIZER	30 036 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	NOVARTIS	19973 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	THERAPHARM	11 106 euros (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
64706	LESIMPLE	Thierry	25/07/2007	VB	DIVERS	108 425 euros (environ 10 000 euros par entreprise) - (Essais thérapeutiques - honoraires et surcoûts)	Centre Eugène Marquis	01/2006	12/2006
60421	LEVY	Vincent	21/01/2010	LD-AR	GSK	Expertise (Board) Ofatumumab	Rémunération personnelle	01/2008	
60421	LEVY	Vincent	21/01/2010	LD-AR	ROCHE	Expertise (Board) GA101 Rituximab	Rémunération personnelle	01/2009	
60421	LEVY	Vincent	21/01/2010	EC-INV		Nombreux essais clinique dans le domaine de la CLC et de la maladie de Waldenström			
60421	LEVY	Vincent	21/01/2010	RE-AUT	PHRC	Tous les ans : hématologie - Méthodologie	Aucune rémunération		
60421	LEVY	Vincent	22/11/2007	LD-AR	GSK	Membre du BOARD	rémunération personnelle	09/2007	12/2007
60421	LEVY	Vincent	22/11/2007	IP-EC	ROCHE - GENMAB - GSK - SERVIER	Comme médecin délégué d'in CIC, je suis co-investigateur de tous les études réalisés avec de très nombreu co-investigateur			
60421	LEVY	Vincent	22/11/2007	IP-CF	AMGEN	Formation des visiteurs médicaux	rémunération personnelle	11/2007	11/2007
60421	LEVY	Vincent	22/11/2007	IP-CF	BMS	ASH 2006 et 2007			
60421	LEVY	Vincent	29/03/2006	CF-AUD	GENMAB	copenhague, réunion investigateur HUMAX			
60421	LEVY	Vincent	29/03/2006	IP-AC	CELLGEN	REVLIMID, conseil méthodologique pour un essai dans la LLC	Rémunération personnelle/institution	04/2006	04/2006
60421	LEVY	Vincent	25/04/2005	Néant					
60421	LEVY	Vincent	02/02/2004	Néant					
60421	LEVY	Vincent	23/01/2004	Néant					
60421	LEVY	Vincent	22/08/2003	Néant					
60421	LEVY	Vincent	28/09/2000	IP-EC	LLC	Membre du conseil scientifique du groupe français LCC - Autogreffe Phase II			
60421	LEVY	Vincent	28/09/2000	IP-CF		Formation des DES d'hématologie - Essais thérapeutiques			
10284	LEVY	Emile	07/10/1999	IP-AUT		Formateur indépendant : séminaires, actions de formation			
10284	LEVY	Emile	05/05/1999	IP-EC	SERVIER	Analyse statistique et économique d'une enquête sur l'ulcère veineux de la jambe			
10284	LEVY	Emile	05/05/1999	IP-EC	GLAXO WELLCOME	Analyse statistique et économique d'une enquête sur l'asthme infantile sévère			
10284	LEVY	Emile	05/05/1999	IP-RE	SANOFI	Synthèse des études phamaco-économiques sur l'épilepsie			
10284	LEVY	Emile	05/05/1999	IP-AC	SANOFI	Conseil sur des projets d'études pharmaco-économique			
10284	LEVY	Emile	05/05/1999	IP-CF	Divers	Economie de la santé (Principalement organisés sans but lucratif)			
10284	LEVY	Emile	01/01/1999	IP-AC	SANOFI	Etude économique et conseils pour divers laboratoires			
10284	LEVY	Emile	01/01/1999	IP-AC	SERVIER				
10284	LEVY	Emile	01/01/1999	IP-AC	SB				
10284	LEVY	Emile	01/01/1999	VB	Divers laboratoires	Taxe d'apprentissage : LEGOS, Centre de recherche de l'université de Paris Dauphine pour le DESS Econo LEGOS			
10284	LEVY	Emile	01/01/1998	IP-AUT	Hoechst				
10284	LEVY	Emile	01/01/1998	IP-AUT	Glaxo				
10284	LEVY	Emile	01/01/1998	IP-AUT	Negma				
10284	LEVY	Emile	01/01/1998	IP-AUT	S.B.				
10284	LEVY	Emile	01/01/1998	IP-AUT	Merck Damerstatt				
10284	LEVY	Emile	01/01/1998	IP-AUT	Servier				
10284	LEVY	Emile	01/01/1998	IP-AUT	Theraplix				
10284	LEVY	Emile	01/01/1998	IP-AUT	Sanofi				
10284	LEVY	Emile	01/01/1998	IP-AUT	Upjohn				
10284	LEVY	Emile	01/01/1998	IP-AUT	Merck-Clevenot				
10284	LEVY	Emile	01/01/1998	VB	Président du Collège des économistes de la santé (Association loi 1901)				
10284	LEVY	Emile	01/01/1998	VB	directeur DESS santé université Paris Dauphine				
10285	LEVY	Jean	01/01/1998	VB	ADIR (Groupe Servier)	Contrat de recherche avec l'Université.			
63609	LEVY-WEIL	Florence	22/05/2006	EC-INV	RESEAU RHUMATO	Physiophatogénie de la PR : rôle du TNF et action des AINS sur le TNF	Investigateur principal	01/2004	
63609	LEVY-WEIL	Florence	22/05/2006	EC-CO	ABBOTT	Humira/Etude observationnelle	collaborateur à l'étude	01/2005	12/2006
63609	LEVY-WEIL	Florence	22/05/2006	RE-DE	AFSSAPS	AMG 162	rémunération personnelle	01/2005	12/2005
63609	LEVY-WEIL	Florence	22/05/2006	IP-AC	MSD	Expert en Ostéoporose	rémunération personnelle	01/2003	
63609	LEVY-WEIL	Florence	22/05/2006	CF-INT	MSD, AVENTIS, P.ET.G, SERVIER, FABRE, WYETH	Sujets traités : Ostéoporose et Rhumatisme Psoriasique	rémunération institution	01/2003	12/2006
63609	LEVY-WEIL	Florence	22/05/2006	CF-AUD	LABORATOIRE ABBOTT	Symposium sur le psoriasis à Monaco		01/2006	
63609	LEVY-WEIL	Florence	26/08/2004	IP-EC		Via l'association du service			
63609	LEVY-WEIL	Florence	26/08/2004	IP-AC	Laboratoires pharmaceutiques (MSD etc)	conseil scientifique			
63609	LEVY-WEIL	Florence	26/08/2004	IP-CF	Laboratoires pharmaceutiques	EPU auprès des spécialistes et des généralistes sur l'ostéoporose principalement			
63609	LEVY-WEIL	Florence	26/08/2004	VB	Laboratoires pharmaceutiques	ADRAR (Association pour le Développement de la Réadaptation et de la Rhumatologie)			
10287	LIARD	François	01/02/2010	IP-AC	RECKITT BENCKISER	elaboration d'un protocle d'étude clinique	Rémunération personnelle	11/2009	01/2010
10287	LIARD	François	01/02/2010	CF-INT	BOERINGHER	forum multidisciplinaire sur la BPCO	Rémunération personnelle	03/2010	03/2010
10287	LIARD	François	01/02/2010	CF-INT	NOVARTIS	Symposium HTA Journées européennes de cardiologie	Rémunération personnelle	01/2010	01/2010
10287	LIARD	François	31/03/2009	CF-INT	ZAMBON	symposium ORL	Rémunération personnelle	06/2009	06/2009
10287	LIARD	François	31/03/2009	EC-CO	GSK	Etude ARIANE. Etude pharmaco économique ARIXTRA	membre du conseil scientifique	12/2007	04/2009
10287	LIARD	François	12/03/2009	CF-INT	JANSSEN	FMC	Rémunération personnelle	03/2009	03/2009
10287	LIARD	François	12/03/2009	CF-INT	MENARINI	Congrès européen Athenes	Rémunération personnelle	05/2009	05/2009
10287	LIARD	François	12/03/2009	IP-AC	ZAMBON	conseils sur la prise en charges des infections urinaires. □□Monuril	Rémunération personnelle	12/2008	07/2009
10287	LIARD	François	12/03/2009	EC-CO	SANOFI PASTEUR MSD	Etude INSERM ZONA	membre du conseil scientifique	01/2009	
10287	LIARD	François	12/03/2009	EC-CO	LUNDBECK	Etude épidémiologique sur la dépression	membre du conseil scientifique	10/2008	
10287	LIARD	François	08/01/2008	CF-INT	TAKEDA	conférences sur la médecine générale	Rémunération personnelle	11/2007	03/2008
10287	LIARD	François	08/01/2008	IP-AC	SANOFI PASTEUR	ZONA rédaction collective livre	Rémunération personnelle	07/2007	01/2008
10287	LIARD	François	08/01/2008	IP-AC	FERRING	Minirin conseil scientifique	Rémunération personnelle	02/2007	01/2008
10287	LIARD	François	08/01/2008	EC-INV	SANOFI AVENTIS	Etude ISPA post commercialisation de Acomplia	membre du conseil scientifique	11/2007	12/2008
10287	LIARD	François	08/01/2008	EC-INV	GSK	etude épidémiologique conditions utilisation Arixtra	membre du conseil scientifique	09/2007	06/2009
10287	LIARD	François	08/01/2008	EC-INV	ABBOTT	conseil scientifique sondage monozeclar	conseil scientifique	09/2007	08/2008
10287	LIARD	François	08/01/2008	EC-INV	MAYOLY SPINDLER	étude Eurobiol	membre conseil scientifique	05/2006	06/2008
10287	LIARD	François	07/01/2008	LD-AR	SANOFI AVENTIS	conseil scientifique Acomplia	Rémunération personnelle	01/2007	12/2008
10287	LIARD	François	07/01/2008	LD-AR	SANOFI AVENTIS	conseil communication douleur Doliprane	Rémunération personnelle	11/2006	01/2009
10287	LIARD	François	07/01/2008	LD-AR	CHIESI	conseil développement IPERTEN	Rémunération personnelle	05/2005	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10287	LIARD	François	06/06/2006	IP-AUT	LUNDBECK	conception pédagogique de groupes de pairs sur la dépression en médecine générale		02/2006	
10287	LIARD	François	06/06/2006	CF-INT	JANSSEN CILAG	pariet	Rémunération personnelle	05/2006	05/2006
10287	LIARD	François	06/06/2006	IP-AC	LABORATOIRES MAYOLY SPINDLER	conseil epidemiologique dans l'insuffisance pancréatique exocrine en médecine générale	Rémunération personnelle	03/2006	
10287	LIARD	François	06/06/2006	EC-INV	MENARINI	Etude de la pratique médicale en médecine générale lors de l'initiation d'un traitement par bétabloquant chez	investigateur principal	02/2006	
10287	LIARD	François	06/06/2006	CF-INT	TAKEDA	Ogast	Rémunération personnelle	05/2006	05/2006
10287	LIARD	François	06/06/2006	IP-AC	FERRING	ETUDE EPIDEMIOLOGIQUE DESMOPRESSINE	Rémunération personnelle	03/2006	
10287	LIARD	François	06/06/2006	IP-AC	CHIESI	CONSEIL MANIDIPINE	Rémunération personnelle	06/2005	
10287	LIARD	François	06/06/2006	IP-AC	SANOFI AVENTIS	CONSEIL RIMONABANT	Rémunération personnelle	06/2006	
10287	LIARD	François	06/06/2006	IP-AC	SANOFI AVENTIS	CONSEIL DOULEUR	Rémunération personnelle	02/2003	
10287	LIARD	François	06/06/2006	EC-INV	SANOFI AVENTIS	An open-label, randomized, multicenter, clinical study to compare the effects of telithromycin, azithromycin a	investigateur principal	05/2005	11/2007
10287	LIARD	François	06/06/2006	CF-INT	JANSSEN CILAG	Symposium - Lisbonne	Aucune rémunération	05/2006	05/2006
10287	LIARD	François	06/06/2006	CF-INT	TAKEDA	CANNES	Aucune rémunération	05/2006	05/2006
10287	LIARD	François	09/09/2005	LD	VIVACTIS FORMATION	conseiller pédagogique temps-partiel		06/2005	12/2005
10287	LIARD	François	09/09/2005	LD	MG RECHERCHES	Conseiller pédagogique temps-partiel		10/1998	03/2006
10287	LIARD	François	09/09/2005	IP-EC	SANOFI AVENTIS	Investigateur principal études		01/2004	
10287	LIARD	François	09/09/2005	IP-EC	ASTRA ZENECA	Etude endurance (imodium) perspective Ketek		01/2005	07/2005
10287	LIARD	François	09/09/2005	IP-AC	SANOFI AVENTIS	conseil rimonabant et antalgie	Aucune rémunération	06/2005	
10287	LIARD	François	09/09/2005	IP-EC	CHIESI	Conseil essais cliniques Manidipine		11/2004	
10287	LIARD	François	09/09/2005	IP-CF	TAKEDA	Colloques Athènes 01/10/2005		10/2005	10/2005
10287	LIARD	François	09/09/2005	IP-CF	LUNDBECK	dans le cadre de VIVACTIS - conception pédagogique tables rondes dépressions en MG		01/2005	
10287	LIARD	François	03/06/2004	LD	MG RECHERCHES	Contrat travail temps partiel pour conception prospective des systèmes informatisés dans recueil de données des réseaux des médecins participant aux essais thérapeutiques			
10287	LIARD	François	03/06/2004	IP-EC	AVENTIS	Investigateur principal étude perspective			
10287	LIARD	François	03/06/2004	IP-EC	ASTRA ZENECA	Investigateur principal étude Vega			
10287	LIARD	François	03/06/2004	IP-RE	AVENTIS THERAPLIX	Expertise Dolirhume			
10287	LIARD	François	03/06/2004	IP-AC	AVENTIS THERAPLIX	Conseil groupe douleur			
10287	LIARD	François	03/06/2004	IP-AC	AVENTIS	Groupe scientifique sinusite enfant			
10287	LIARD	François	03/06/2004	IP-AC	PHARMAFARM	Conseil scientifique étude AMA			
10287	LIARD	François	03/06/2004	IP-CF	TAKEDA	FMC Actos Expert formation			
10287	LIARD	François	03/06/2004	IP-CF	PFIZER	Expert formation médicale			
10287	LIARD	François	03/06/2004	IF	SFAD (formation médicale et aide à la décision)	Actionnaire 20%			
10287	LIARD	François	17/04/2003	LD	MG Recherches	Consultant permanent			
10287	LIARD	François	17/04/2003	IP-EC	LUNDBECK	Conseil scientifique étude épidémiologique			
10287	LIARD	François	17/04/2003	IP-AC	CHIESI	Comité scientifique HTA			
10287	LIARD	François	17/04/2003	IP-AC	ZAMBON	Comité scientifique MAC			
10287	LIARD	François	17/04/2003	IP-CF	TAKEDA	FMC			
10287	LIARD	François	30/05/2000	LD	MG Recherches (réseau de médecins généralistes réalisant des essais thérapeutiques et des études épidémiologiques)	Conseiller scientifique - salarié - un jour par semaine			
10287	LIARD	François	30/05/2000	LD	BAYER	Conseiller en matière de formation médicale continue - rémunération forfaitaire annuelle (fin en octobre 2000)			
10287	LIARD	François	30/05/2000	IP-EC	BAYER	Comité de pilotage : étude RECIPE			
10287	LIARD	François	30/05/2000	IP-EC	ROCHE	Comité scientifique : étude pharmaco-épidémiologique			
10287	LIARD	François	30/05/2000	IP-RE	ABBOT ; BIOGALENIQUE ; BOEHRINGER ; BOUCHARA ; BYK ; GENEVRIER ; LEURQUIN ; PARKE DAVIS ; PHARMA 2000 ; UPSA ; WHITEHALL ; ZAMBON	Laboratoires réunis pour expertise sur la classe des mucorégulateurs : une action en mars 2000			
10287	LIARD	François	30/05/2000	IP-AC	THERAPLIX	Comité scientifique sur l'évaluation de la douleur (3 réunions)			
10287	LIARD	François	19/03/2000	LD	BAYER	Contrat de travail comme conseiller en matière d'évaluation et de Formation médicale continue			
10287	LIARD	François	19/03/2000	IP-EC	MGRecherche (Association de recherche en médecine générale effectuant des essais thérapeutiques)	Lien permanent			
10287	LIARD	François	19/03/2000	IP-EC	BAYER	Membre du comité de pilotage de l'étude RECIPE			
10287	LIARD	François	19/03/2000	IP-RE	ABBOTT	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	BIOGALENIQUE	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	BOEHRINGER	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	Dr E. BOUCHARA	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	BYK	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	GENEVRIER	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	LEURQUIN	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	PARKE DAVIS	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	PHARMA 2000	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-AC	UPSA	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-AC	WHITEHALL	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-RE	ZAMBON	Expertise sur les mucorégulateurs			
10287	LIARD	François	19/03/2000	IP-AC	BAYER				
10287	LIARD	François	19/03/2000	IP-EC	ROCHE	Membre du conseil scientifique d'une étude de pharmacoépidémiologie concernant le Xénical			
10287	LIARD	François	01/01/1999	LD	BAYER	Contrat de travail comme conseiller en matière d'évaluation et de formation médicale continue			
10287	LIARD	François	01/01/1999	LD	MGRecherches (association de recherches en médecine générale effectuant des essais thérapeutiques)	Lien permanent			
10287	LIARD	François	01/01/1999	IP-EC	LIPHA				
10287	LIARD	François	01/01/1999	IP-EC	SANOFI				
10287	LIARD	François	01/01/1999	IP-EC	GLAXO WELLCOME				
10287	LIARD	François	01/01/1999	IP-EC	SMITHKLINE BEECHAM				
10287	LIARD	François	01/01/1999	IP-RE	LIPHA				
10287	LIARD	François	01/01/1999	IP-AC	EISAI				
10287	LIARD	François	01/01/1999	IP-CF	MSD-CHIBRET				
10287	LIARD	François	01/01/1999	IP-CF	LIPHA				
10287	LIARD	François	27/02/1998	LD	BAYER	Contrat de travail comme conseiller en matière d'évaluation et de formation médicale continue			
10287	LIARD	François	27/02/1998	LD	MGRecherches (association de recherche en médecine générale effectuant des essais thérapeutique)	Lien permanent			
10287	LIARD	François	27/02/1998	IP-EC	LIPHA ; SANOFI ; GLAXO-WELLCOME ; SMITHKLINE BEECHAM	Tous avec MGRecherches			
10287	LIARD	François	27/02/1998	IP-RE	LIPHA				
10287	LIARD	François	27/02/1998	IP-AC	EISAI				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10287	LIARD	François	27/02/1998	IP-CF	MSD-CHIBRET et LIPHA				
10287	LIARD	François	01/01/1998	LD	MG Recherches				
10287	LIARD	François	01/01/1998	IP-AUT	Servier				
10287	LIARD	François	01/01/1998	IP-AUT	Lipha				
10287	LIARD	François	01/01/1998	IP-AUT	Glaxo				
10287	LIARD	François	01/01/1998	IP-AUT	Lilly				
10287	LIARD	François	01/01/1998	IP-AUT	SKB				
10287	LIARD	François	01/01/1998	IP-AUT	Bayer Pharma				
10289	LIEVRE	Michel	24/03/2010	CF-INT	SERVIER	Cours intensif NFA/SERVIER "Evaluation du risque d'athérosclérose"□□Montigny le Bretonneux	Rémunération institution	03/2010	03/2010
10289	LIEVRE	Michel	24/03/2010	EC-CO	TAKEDA ET ASTRAZENECA	Etude d'observation de l'utilisation du candesartan dans l'insuffisance cardiaque (à la demande de l'HAS)	Membre du comité scientifique□ Rémunération institution	11/2005	
10289	LIEVRE	Michel	31/03/2009	IP-AUT	MERCK (MSD)	Formation à la méthodologie des essais cliniques	Aucune rémunération	01/2009	01/2009
10289	LIEVRE	Michel	17/06/2008	EC-CO	PROCTER & GAMBLE	Etude de validation du logiciel INR+ de prédiction de la posologie de Previscan	Membre du comité scientifique	06/2008	
10289	LIEVRE	Michel	20/09/2007	CF-INT	EXELGYN	Valence (Espagne)□□3re international symposium Misoprostol and mifepristone in obstetrics and gynecolog	Aucune rémunération	10/2007	10/2007
10289	LIEVRE	Michel	20/09/2007	EC-CO	NOVARTIS	Etude pharmacoépidémiologique sur Lucentis® à la demande des autorités de santé	Coordination□ Membre du comité scientifique	07/2007	
10289	LIEVRE	Michel	23/05/2007	CF-INT	EXELGYN	Congrès FIAPAC, Rome - Méta-analyse mifepristone	Aucune rémunération	10/2006	10/2006
10289	LIEVRE	Michel	18/09/2006	IP-AC	EXELGYN	Méta-analyse, mifepristone	Aucune rémunération	02/2006	
10289	LIEVRE	Michel	10/07/2006	CF-INT	EXELGYN	FIAPAC, Rome 13-14 octobre 2006	Aucune rémunération	10/2006	10/2006
10289	LIEVRE	Michel	10/07/2006	RE-DE	EXELGYN	mifepristone:(rapport bénéfice / risque de 200 mg vs 600 mg en association à un analogue de PG)	Rémunération institution	02/2006	06/2006
10289	LIEVRE	Michel	05/04/2006	CF-INT	ICTA	Journée de formation, Dijon	Rémunération institution	09/2005	09/2005
10289	LIEVRE	Michel	05/04/2006	EC-CO	MERCK LIPHA SANTE	Niaspan" Etude à la demande de l'HAS	Comité scientifique	01/2006	12/2007
10289	LIEVRE	Michel	05/04/2006	RE-DE	ANDRE REY CONSULTANTS	Mifepristone	Rémunération institution	02/2006	06/2006
10289	LIEVRE	Michel	24/03/2005	CF-INT	SERVIER	En 2001 - "Prévention des complications cérébrovasculaires du diabète de type2"	Aucune rémunération	01/2001	01/2001
10289	LIEVRE	Michel	24/03/2005	CF-AUD	NOVARTIS	2003 - Athérosclérose		10/2003	10/2003
10289	LIEVRE	Michel	24/03/2005	VB	SANOFI AVENTIS	Contrats liés à la réalisation d'études	EZUS LYON-1	05/2004	03/2007
10289	LIEVRE	Michel	24/03/2005	VB	TAKEDA	Contrats liés à la réalisation d'études	EZUS LYON-1	01/2003	03/2006
10289	LIEVRE	Michel	24/03/2005	CF-INT	WYETH	Contrats liés à la réalisation d'études	Rémunération versée à une institution	05/2004	05/2004
10289	LIEVRE	Michel	24/03/2005	VB	NOVO NORODISK	Contrats liés à la réalisation d'études	EZUS LYON-1	01/2002	08/2003
10289	LIEVRE	Michel	24/03/2005	VB	3M SANTE	Contrats liés à la réalisation d'études	EZUS LYON-1	09/2004	07/2005
10289	LIEVRE	Michel	24/03/2005	PAR	SANOFI PASTEUR		Conjoint	12/1999	05/2006
10289	LIEVRE	Michel	24/03/2005	EC-CO	JOHNSON & JOHNSON	Stent actif - Comité scientifique	Aucune rémunération	02/2005	
10289	LIEVRE	Michel	24/03/2005	EC-CO	BOSTON SCIENTIFIC	Stent actif - Comité scientifique	Aucune rémunération	02/2005	
10289	LIEVRE	Michel	17/03/2005	IP-AC		Président du comité de surveillance (DSMB) de l'étude SECRET (2003) - Responsable de l'étude SECRET (	Aucune rémunération		
10289	LIEVRE	Michel	24/02/2005	IF	SANOFI AVENTIS	< 5000 €	<5000 € ou <5% du capital	01/1990	04/2005
10289	LIEVRE	Michel	01/03/2004	IF	AVENTIS	89 actions			
10289	LIEVRE	Michel	01/03/2004	VB	AVENTIS	EZUS Lyon I			
10289	LIEVRE	Michel	01/03/2004	VB	NOVARTIS	EZUS Lyon I			
10289	LIEVRE	Michel	01/03/2004	VB	WYETH	EZUS Lyon I			
10289	LIEVRE	Michel	01/03/2004	VB	TAKEDA	EZUS Lyon I			
10289	LIEVRE	Michel	01/03/2004	VB	NOVO-NORDISK	EZUS Lyon I			
10289	LIEVRE	Michel	01/03/2004	(Autre)	AVENTIS-PASTEUR	Conjoint			
10289	LIEVRE	Michel	01/03/2004	(Autre)	NOVO-NORDISK, NOVARTIS	Subvention de participation à Congrès			
10289	LIEVRE	Michel	02/12/2003	IF	AVENTIS	89 actions			
10289	LIEVRE	Michel	02/12/2003	VB	AVENTIS, NOVO-NORDISK, NOVARTIS, WYETH	Ezus - Lyon 1			
10289	LIEVRE	Michel	02/12/2003	PAR	AVENTIS	Conjoint			
10289	LIEVRE	Michel	02/12/2003	(Autre)	NOVARTIS	Prise en charge pour 2 congrès (1999 et 2003)			
10289	LIEVRE	Michel	28/02/2003	VB	AVENTIS	EZUS Lyon 1			
10289	LIEVRE	Michel	28/02/2003	VB	NOVO NORDISK	EZUS Lyon 1			
10289	LIEVRE	Michel	28/02/2003	VB	WYETH	EZUS Lyon 1			
10289	LIEVRE	Michel	28/02/2003	PAR	AVENTIS	Conjoint			
10289	LIEVRE	Michel	04/12/2002	VB	LABORATOIRE	EZUS (filiale Universite Lyon 1)			
10289	LIEVRE	Michel	04/12/2002	VB	NOVARTIS	EZUS			
10289	LIEVRE	Michel	04/12/2002	VB	MERCK-LIPHA	EZUS			
10289	LIEVRE	Michel	04/12/2002	PAR	AVENTIS PASTEUR	Conjoint			
10289	LIEVRE	Michel	07/12/2000	VB	AVENTIS	EZUS (filiale Université Lyon 1)			
10289	LIEVRE	Michel	07/12/2000	VB	NOVARTIS	EZUS			
10289	LIEVRE	Michel	07/12/2000	VB	MERCK LIPHA	EZUS			
10289	LIEVRE	Michel	07/12/2000	PAR	AVENTIS PASTEUR	Conjoint			
10289	LIEVRE	Michel	28/09/2000	VB	AVENTIS	EZUS (Filiale de l'Université Claude Bernard)			
10289	LIEVRE	Michel	28/09/2000	VB	NOVARTIS	EZUS			
10289	LIEVRE	Michel	28/09/2000	VB	MERCK LIPHA	EZUS			
10289	LIEVRE	Michel	28/09/2000	PAR	AVENTIS-PASTEUR	Conjoint			
10289	LIEVRE	Michel	02/05/2000	VB	AVENTIS	EZUS (filiale de l'Université Claude Bernard, Lyon)			
10289	LIEVRE	Michel	02/05/2000	VB	NOVARTIS	EZUS			
10289	LIEVRE	Michel	02/05/2000	VB	MERCK-LIPHA	EZUS			
10289	LIEVRE	Michel	02/05/2000	PAR	AVENTIS	Conjoint			
10289	LIEVRE	Michel	26/08/1999	IP-AC	ICTA (Dijon)	Méthodologie des essais cliniques			
10289	LIEVRE	Michel	26/08/1999	IP-CF	HOECHST MARION ROUSSEL	Diurétiques dans l'HTA chez les diabétiques de type 2			
10289	LIEVRE	Michel	26/08/1999	VB	HOECHST MARION ROUSSEL	APRET- EZUS			
10289	LIEVRE	Michel	26/08/1999	VB	NOVARTIS	APRET- EZUS			
10289	LIEVRE	Michel	26/08/1999	VB	MERCK-CLEVENOT	APRET EZUS			
10289	LIEVRE	Michel	26/08/1999	VB	UPSA	APRET-EZUS			
10289	LIEVRE	Michel	26/08/1999	PAR	RHONE-POULENC RORER	Conjoint			
10289	LIEVRE	Michel	17/06/1999	IP-AC	Société ICTA (Dijon)	Conseil méthodologie et statistique			
10289	LIEVRE	Michel	17/06/1999	VB	HOECHST	APRET EZUS			
10289	LIEVRE	Michel	17/06/1999	VB	NOVARTIS	APRET EZUS			
10289	LIEVRE	Michel	17/06/1999	VB	MERCK CLEVENOT	APRET EZUS			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10289	LIEVRE	Michel	17/06/1999	(Autre)	RHONE POULENC RORER	Conjoint			
10289	LIEVRE	Michel	01/01/1999	IP-AUT	BAYER	(1997) : Prise en charge de frais de congrès à l'étranger			
10289	LIEVRE	Michel	01/01/1999	VB	HOECHST HOUDE	Association APRET (essai thérapeutique)			
10289	LIEVRE	Michel	01/01/1999	VB	MERCK LIPHA	Essai thérapeutique, conseil méthodologique : Association APRET			
10289	LIEVRE	Michel	01/01/1999	VB	UPSA	Rapport d'expert : Association APRET			
10289	LIEVRE	Michel	01/01/1999	PAR	RHONE POULENC RORER	Conjoint salarié			
10289	LIEVRE	Michel	01/01/1998	IP-AUT	Hoechst				
10289	LIEVRE	Michel	01/01/1998	IP-AUT	Servier				
10289	LIEVRE	Michel	01/01/1998	VB	Hoechst		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	VB	Houdé		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	VB	Upsa		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	VB	Bayer		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	VB	Merck-Clévenot		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	VB	Novo-Nordisk		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	VB	Servier		Essais thérapeutiques, rapports d'expertise. Bénéficiaire : Association pour la promotion de la recherche et de l'évaluation en thérapeutique		
10289	LIEVRE	Michel	01/01/1998	PAR	Conjoint salarié de RPR				
61027	LOK	Catherine	30/08/2000	IP-EC	INNOTHERA	Essai clinique			
61027	LOK	Catherine	30/08/2000	IP-AC	SERVIER	Conseiller scientifique (secteur angiologie phlébologie)			
61027	LOK	Catherine	30/08/2000	IP-AC	ASTRA ZENECA	Conseiller scientifique (secteur anesthésie)			
61027	LOK	Catherine	30/08/2000	IP-CF	ASTRA ZENECA	Formation (secteur anesthésie)			
60126	LOKIEC	François	09/03/2010	VB	LIGUE CONTRE LE CANCER 92	Achat de matériel	Institut Curie - Hopital rené Huguenin	09/2009	09/2011
60126	LOKIEC	François	09/03/2010	CF-INT	ASTRA ZENECA	AACR Washington	Aucune rémunération	04/2010	04/2010
60126	LOKIEC	François	09/03/2010	CF-INT	ROCHE	Biennale de Monaco	Aucune rémunération	01/2010	01/2010
60126	LOKIEC	François	09/03/2010	CF-INT	GSK	SABCS	Aucune rémunération	12/2009	12/2009
60126	LOKIEC	François	09/03/2010	EC-CO	ALLOS	Etude pharmacocinétique, pralatrexate	expérimentateur	01/2008	
60126	LOKIEC	François	09/03/2010	EC-CO	AB SCIENCES	Etude pharmacocinétique, masitinib	expérimentateur	02/2010	
60126	LOKIEC	François	09/03/2010	LD-AR	SERVIER	Consultant	Rémunération personnelle	10/1993	
60126	LOKIEC	François	09/03/2010	EC-CO	SERVIER	Etude pharmacocinétique		03/2010	
60126	LOKIEC	François	24/06/2008	CF-AUD	ABBOTT	Chicago Congès de l'ASCO		05/2008	06/2008
60126	LOKIEC	François	24/06/2008	CF-AUD	ASTRA ZENECA	San Diego/Congrès de l'AACR		04/2008	04/2008
60126	LOKIEC	François	24/06/2008	CF-INT	ASTRA ZENECA	Paris Post AACR/Molécules de tout à l'heure	Aucune rémunération	05/2008	05/2008
60126	LOKIEC	François	24/06/2008	IP-AC	BIONEST	Evaluation de portefeuille	Rémunération personnelle	04/2009	04/2009
60126	LOKIEC	François	24/06/2008	LD-ODE	SERVIER	Expert	rémunération personnelle	01/1992	
60126	LOKIEC	François	24/06/2008	LD-ODE	GSK	Board experts nationaux	rémunération personnelle	01/2003	
60126	LOKIEC	François	24/06/2008	LD-ODE	SANOFI AVENTIS	Board international	rémunération personnelle	01/2003	
60126	LOKIEC	François	24/06/2008	CF-INT	AMGEN	Sorrente /Echanges Européens Soins de Support en Oncologie/Cardiotoxicité des fluoropyrimidines	Rémunération personnelle	05/2009	05/2009
60126	LOKIEC	François	24/06/2008	EC-CO	ALLOS	Etude préclinique/Pralatrexate	collaborateur	12/2007	
60126	LOKIEC	François	24/06/2008	EC-CO	ACCESS PHARMACEUTICAL	Etude préclinique/Prolindac	collaborateur	12/2007	
60126	LOKIEC	François	17/03/2008	LD-AR	SERVIER	Consultant	Rémunération personnelle	01/1999	
60126	LOKIEC	François	17/03/2008	EC-INV	BIOALLIANCE	IRN - Transdrug	Expérimentateur principal	01/2008	
60126	LOKIEC	François	17/03/2008	EC-INV	BIOALLIANCE	Loramyc	Expérimentateur principal	01/2009	
60126	LOKIEC	François	17/03/2008	EC-INV	ALLOS	Pralatrexate	Expérimentateur principal	01/2006	
60126	LOKIEC	François	17/03/2008	EC-CO	ACCESS	Etude PK	Collaborateur	01/2006	
60126	LOKIEC	François	17/03/2008	RE-DE	WYETH	Exertise dossier	Rémunération personnelle	01/2008	12/2008
60126	LOKIEC	François	17/03/2008	RE-DE	ENJON	Expertise dossier EZN-260		01/2009	12/2009
60126	LOKIEC	François	17/03/2008	CF-INT	ASTRA ZENECA	Congrès de l'AACR - Pas de produit	Aucune rémunération	01/2008	12/2008

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60126	LOKIEC	François	17/03/2008	CF-INT	ABBOTT	Congrès de l'ASCO - Pas de produit	Aucune rémunération		
60126	LOKIEC	François	17/03/2008	LD-AR	SERVIER	consultant	rémunération personnelle	01/1999	
60126	LOKIEC	François	17/03/2008	EC-INV	BIOALLIANCE	IRN-TRANSDURG	Expérimentateur principal	01/2008	
60126	LOKIEC	François	17/03/2008	EC-INV	BIOALLIANCE	LORAMYC	Expérimentateur principal	01/2009	
60126	LOKIEC	François	17/03/2008	EC-INV	ALLOS	PRALATREXATE	collaborateur	01/2006	
60126	LOKIEC	François	17/03/2008	EC-CO	ACCESS	Etude PK	collaborateur	01/2008	12/2008
60126	LOKIEC	François	17/03/2008	IP-RE	WYETT	Expertise dossier	rémunération personnelle	01/2008	12/2008
60126	LOKIEC	François	17/03/2008	EC-CO	ENJON	Expertise dossier EZN-260		01/2009	12/2009
60126	LOKIEC	François	17/03/2008	CF-INT	ASTRA ZENECA	congrès de l'AACR. Pas de produit	aucune rémunération	01/2008	
60126	LOKIEC	François	17/03/2008	CF-INT	ABBOTT	congrès de l'ASCO . Pas de produit	aucune rémunération		
60126	LOKIEC	François	03/11/2006	LD-AR	SANOFI AVENTIS	Board international	rémunération personnelle	01/2003	
60126	LOKIEC	François	03/11/2006	LD-AR	GSK	Board experts nationaux	rémunération personnelle	01/2003	
60126	LOKIEC	François	03/11/2006	LD-AR	SERVIER	expert	rémunération personnelle	01/1992	
60126	LOKIEC	François	03/11/2006	EC-INV	ETHYPHARM	Etude de biodisponibilité - Cisplatine	expérimentateur principal	01/2001	12/2006
60126	LOKIEC	François	03/11/2006	EC-INV	MGI PHARMA	Etude pharmacocinétique et de métabolisme - Irofulven	expérimentateur principal	01/1999	12/2005
60126	LOKIEC	François	03/11/2006	EC-INV	ACCESS PHARMACEUTICALS	Etude pharmacocinétique - AP5346	expérimentateur principal	01/2006	
60126	LOKIEC	François	03/11/2006	EC-INV	GENTA INCORPORATED	étude pharmacocinétique - Genasense + Dacarbazine	expérimentateur principal	01/2006	12/2007
60126	LOKIEC	François	03/11/2006	EC-INV	GSK	Etude pharmacocinétique -Lapalinib + Tamoxifène	expérimentateur principal	01/2006	
60126	LOKIEC	François	03/11/2006	CF-INT	CTI	Malte - symposium pharmaceutique - chimiothérapie anticancéreuse : influence de l'insuffisance hépatique e	rémunération personnelle		
60126	LOKIEC	François	03/11/2006	CF-INT	BAXTER	Lugano - symposium Satellite - Ifosfamide : pharmacokinetic properties for CNS metastasis prevention - Ifos	rémunération personnelle		
60126	LOKIEC	François	03/11/2006	CF-INT	LILLY	Lisbonne- symposium de lancement - Alimta : Nouvel antimétabolite multicible (2005)	rémunération personnelle		
60126	LOKIEC	François	03/11/2006	CF-INT	BMS	Deauville - symposium régional Grand Ouest - Fluoropyrimidines orales : approches pharmacologiques (200	rémunération personnelle		
60126	LOKIEC	François	03/11/2006	CF-AUD	SERVIER	Washington - AACR (2006)			
60126	LOKIEC	François	03/11/2006	CF-AUD	SERVIER	Atlanta - ASCO (2006)			
60126	LOKIEC	François	03/11/2006	CF-AUD	SERVIER	Anaheim - AACR (2005)			
60126	LOKIEC	François	03/11/2006	CF-AUD	SERVIER	Orlando - ASCO (2005)			
60126	LOKIEC	François	03/11/2006	CF-AUD	BMS	San Antonio - Breast cancer conference (2005)			
60126	LOKIEC	François	30/05/2006	IF	SANOFI	Bourse	<5000 € ou <5% du capital	02/2006	
60126	LOKIEC	François	30/05/2006	LD-AR	SERVIER	Expert	rémunération personnelle	01/1998	
60126	LOKIEC	François	30/05/2006	EC-CO	SANOFI	étude PK / Amétycine	collaborateur	09/2003	07/2004
60126	LOKIEC	François	30/05/2006	EC-CO	ASTRA ZENECA	étude PK / Iressa	collaborateur	09/2004	10/2005
60126	LOKIEC	François	30/05/2006	EC-CO	MGI PHARMA	étude PK : Irofulven	collaborateur	09/2002	06/2005
60126	LOKIEC	François	30/05/2006	EC-CO	ETHY PHARM	étude PK / Cisplatine oral	collaborateur	11/2000	08/2005
60126	LOKIEC	François	30/05/2006	EC-CO	GSK	étude PK / Valacyclovir	collaborateur	04/2002	02/2006
60126	LOKIEC	François	30/05/2006	EC-CO	MAT	étude PK / Ferritarg	collaborateur	06/2006	
60126	LOKIEC	François	30/05/2006	EC-CO	ALGETA	étude PK / Alpharadin	collaborateur	03/2006	12/2006
60126	LOKIEC	François	30/05/2006	RE-DE	LILLY	Gemcitabine - cancer du sein	rémunération personnelle	04/2003	04/2003
60126	LOKIEC	François	30/05/2006	RE-DE	LILLY	Gemcitabine - cancer de l'ovaire	rémunération personnelle	09/2004	09/2004
60126	LOKIEC	François	30/05/2006	IP-AC	IPSEN BEAUFOUR	conseil / Diflomotecan	rémunération personnelle	11/2004	11/2004
60126	LOKIEC	François	30/05/2006	IP-AC	LFB	conseil / Vialebex	rémunération personnelle	08/2004	09/2004
60126	LOKIEC	François	30/05/2006	IP-AC	BMS	conseil / UFT	rémunération personnelle	06/2004	06/2004
60126	LOKIEC	François	30/05/2006	CF-INT	BMS	Deauville / Fluoropyrimidines orales	rémunération personnelle	09/2004	09/2004
60126	LOKIEC	François	30/05/2006	CF-INT	BMS	Paris / cancer du sein métastatique	rémunération pesonnelle	05/2004	05/2004
60126	LOKIEC	François	30/05/2006	CF-AUD	SERVIER	AACR - Washington USA		03/2006	04/2006
60126	LOKIEC	François	30/05/2006	CF-AUD	BMS	Breast Cancer Symposium - San Antonio USA		12/2005	12/2005
60126	LOKIEC	François	28/08/2003	LD	ADIR	Durable	rémunération personnelle	10/1997	
60126	LOKIEC	François	28/08/2003	RE-DE	ELI LILLY	Cancer du sein		09/2003	09/2003
60126	LOKIEC	François	28/08/2003	IP-CF	PHARMA MAR	Conférence			
60126	LOKIEC	François	28/08/2003	IP-CF	BRISTOL MYERS SQUIBB	Conférence			
60126	LOKIEC	François	28/08/2003	IP-CF	PIERRE FABRE Oncologie	Conférence			
60126	LOKIEC	François	28/08/2003	VB	MGI PHARMA	Centre René Hugenin			
60126	LOKIEC	François	28/08/2003	VB	ETHYPHARM	Centre René Hugenin			
60126	LOKIEC	François	28/08/2003	VB	SANOFI SYNTHELABO	Centre René Hugenin			
60126	LOKIEC	François	28/08/2003	VB	GLAXO SMITHKLINE	Centre René Hugenin			
60126	LOKIEC	François	28/08/2003	LD	CAC	Durable	rémunération personnelle	01/2002	
60126	LOKIEC	François	28/09/2000	IP-EC	MGI PHARMA	Phase I Pharmacocinétique			
60126	LOKIEC	François	28/09/2000	IP-EC	GLAXO WELLCOME	Etudes pharmacocinétiques			
60126	LOKIEC	François	28/09/2000	IP-EC	ROCHE	Etudes pharmacocinétiques			
60126	LOKIEC	François	28/09/2000	IP-EC	SANOFI SYNTHELABO	Etudes de stabilité			
60126	LOKIEC	François	28/09/2000	IP-RE	SANOFI SYNTHELABO	Stabilité des anticancéreux			
60126	LOKIEC	François	28/09/2000	IP-RE	GLAXO WELLCOME	Expertise analytique			
60126	LOKIEC	François	28/09/2000	IP-AC	ADIR	Conseil en développement			
62658	LOPES	Patrice	09/05/2005	IP-EC	NOVO NORDISK	Etude ALD 1537 - essai clinique THM (Traitement Hormonal de la Ménopause)			
62658	LOPES	Patrice	09/05/2005	IP-AC	SANOFI AVENTIS	3 réunions à Paris		04/2005	04/2005
62658	LOPES	Patrice	09/05/2005	IP-CF	NOVARTIS	1 conférence à Paris le 30/04/2005 sur THM et cancer du sein			
62658	LOPES	Patrice	08/08/2003	LD	SERVIER	Consultant - Aerodiol European Board (réunions rémunérées - 1 à 2 /an)			
62658	LOPES	Patrice	08/08/2003	LD	SCHERING GYNECOLOGY CONTACT	Réponse aux questions, éditorial			
62658	LOPES	Patrice	08/08/2003	IP-EC	THERAMEX	Essai Naenies			
62658	LOPES	Patrice	08/08/2003	IP-RE	THERAMEX	Expertise Naenies			
62658	LOPES	Patrice	08/08/2003	IP-RE	PROCTER GAMBLE	Expert			
62658	LOPES	Patrice	08/08/2003	IP-CF	SCHERING	Lancement Avadine			
62658	LOPES	Patrice	08/08/2003	IP-CF	SOLVAY PHARMA	Colloque endomètre			
62658	LOPES	Patrice	08/08/2003	IP-CF	CONCEPTUS	Système Essire			
62658	LOPES	Patrice	08/08/2003	IP-CF	WYETH	Lancement Successa			
62658	LOPES	Patrice	08/08/2003	IP-CF	THERAMEX	Lancement Naenies			
62658	LOPES	Patrice	08/08/2003	VB	SERVIER	ANEPRH			
62658	LOPES	Patrice	08/08/2003	VB	PROCTER GAMBLE	Etude clinique phase II - ANEPRH			
62658	LOPES	Patrice	08/08/2003	VB	SERVIER	Etude 21405.005 - ANEPRH			
62658	LOPES	Patrice	11/10/2002	IP-EC		Etude Aerodiol* (en 2000) - Coordination de l'essai européen			
62658	LOPES	Patrice	11/10/2002	IP-EC		Etude "Essare" - Coordinateur essai français			
62658	LOPES	Patrice	11/10/2002	IP-EC		Etude "Naémis" - Coordinateur essai français			
62658	LOPES	Patrice	11/10/2002	IP-EC		Etude Parck testust - Phase II, essai clinique			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62658	LOPES	Patrice	11/10/2002	IP-AC		Aerodiol Advisory Board : 2 réunions/an (1 jour en 2002 à Paris)			
62658	LOPES	Patrice	11/10/2002	IP-CF	THERAMIX	Conférence - Paris, Vienne			
62658	LOPES	Patrice	11/10/2002	IP-CF	SERVIER	Conférence Istanbul, Ankara, Paris			
62658	LOPES	Patrice	11/10/2002	IP-CF	OMAPTUS	Conférence Portugal			
60283	LUCAS	Christian	01/04/2010	CF-AUD	LABORATOIRES MSD	American headache society. Congrès à Los Angeles USA		06/2010	06/2010
60283	LUCAS	Christian	01/04/2010	CF-INT	LABORATOIRES PFIZER	Universités migraine	Rémunération personnelle	05/2010	05/2010
60283	LUCAS	Christian	01/04/2010	IP-AC	LABORATOIRES MSD	groupes d'experts migraine	Rémunération personnelle	01/2008	
60283	LUCAS	Christian	01/04/2010	IP-AC	LABORATOIRES ALLERGAN	groupes d'experts migraine	Rémunération personnelle	01/2009	
60283	LUCAS	Christian	01/04/2010	IP-AC	LABORATOIRES ALMIRALL	groupe d'experts migraine	Rémunération personnelle	01/2008	
60283	LUCAS	Christian	01/04/2010	EC-INV	LABORATOIRES MSD	études de phase 2 et 3 dans le traitement de la crise de migraine	Investigateur coordonnateur au CHRU de Lille	10/2008	02/2010
60283	LUCAS	Christian	01/10/2008	CF-AUD	MéNARINI	Migraine Trust Londres		09/2008	09/2008
60283	LUCAS	Christian	01/10/2008	CF-INT	GSK	10° universités de la migraine. Aix en Provence	Aucune rémunération	09/2008	09/2008
60283	LUCAS	Christian	01/10/2008	EC-CO	SANOFI	etude Borealis: idrabiotaparinux vs warfarine en prévention II de la FA		09/2008	04/2010
60283	LUCAS	Christian	01/10/2008	EC-INV	BOEHRINGER	étude phase 2 antagoniste des récepteurs du CGRP dans le traitement de la crise de migraine	Investigateur coordonnateur au CHRU de Lille	11/2008	12/2009
60283	LUCAS	Christian	01/10/2008	EC-INV	PHRC CLOSE	fermeture du FOP dans l'infarctus cérébral de cause inconnue	Investigateur coordonnateur au CHRU de Lille	04/2008	
60283	LUCAS	Christian	01/10/2008	LD-AR	MSD	groupe d'experts migraine	Rémunération personnelle	01/2008	
60283	LUCAS	Christian	15/12/2007	EC-INV	SERVIER	essai clinique térutroban en prévention secondaire des AVC	investigateur principal	01/2007	
60283	LUCAS	Christian	15/12/2007	EC-INV	MSD	essai clinique migraine: antagoniste des récepteurs du CGRP dans la crise de migraine	investigateur principal	01/2007	
60283	LUCAS	Christian	15/12/2007	LD-AR	MéNARINI	groupe d'experts migraine	Rémunération personnelle		
60283	LUCAS	Christian	15/12/2007	LD-AR	ALLERGAN	groupe d'expert migraine	Rémunération personnelle		
60283	LUCAS	Christian	03/01/2007	LD-AR	GSK	groupe d'experts Migraine (en cours)	rémunération personnelle	01/2004	
60283	LUCAS	Christian	03/01/2007	LD-AR	SCHWARTZ PHARMA	groupe d'experts Migraine (en cours)	rémunération personnelle	01/2005	12/2006
60283	LUCAS	Christian	03/01/2007	LD-AR	PFIZER	groupe d'experts Migraine (en cours)	rémunération personnelle	01/2006	
60283	LUCAS	Christian	03/01/2007	EC-INV	GSK	essai migraine (NOS) -(en cours)	coordonnateur national	01/2005	
60283	LUCAS	Christian	03/01/2007	EC-INV	BOEHRINGER	Thrombolyse AVC (Ecass 3) - en cours)	investigateur principal	01/2004	12/2007
60283	LUCAS	Christian	03/01/2007	EC-INV	ASTRA ZENECA	protection Neurovasc (étude Saint I et II)	investigateur principal	01/2005	12/2006
60283	LUCAS	Christian	20/01/2005	IP-EC	BOEHRINGER INGELHEIM - ASTRA ZENECA - SANOFI AVENTIS	Essais cliniques de phase III dans le domaine de la pathologie neurovasculaire			
60283	LUCAS	Christian	20/01/2005	IP-EC	ASTRA ZENECA - GSK - PFIZER- JANSEN CILAG - AMIRALL	Essais clinique de phase III dans le domaine céphalées migraines			
60283	LUCAS	Christian	20/01/2005	IP-AC	GSK - SCHWARTZ PHARMA - JANSSEN CILAG	Mission de conseil scientifique			
60283	LUCAS	Christian	30/01/2004	LD	ASTRA ZENECA - GSK - AVENTIS - PFIZER - BOEHRINGER	Essais Phase III			
60283	LUCAS	Christian	30/01/2004	LD	SCHWARTZ PHARMA - ALMIRALL - SANOFI SYNTHELABO	Essai phase III			
60283	LUCAS	Christian	30/01/2004	IP-AC	GSK - ALMIRALL - ASTRA ZENECA - PFIZER	Conseils stratégiques sur migraine et AVC			
60283	LUCAS	Christian	30/01/2004	IP-AC	SCHWARTZ PHARMA - BOEHRINGER - SANOFI SYNTHELABO	Conseils stratégiques sur migraine et AVC			
60283	LUCAS	Christian	30/01/2004	IP-CF	LABORATOIRE MEINES	EPU régionaux, nationaux ou congrès internationaux			
60283	LUCAS	Christian	17/07/2000	IP-EC	GLAXO WELLCOME ; ASTRA ZENECA ; RPR ; SANOFI	Essais cliniques phase III			
60283	LUCAS	Christian	17/07/2000	IP-AC	ASTRA ZENECA	Stratégie de développement.			
60283	LUCAS	Christian	17/07/2000	IP-AC	SERVIER INTERNATIONAL	Stratégie de développement.			
60283	LUCAS	Christian	17/07/2000	IP-CF	ASTRA ZENECA ; GLAXO WELLCOME ; SANOFI ; SERVIER	FMC migraine / neurovasculaire			
60283	LUCAS	Christian	17/07/2000	IP-EC	GLAXO WELLCOME	Essais cliniques phase III			
60283	LUCAS	Christian	17/07/2000	IP-EC	ASTRA ZENECA	Essais cliniques phase III			
60283	LUCAS	Christian	17/07/2000	IP-EC	RPR	essais cliniques phase 3			
60283	LUCAS	Christian	17/07/2000	IP-EC	SANOFI	essais cliniques phase 3			
60283	LUCAS	Christian	17/07/2000	IP-AC	ASTRA ZENECA	stratégies de développement			
60283	LUCAS	Christian	17/07/2000	IP-CF	SERVIER INTERNATIONAL	stratégies de développement			
60283	LUCAS	Christian	17/07/2000	IP-CF	ASTRA ZENECA	FMC migraine ,neurovasculaire			
60283	LUCAS	Christian	17/07/2000	IP-AUT	GLAXO WELLCOME	FMC migraine ,neurovasculaire			
60283	LUCAS	Christian	17/07/2000	IP-CF	SANOFI	FMC migraine, neurovasculaire			
60283	LUCAS	Christian	17/07/2000	IP-CF	SERVIER	FMC migraine, neurovasculaire			
63358	MACCARIO	Jean	25/04/2004	IP-AC	SERVIER	Pharmacotechnie - assurance qualité			
63358	MACCARIO	Jean	25/04/2004	IP-AC	L'OREAL	Planification expérimentale			
63358	MACCARIO	Jean	25/04/2004	IP-CF	INSERM	Formations statistiques			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	IF	RHONE-POULENC	11 actions.			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	LD	SERVIER	Contrat de Conseiller.			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	IP-EC	NOVARTIS	1 essai clinique en cours.			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	IP-EC	SEARLE	1 essai clinique en cours.			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	IP-RE	SERVIER	1 rapport d'expertise.			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	IP-CF	PARKE-DAVIS	1 conférence en sept. 98.			
55621	MAHIEUX-LAURENT	Florence	01/01/1999	IP-AUT	IPSEN	Soutien du DIU dont je m'occupe (polycopié, aide aux voyages des conférenciers).	Rémunération personnelle	01/2010	06/2010
10294	MAINCENT	Philippe	17/05/2010	RE-AUT	PANMEDICA	Rapport d'expertise dans le cadre d'une procédure arbitrale	Rémunération personnelle	02/2010	05/2010
10294	MAINCENT	Philippe	20/04/2010	RE-DE	JUVISE PHARMACEUTICALS	Variation/Changement de formule	Rémunération personnelle	03/2010	
10294	MAINCENT	Philippe	20/04/2010	RE-DE	EFFIK	Variation/Chgt de site	Rémunération personnelle	01/2010	
10294	MAINCENT	Philippe	20/04/2010	RE-DE	LABORATOIRES LEHNING	Produits phytothérapiques et homéopathiques	Rémunération personnelle	09/2009	09/2009
10294	MAINCENT	Philippe	22/10/2009	RE-DE	IDD	QOS	Rémunération personnelle	09/2008	10/2008
10294	MAINCENT	Philippe	14/10/2008	RE-DE	SUNSTAR/PHARMADENT	Paroex	Rémunération personnelle	01/2008	12/2008
10294	MAINCENT	Philippe	11/07/2008	CF-INT	IFIS	4 à 6 séminaires/an sur le dossier pharmaceutique	Rémunération personnelle	07/2008	07/2008
10294	MAINCENT	Philippe	11/07/2008	RE-DE	LABORATOIRES GENEVRIER	rédaction de QOS	Rémunération personnelle	06/2008	07/2008
10294	MAINCENT	Philippe	11/07/2008	RE-DE	MACO PHARMA	rédaction de QOS	Rémunération personnelle	03/2007	07/2007
10294	MAINCENT	Philippe	16/10/2007	RE-DE	NOVAGALI	rédaction de QOS		10/2006	
10294	MAINCENT	Philippe	21/09/2007	(Autre)	ROVI (MADRID, ESPAGNE)	Cession d'une licence de brevet□□Membre du Conseil Scientifique	Rémunération personnelle	01/2006	
10294	MAINCENT	Philippe	21/09/2007	CF-INT	IFIS	4 cessions d'une journée par an	Rémunération personnelle	07/2007	07/2007
10294	MAINCENT	Philippe	21/09/2007	CF-INT	ARC	Seminaire	Rémunération personnelle	10/2007	
10294	MAINCENT	Philippe	21/09/2007	RE-DE	SUBSTIPHARM	rédaction de QOS			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10294	MAINCENT	Philippe	21/09/2007	RE-DE	BIOGARAN, GALENIX, ARROW	rédaction de QOS	Rémunération personnelle	01/2007	
10294	MAINCENT	Philippe	07/03/2007	RE-DE	BIOGARAN	Cefixime	Rémunération personnelle	02/2007	03/2007
10294	MAINCENT	Philippe	07/03/2007	RE-DE	BIOGARAN	Cefixime Biogaran	Rémunération personnelle	02/2007	02/2007
10294	MAINCENT	Philippe	27/02/2006	CF-AUD	THERAMEX	Académie Theramex des Sciences Pharmaceutiques□□Monaco		05/2002	
10294	MAINCENT	Philippe	27/02/2006	CF-INT	IDD, ARC CONSULTANTS, IFIS	Séminaires	Rémunération personnelle	02/2003	
10294	MAINCENT	Philippe	22/02/2005	LD	BIOGARAN	Contrat consultance (jusqu'au 1er mars 2003)			03/2003
10294	MAINCENT	Philippe	22/02/2005	IP-AC	SUBSTIPHARM		Aucune rémunération	02/1999	04/2003
10294	MAINCENT	Philippe	22/02/2005	RE-DE	SUBSTIPHARM, GALENIC, BIOGARAN, VENIPHARM			03/1999	04/2003
10294	MAINCENT	Philippe	22/02/2005	VB	BIOCODEX, SCHERING, STIEFEL, ALCON,LCO SANTE, ABBOTT FRANCE, ALTANA, GALDERMA, SERVIER, EUROGENERICS, CERP, VETOQUINOL, OPOCALCIUM, SCREP, MAYOLY SPINDLER, GGAM, DELBERT, SANOFI SYNTHELABO, ZYDUS FRANCE, FAULDING, INITIAL BTB, PFIZER, TEVA CLASSICS, LAB F	Taxes d'apprentissage	Laboratoire de pharmacie galénique, Faculté de Pharmacie□ Nancy		
10294	MAINCENT	Philippe	16/04/2003	LD	BIOGARAN				
10294	MAINCENT	Philippe	16/04/2003	IP-RE	BIOGARAN, ITEC, TEVA, RATIOPHARM, PIERRE FABRE, MERCK MEDICATION FAMILIALE, AMISTAD PHARMA				
10294	MAINCENT	Philippe	16/04/2003	IP-AC	SUBSTIPHARM, ELLIPSE				
10294	MAINCENT	Philippe	16/04/2003	IP-CF	IFIS, ARC				
10294	MAINCENT	Philippe	01/10/2001	IP-AC	SUBSTIPHARM				
10294	MAINCENT	Philippe	27/02/2001	IP-RE	BAYER CLASSICS ; VENIPHARM		Actualisation DPI sur papier libre		
10294	MAINCENT	Philippe	28/08/2000	IP-RE	BESINS-ISCOVESCO	Rapport d'expertise			
10294	MAINCENT	Philippe	28/08/2000	IP-AC	ETHYPHARM	Conseil			
10294	MAINCENT	Philippe	05/05/2000	LD	BIOGARAN				
10294	MAINCENT	Philippe	05/05/2000	LD	REDDY CHEMINOR S.A.				
10294	MAINCENT	Philippe	05/05/2000	IP-RE	DOMS-ADRIAN, BOIRON, IPSOR, IDD, BIOGARAN, REDDY-CHEMINOR S.A., MSD, ZAMBON	Rapports sur les parties II A, II B, II E et II F2 du dossier pharmaceutique			
10294	MAINCENT	Philippe	05/05/2000	IP-CF	IFIP	Conférences sur le dossier pharmaceutique			
10294	MAINCENT	Philippe	05/05/2000	IP-CF	ANDRE REY CONSULTANTS				
10294	MAINCENT	Philippe	14/04/2000	IP-RE	DOMS-ADRIAN				
10294	MAINCENT	Philippe	27/02/2000	IP-RE	BAYER CLASSICS et VENIPHARM	Rapports d'expertise			
10294	MAINCENT	Philippe	01/01/1999	LD	Société REDDY CHEMINOR				
10294	MAINCENT	Philippe	01/01/1999	IP-RE	Société REDDY CHEMINOR (Paris)				
10294	MAINCENT	Philippe	01/01/1999	IP-RE	ZAMBON France				
10294	MAINCENT	Philippe	01/01/1999	IP-RE	MSD CHIBRET				
10294	MAINCENT	Philippe	01/01/1999	IP-RE	IDD				
10294	MAINCENT	Philippe	01/01/1999	IP-RE	IPSOR				
10294	MAINCENT	Philippe	01/01/1998	IP-AUT	Boiron				
10294	MAINCENT	Philippe	01/01/1998	IP-AUT	Biogaran (filiale Servier)				
10294	MAINCENT	Philippe	01/01/1998	IP-AUT	Macors				
61831	MAISON	Patrick	21/01/2010	PAR	COVANCE	manager	conjoint	10/2004	
61831	MAISON	Patrick	21/01/2010	EC-CO	COVANCE	sorafenib	collaborateur	10/2008	
61831	MAISON	Patrick	21/01/2010	EC-INV	EUSA PHARMA	Etude Pharmaco-épidémiologique	expérimenteur	08/2009	
61831	MAISON	Patrick	28/11/2008	EC-CO	CELGENE	revlimid	consultant	11/2007	12/2007
61831	MAISON	Patrick	20/11/2007	PAR	COVANCE	manager	conjoint	10/2005	
61831	MAISON	Patrick	20/11/2007	IP-AC	CELGENE	expertise pharmaco-épidémiologie	Rémunération personnelle	11/2007	11/2007
61831	MAISON	Patrick	22/12/2006	RE-DE	LILLY	expertise sur neuroleptique et troubles métaboliques	aucune rémunération	06/2006	12/2006
61831	MAISON	Patrick	22/12/2006	CF-INT	PFIZER	hormone de croissance et risque cardio vasculaire,	rémunération personnelle	04/2006	
61831	MAISON	Patrick	24/02/2006	IP-AC	SERVIER	Synthèse sur classes thérapeutiques	rémunération personnelle	09/2004	02/2006
61831	MAISON	Patrick	24/02/2006	CF-INT	PFIZER	GH et facteur risques cardio vasculaire - méta analyse	rémunération personnelle	03/2005	
61831	MAISON	Patrick	29/01/2004	IP-CF	LILLY	Colloques sur GH chez l'adulte	investigateur - coordinateur	01/2005	
65034	MALLET	Luc	08/04/2008	EC-INV	MEDTRONIC - AP HP (PHRC)	STIC - Stimulation cérébrale profonde - ACTIVA	responsable scientifique	01/2007	
65034	MALLET	Luc	08/04/2008	EC-INV	MEDTRONIC - AP HP (PHRC)	STIC - Stimulation cérébrale profonde	co-investigateur	01/2008	
65034	MALLET	Luc	08/04/2008	EC-CO	MEDTRONIC - DRC CHU RENNES	Stimulation cérébrale profonde	rémunération personnelle	04/2004	12/2004
65034	MALLET	Luc	08/04/2008	IP-AC	BOEHRINGER	PRAMIPEXOLE - dossier d'AMM		04/2008	04/2008
65034	MALLET	Luc	08/04/2008	CF-AUD	MERCK - SERONO	AAN 2008 - Neurologie / Chicago		04/2008	04/2008
65034	MALLET	Luc	08/04/2008	CF-AUD	SERVIER	SNLF 2008 - neurologie - TRIVASTAL / Bordeaux		01/2006	12/2007
65583	MARANGONI	Elisabetta	25/11/2009	EC-INV	PIERRE FABRE	Evaluation de l'efficacité anti-tumorale d'une nouvelle drogue	investigateur principal	01/2008	
65583	MARANGONI	Elisabetta	25/11/2009	EC-INV	SERVIER	Evaluation de l'efficacité anti-tumorale d'une nouvelle drogue (en cours)	investigateur principal	01/2007	12/2008
65583	MARANGONI	Elisabetta	25/11/2009	EC-INV	NOVARTIS	Evaluation de l'efficacité anti-tumorale d'une nouvelle drogue	investigateur principal	01/2009	12/2011
65583	MARANGONI	Elisabetta	25/11/2009	EC-INV	ROCHE	Evaluation de l'efficacité anti-tumorale d'une nouvelle drogue	investigateur principal	01/2008	
65583	MARANGONI	Elisabetta	25/11/2009	EC-INV	MERCK SERONO	Evaluation de l'efficacité anti-tumorale d'une nouvelle drogue (en cours)	co-investigateur	01/2007	12/2008
65583	MARANGONI	Elisabetta	25/11/2009	EC-CO	LILLY	Evaluation de l'efficacité anti-tumorale d'une nouvelle drogue	rémunération personnelle	09/1999	10/2005
61159	MARCELLI	Christian	28/06/2006	LD-AR	ROCHE	Expert - ostéoporose - Bonviva	rémunération personnelle	09/2001	09/2004
61159	MARCELLI	Christian	28/06/2006	LD-AR	PIERRE FABRE	Expels - ostéoporose - Optruma	co-investigateur	01/1996	12/2005
61159	MARCELLI	Christian	28/06/2006	EC-CO	SERVIER	PROTELOS - études SOTI et TROPOS	co-investigateur	01/2003	
61159	MARCELLI	Christian	28/06/2006	EC-CO	ABBOTT	HUMIRA - Etude REACT et RHAPSODY	co-investigateur	01/2002	12/2003
61159	MARCELLI	Christian	28/06/2006	EC-CO	MSD	VIOXX	co-investigateur	01/2003	
61159	MARCELLI	Christian	28/06/2006	EC-CO	KYPHON	Kyphoplastie - protocole Kyphoplastie SP 0201	rémunération personnelle	12/2005	12/2005
61159	MARCELLI	Christian	28/06/2006	CF-INT	LILLY	congrès français de rhumatologie - traitement de l'ostéoporose - Evista (symosium)	rémunération personnelle	11/2004	11/2004
61159	MARCELLI	Christian	28/06/2006	CF-INT	SERVIER	Congrès français de rhumatologie - symposium traitement de l'ostéoporose - Protelos		12/2005	12/2005
61159	MARCELLI	Christian	28/06/2006	CF-AUD	PROCTER & GAMBLE	congrès français de rhumatologie - Paris - Actonel		09/2005	09/2005
61159	MARCELLI	Christian	28/06/2006	CF-AUD	ROCHE	Congrès de l'American Society for Bone and Mineral Research - Nashville (USA)			
61159	MARCELLI	Christian	06/11/2000	IP-AC	ROCHE	Conseil scientifique			
61159	MARCELLI	Christian	06/11/2000	IP-CF	PROCTER & GAMBLE	Animateur du groupe GESO Nord-Ouest			
10297	MARIÉ	Alain	20/10/2009	Néant					
10297	MARIÉ	Alain	18/11/2008	LD	LE QUOTIDIEN DU MEDECIN				
10297	MARIÉ	Alain	11/10/2007	Néant					
10297	MARIÉ	Alain	13/07/2006	Néant					

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10297	MARIÉ	Alain	24/01/2006	Néant					
10297	MARIÉ	Alain	14/12/2004	LD	QUOTIDIEN DU MEDECIN				
10297	MARIÉ	Alain	14/12/2004	IP-AC	QUOTIDIEN DU MEDECIN	Quelques dossiers de presse multiples pour le compte du Quotidien			
10297	MARIÉ	Alain	14/12/2004	IP-CF	QUOTIDIEN DU MEDECIN				
10297	MARIÉ	Alain	27/05/2003	LD	Groupe Quotidien Santé	Directeur Médical			
10297	MARIÉ	Alain	12/01/2000	IP-AC		Divers sans aucune régularité			
10297	MARIÉ	Alain	12/01/2000	IP-CF		Divers sans régularité			
10297	MARIÉ	Alain	01/01/1999	IP-AUT	ASTRA	Rédaction occasionnelle de dossiers de presse, articles ou brochures.			
10297	MARIÉ	Alain	01/01/1999	IP-AUT	JACQUEMAIRE				
10297	MARIÉ	Alain	01/01/1999	IP-AUT	SOLVAY				
10297	MARIÉ	Alain	01/01/1999	IP-AUT	SERVIER				
10297	MARIÉ	Alain	01/01/1999	IP-AUT	TAKEDA				
10297	MARIÉ	Alain	01/01/1999	IP-AUT	WYETH-LEDERLE				
10297	MARIÉ	Alain	01/01/1999	IP-AUT	LA ROCHE-POSAY				
10297	MARIÉ	Alain	01/01/1999	VB		Cours DU de journalisme médical.			
10297	MARIÉ	Alain	01/01/1998	IP-AUT	Wyeth-Solvay		rédaction de brochures scientifiques et dossiers presse		
10297	MARIÉ	Alain	01/01/1998	IP-AUT	Astra		rédaction de brochures scientifiques et dossiers presse		
10297	MARIÉ	Alain	01/01/1998	IP-AUT	Servier		rédaction de brochures scientifiques et dossiers presse		
60169	MARIOTTE	Anne-Marie	22/11/2009	VB	ARKOPHARMA, PFABRE,BOIRON, MYLAN	taxe d'apprentissage<15%	labo pharmacognosie	01/2009	12/2009
60169	MARIOTTE	Anne-Marie	22/11/2009	IP-AUT	COLETICA/BASF	Brevets cosmetologie		01/1999	12/2005
60169	MARIOTTE	Anne-Marie	22/11/2009	IP-AC	SYNADIET	comité scientifique	Aucune rémunération	02/2006	02/2006
60169	MARIOTTE	Anne-Marie	22/11/2009	RE-DE	ARKOPHARMA	rapport d'expertise Harpadol, Activox	Rémunération institution	01/2003	12/2005
60169	MARIOTTE	Anne-Marie	25/03/2009	IP-AC	SYNADIET	comité scientifique	Aucune rémunération	02/2006	02/2006
60169	MARIOTTE	Anne-Marie	25/03/2009	RE-DE	ARKOPHARMA	dossier AMM hardadol gel ,activox	Rémunération institution	04/2003	04/2005
60169	MARIOTTE	Anne-Marie	25/03/2009	EC-CO	COLETICA-ENGHEHARD-BASF	3 brevets actifs de cosmetologie	co-investigateur	01/2003	12/2007
60169	MARIOTTE	Anne-Marie	25/03/2009	EC-CO	COLETICA-ENGHELHARD-BASF	3 brevets actifs de cosmétologie	co-investigateur	01/2003	12/2007
60169	MARIOTTE	Anne-Marie	23/02/2009	VB	ARKOPHARMA, PFABRE, BOIRON , MERCK	taxe d'apprentissage<15%	Université Joseph Fourier Labo pharmacognosie	01/2008	02/2009
60169	MARIOTTE	Anne-Marie	23/02/2009	IP-AC	SYNADIET	comité scientifique	Aucune rémunération	02/2006	02/2006
60169	MARIOTTE	Anne-Marie	23/02/2009	EC-CO	COLETICA- ENGELHARD-BASF	3 brevets actifs de cosmetologie	co investigateur	01/2003	12/2007
60169	MARIOTTE	Anne-Marie	23/02/2009	RE-DE	ARKOPHARMA	dossier AMM : Harpadol gel, Activox	Rémunération institution	04/2003	04/2003
60169	MARIOTTE	Anne-Marie	23/02/2009	RE-DE	ARKOPHARMA	HARPADOL gel ACTIVOX	Rémunération institution	04/2003	04/2003
60169	MARIOTTE	Anne-Marie	03/06/2008	VB	PIERRE FABRE DERMO COSMETIQUE	taxe d'apprentissage	UJF laboratoire de pharmacognosie		
60169	MARIOTTE	Anne-Marie	03/06/2008	VB	BOIRON -URGO	taxe d'apprentissage	UJF laboratoire de pharmacognosie		
60169	MARIOTTE	Anne-Marie	03/06/2008	VB	ARKOPHARMA-MERCK GENERIQUE	taxe d'apprentissage	UJF laboratoire de pharmacognosie	03/2007	12/2007
60169	MARIOTTE	Anne-Marie	03/06/2008	IP-AUT	COLETICA-ENGELHARD- BASF	actifs cosmétologie/brevets(3)	1 brevet actif/ redevances à l'institution et à moi même	03/2003	
60169	MARIOTTE	Anne-Marie	03/06/2008	IP-AC	SYNADIET	Comité scientifique	Aucune rémunération	02/2006	02/2006
60169	MARIOTTE	Anne-Marie	03/06/2008	RE-DE	ARKOPHARMA	HARPADOL Gel ACTIVOX PAST	Rémunération institution	04/2003	04/2003
60169	MARIOTTE	Anne-Marie	07/06/2006	RE-DE	ARKOPHARMA	Rapport d'expertise dossier d'AMM : HARPADOL gel ; ACTIVOX past	rémunération versée à une institution	04/2003	04/2005
60169	MARIOTTE	Anne-Marie	07/06/2006	IP-AC	PIERRE FABRE	Entretien du Carla : phytothérapie	aucune rémunération	12/2003	12/2003
60169	MARIOTTE	Anne-Marie	07/06/2006	IP-AC	SYNADIET	Comité scientifique - Grenoble	aucune rémunération	02/2006	02/2006
60169	MARIOTTE	Anne-Marie	07/06/2006	IP-AUT	COLETICA / ENGELHARD (LYON ET UJF GRENOBLE - CO-PROPRIÉTAIRES)	3 brevets actifs pour la cosmétologie (1999 et 2005)			
60169	MARIOTTE	Anne-Marie	07/06/2006	VB	ARKOPHARMA,PIERRE FABRE,MERCK GENERIQUES,AGUETTANT,BOIRON, SERVIER, URGO	Taxe d'apprentissage < 15%	laboratoire de pharmacognosie UJF de Grenoble	04/2004	09/2006
60169	MARIOTTE	Anne-Marie	07/06/2006	VB	INSTITUT KLORANE	Bourse de thèse pharmacognosie			
60169	MARIOTTE	Anne-Marie	15/03/2005	IP-RE	AKOPHARMA	Harpadol Gel			
60169	MARIOTTE	Anne-Marie	15/03/2005	VB	ARKOPHARMA	Taxes d'apprentissage, financements < 15% du budget du service			
60169	MARIOTTE	Anne-Marie	15/03/2005	VB	PIERRE FABRE	Taxes d'apprentissage, financements < 15% du budget du service			
60169	MARIOTTE	Anne-Marie	15/03/2005	VB	MERCK GENERIQUES	Taxes d'apprentissage, financements < 15% du budget du service			
60169	MARIOTTE	Anne-Marie	15/03/2005	VB	AGUETTANT	Taxes d'apprentissage, financements < 15% du budget du service			
60169	MARIOTTE	Anne-Marie	15/03/2005	VB	BOIRON	Taxes d'apprentissage, financements < 15% du budget du service			
60169	MARIOTTE	Anne-Marie	15/03/2005	VB	SERVIER	Taxes d'apprentissage, financements < 15% du budget du service			
60169	MARIOTTE	Anne-Marie	15/03/2005	IP-AUT	PIERRE FABRE	Projet de création d'une Société de Phytothérapie Européenne, initiateur			
60169	MARIOTTE	Anne-Marie	23/06/2004	IP-RE	ARKOPHARMA	Harpadol gel, avril 2003			
60169	MARIOTTE	Anne-Marie	23/06/2004	IP-CF	PIERRE FABRE	Colloque sur la plastothérapie, entretien de carla décembre 2003			
60169	MARIOTTE	Anne-Marie	23/06/2004	VB	ARKOPHARMA	Rapport d'expertise laboratoire de pharmacognosie (université de grenoble)			
60169	MARIOTTE	Anne-Marie	23/06/2004	(Autre)		Membre de l'AFSSA CES nutrition compléments alimentaire à base de plantes			
60169	MARIOTTE	Anne-Marie	03/09/2003	IP-RE	ARKOPHARMA	Harpadol Gel (avril 2003)			
60169	MARIOTTE	Anne-Marie	03/09/2003	IP-CF	ARCHIMEX	Médicaments à base de plantes			
60169	MARIOTTE	Anne-Marie	03/09/2003	VB	ARKOPHARMA	Rapport d'expertise - Laboratoire de pharmacologie, Université de Grenoble			
60169	MARIOTTE	Anne-Marie	30/06/2000	IP-RE	ARKOPHARMA	Février 1997 - uristil			
60169	MARIOTTE	Anne-Marie	30/06/2000	IP-CF	ARCHIMEX	Formation : réglementation des phyto médicaments et produits alimentaires supplémentés à base de plantes - juin 2000			
60169	MARIOTTE	Anne-Marie	30/06/2000	IP-AUT	Institut KLORANE	Bourse de thèse pour l'année 1999-2000			
64259	MARRE	Michel	28/08/2006	EC-INV	SANOFI AVENTIS	Essai ORIGIN / insuline LANTUS	Coordonnateur principal	01/2002	12/2008
64259	MARRE	Michel	28/08/2006	EC-INV	SANOFI AVENTIS	Essai CHARISMA / Plavix	investigateur	01/2002	12/2006
64259	MARRE	Michel	28/08/2006	EC-INV	SANOFI AVENTIS	Essai CRESCENDO / Rimonabant	coordonnateur national	01/2006	12/2010
64259	MARRE	Michel	28/08/2006	EC-INV	ASTRA ZENECA	Essai Direct / Candesartan	investigateur	01/2001	12/2006
64259	MARRE	Michel	28/08/2006	EC-INV	ASTRA ZENECA	Etude Gallant 7 / Tesaglitazar / phase 2	coordonnateur national	01/2005	12/2006
64259	MARRE	Michel	28/08/2006	EC-INV	SERVIER	Essai ADVANCE	coordonnateur principal	01/2000	12/2008

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64259	MARRE	Michel	28/08/2006	EC-INV	SERVIER	S18886 / phase 2	investigateur principal	01/2003	12/2006
64259	MARRE	Michel	28/08/2006	EC-INV	MSD	MK 431 / phase 2	coordonnateur principal / investigateur	01/2004	12/2006
64259	MARRE	Michel	28/08/2006	EC-INV	SANKYO	étude ROADMAP	coordonnateur principal	01/2006	12/2008
64259	MARRE	Michel	28/08/2006	EC-INV	GSK	Rosiglitazone - rétention hydrosodée - étude explicative (CIC)	investigateur	01/2003	12/2004
64259	MARRE	Michel	28/08/2006	EC-INV	NOVARTIS	Antirénine - phase 2	investigateur	01/2005	12/2005
64259	MARRE	Michel	28/08/2006	EC-INV	PFIZER	insuline pulmonaire - phase 3	investigateur	01/2006	12/2007
64259	MARRE	Michel	28/08/2006	EC-INV	NOVO NORDISK	PREDICTIVE - insuline LEVEMIR - Observationnelle	coordonnateur national	01/2005	12/2007
64259	MARRE	Michel	28/08/2006	EC-INV	NOVO NORDISK	LIRAGLUTIDE - phase 2	coordonnateur européen	01/2006	12/2008
64259	MARRE	Michel	28/08/2006	RE-DE	TAKEDA	COKENZEN - indication dans la microalbuminurie des diabétiques	aucune rémunération	01/2006	12/2006
64259	MARRE	Michel	28/08/2006	IP-AC	SANOFI AVENTIS	Groupe d'experts : insuline LANTUS - durée : 1 an renouvelable	Rémunération partagée personnelle / institution	01/2005	12/2005
64259	MARRE	Michel	28/08/2006	IP-AC	SANOFI AVENTIS	Groupe d'experts : Rimonabant - durée : 1 an renouvelable	Rémunération partagée personnelle / institution	01/2006	12/2006
64259	MARRE	Michel	28/08/2006	IP-AC	NOVO NORDISK	Groupe d'experts : Insuline LEVEMIR - durée : 1 an renouvelable	Rémunération partagée personnelle / institution	01/2004	12/2004
64259	MARRE	Michel	28/08/2006	IP-AC	MSD	Groupe d'experts : MK 431 - durée : 1 an renouvelable	Rémunération partagée personnelle / institution	01/2006	12/2006
64259	MARRE	Michel	28/08/2006	CF-INT	SERVIER	EASD Athènes - Sulfonylurias in type 2 diabetes - gliclazide	Rémunération partagée personnelle / institution	09/2005	09/2005
64259	MARRE	Michel	28/08/2006	CF-INT	NOVO NORDISK	ALFEDIAM Paris - LEVEMIR - table ronde	Rémunération partagée personnelle / institution	03/2006	03/2006
64259	MARRE	Michel	28/08/2006	CF-INT	MSD	ALFEDIAM Paris - Losartan - symposium	Rémunération partagée personnelle / institution	03/2006	03/2006
64259	MARRE	Michel	28/08/2006	CF-INT	PFIZER	ALFEDIAM Paris - Atorvastatine - symposium	Rémunération partagée personnelle / institution	03/2006	03/2006
64259	MARRE	Michel	28/08/2006	CF-INT	MSD	Société Française d'Endocrinologie - Montpellier - MK 431 - symposium	Rémunération partagée personnelle / institution	09/2006	09/2006
64259	MARRE	Michel	28/08/2006	CF-INT	FOURNIER	Société Française d'Endocrinologie - Montpellier - Fénofibrate - symposium	Rémunération partagée personnelle / institution	09/2006	09/2006
64259	MARRE	Michel	28/08/2006	PAR	SERVIER	Directeur médical Servier France	conjoint		
10300	MARTY	Michel	24/03/2009	RE-AUT	PIERRE FABRE ONCOLOGIE	IDMC etude vinflunine	Rémunération personnelle	04/2008	
10300	MARTY	Michel	24/03/2009	LD-AR	CYCLACEL	Etude d'inhibiteurs de kinases cyclines dépendantes	Rémunération personnelle	01/2007	04/2008
10300	MARTY	Michel	19/03/2009	CF-INT	GSK	Congrès national marocain de cancérologie	Aucune rémunération	04/2009	04/2009
10300	MARTY	Michel	19/03/2009	CF-INT	SANOFI-AVENTIS	SABCS	Aucune rémunération	12/2008	12/2008
10300	MARTY	Michel	19/03/2009	IP-AC	SANOFI-AVENTIS	etude de l'organisation de la R&D oncologie	Rémunération personnelle	10/2008	
10300	MARTY	Michel	19/03/2009	IP-AC	PHARMAMAR	Modalités thérapeutiques des cancers du sein triple négatifs	Aucune rémunération	11/2008	
10300	MARTY	Michel	19/03/2009	RE-AUT	VAXON/INSERM TRANSFERT	Vaccins antitumoraux dans les cancers bronchiques	Rémunération personnelle	11/2008	
10300	MARTY	Michel	19/03/2009	RE-AUT	MEDSQUAL/PARIS BIOTECH	Développement de médicaments vectorisés	Rémunération personnelle	06/2008	09/2008
10300	MARTY	Michel	19/03/2009	EC-CO	GSK	étude de phase I de l'association lapatinib-docetaxel	co-investigateur	02/2008	
10300	MARTY	Michel	19/03/2009	EC-INV	SANOFI-AVENTIS	Essai de phase II randomisé du larotaxel en situation neoadjuvante dans les cancers du sein	investigateur coordonateur	04/2007	
10300	MARTY	Michel	19/03/2009	LD-AR	GSK	Groupe NEO: etude des pratiques médicales en cancérologie	Rémunération personnelle	02/2008	
10300	MARTY	Michel	19/03/2009	LD-AR	DEBIOPHARM	Etudes d'opportunités de licensing in d'agents anticancéreux	Rémunération personnelle	06/2008	
10300	MARTY	Michel	27/03/2008	CF-INT	ROCHE	Paris/Journées de Cancerologie/moderateur/Imagerie fonctionnelle	Rémunération personnelle	03/2008	03/2008
10300	MARTY	Michel	27/03/2008	IP-AC	ANTIGENICS	Choix des criteres pharmacodynamiques dans les études de vaccination anitumorale	Rémunération personnelle	12/2007	12/2007
10300	MARTY	Michel	27/03/2008	CF-INT	PFIZER	Cannes/Journées interdisciplinaire/Place de la France dans la recherche et l'évaluation en Europe	Rémunération personnelle	11/2007	11/2007
10300	MARTY	Michel	27/03/2008	CF-AUD	SANOFI AVENTIS	San Antonio Breast Cancer Conference		12/2007	12/2007
10300	MARTY	Michel	27/03/2008	RE-AUT	PARIS BIOTECH	vectorisation d'antimétabolites; construction d'essais exploratoires	Rémunération personnelle	09/2007	09/2007
10300	MARTY	Michel	27/03/2008	EC-CO	GSK	etudes randomisées en situation adjuvante (ALTTO) et neoadjuvante du lapatinib dans les cancers du sein	co-investigateur	05/2007	
10300	MARTY	Michel	27/03/2008	EC-INV	SANOFI AVENTIS	etude de phase 3 du larotaxel pour le traitement neoadjuvant de cancers du sein	coordonateur	04/2007	11/2008
10300	MARTY	Michel	27/03/2008	RE-AUT	PIERRE FABRE MEDICAMENTS	Choix des critères de jugement pour des études prospectives dans les cancers urologiques métastatiques	Rémunération personnelle	04/2007	06/2008
10300	MARTY	Michel	27/03/2008	IP-AC	GSK	développement d'inhibiteurs de tyrosine kinase	Rémunération personnelle	04/2006	
10300	MARTY	Michel	28/05/2006	LD-AR	PHARMION	Opportunités de développement, molécules en licence	rémunération personnelle	01/2005	01/2007
10300	MARTY	Michel	28/05/2006	LD-AR	SANOFI AVENTIS	Sélections d'agents pour les études exploratoires , études pharmacodynamiques	rémunération personnelle	01/2004	01/2007
10300	MARTY	Michel	28/05/2006	LD-AR	GSK	Sélections d'agents pour les études exploratoires, études pharmacodynamiques	rémunération personnelle	01/2004	01/2007
10300	MARTY	Michel	28/05/2006	EC-INV	PIERRE FABRE ONCOLOGIE	Essais exploratoires Vinflunine	coordonnateur	01/2004	01/2007
10300	MARTY	Michel	28/05/2006	EC-INV	ROCHE	Etude de phase II randomisée Docetaxel vs Docetaxel + trastuzumab dans le traitement de première ligne d	coordonnateur	01/2000	12/2005
10300	MARTY	Michel	28/05/2006	EC-CO	GSK	Etudes de phase I & II du lapatinib dans le traitement des cancers du sein métastatique	expérimentateur	01/2006	
10300	MARTY	Michel	28/05/2006	IP-AC	AB SCIENCES	Audit	rémunération personnelle	01/2006	06/2007
10300	MARTY	Michel	28/05/2006	IP-AC	SANOFI AVENTIS	groupe de travail international cancers du sein	rémunération personnelle	01/2005	
10300	MARTY	Michel	28/05/2006	IP-AC	DNA THERAPEUTICS	Conseil sur les études phase I avec un ADN double-brin de petite taille	rémunération personnelle	01/2005	09/2007
10300	MARTY	Michel	28/05/2006	CF-INT	PHARMION	Pharmion, formation de l'équipe VM à la cancérologie	rémunération personnelle	01/2006	
10300	MARTY	Michel	28/05/2006	CF-INT	ASTRA ZENECA	Nouveautés en recherche clinique en cancérologie - Reims	rémunération personnelle	01/2006	
10300	MARTY	Michel	28/05/2006	CF-INT	SANOFI AVENTIS	GI WORLD SUMMIT - Varsovie	rémunération personnelle	01/2006	
10300	MARTY	Michel	28/05/2006	CF-AUD	GSK, ELI LILLY, SANOFI AVENTIS	San Antonio Breast Cancer Conference		01/2002	12/2005
10300	MARTY	Michel	28/05/2006	VB	ASTRA ZENECA, BMS, ELI LILLY, GSK, MERCK LIPHA, MSD, NOVARTIS, PFIZER, PIERRE FABRE ONCOLOGIE, ROCHE, SANOFI AVENTIS, WYETH LEDERLE	partenariat Eurocancer	Eurocancer 3E	01/1987	
10300	MARTY	Michel	28/05/2006	VB		congrès Eurocancer : partenariat industriel - congrès annuel depuis 1987			
10300	MARTY	Michel	02/09/2003	IP-EC	ROCHE	Essai			
10300	MARTY	Michel	02/09/2003	IP-EC	GLAXO SMITHKLINE	Essai			
10300	MARTY	Michel	02/09/2003	IP-EC	PIERRE FABRE Oncologie				
10300	MARTY	Michel	02/09/2003	IP-EC	WYETH LEDERLE	Essai Phase II			
10300	MARTY	Michel	02/09/2003	IP-EC	AVENTIS	Essais PACS			
10300	MARTY	Michel	02/09/2003	IP-EC	PFIZER				
10300	MARTY	Michel	02/09/2003	IP-AC	ASTRA ZENECA	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	AVENTIS	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	BEAUFOUR IPSEN	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	BERLEX	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	BIO ALLIANCE	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	CYCLACELL	Conseil en développement			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10300	MARTY	Michel	02/09/2003	IP-AC	DEBIOPHARM	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	EISAI	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	ELI LILLY	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	GLAXO SMITHKLINE	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	MERCK LIPHA	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	MERCK SHARP & DOHME	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	OTL	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	PIERRE FABRE ONCOLOGIE	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	PFIZER	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	PHARMAMAR	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	ROCHE PHARMA	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	SANOFI SYNTHELABO	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-AC	WYETH LEDERLE	Conseil en développement			
10300	MARTY	Michel	02/09/2003	IP-CF	AVENTIS	Symposium satellite : docetaxel			
10300	MARTY	Michel	02/09/2003	IP-CF	ELI LILLY	Conférences : cancer du sein métastatique			
10300	MARTY	Michel	02/09/2003	IP-CF	MERCK LIPHA	Conférences : agents ciblés			
10300	MARTY	Michel	02/09/2003	IP-CF	PIERRE FABRE ONCOLOGIE	Conférences : pharmacodynamique			
10300	MARTY	Michel	02/09/2003	IP-CF	ROCHE PHARMA	Symposium satellite : herceptin et associations			
10300	MARTY	Michel	02/09/2003	IP-CF	SANOFI SYNTHELABO	Symposium satellite : organoplatines			
10300	MARTY	Michel	02/09/2003	VB	IGR	Immuno designed molecules - Conseil en développement			
10300	MARTY	Michel	29/09/2000	IP-EC	AVENTIS, ROCHE, MEDIMMUNE, SANOFI SYNTHELABO, PHARMAMAR, M4I, P & U	Phases I et II			
10300	MARTY	Michel	29/09/2000	IP-AC	ROCHE, MEDIMMUNE, SERVIER, MERCK LIPHA, SANOFI SYNTHELABO				
10300	MARTY	Michel	29/09/2000	IP-CF	AVENTIS	Symposium			
10300	MARTY	Michel	29/09/2000	IP-CF	SANOFI SYNTHELABO	Symposium			
10300	MARTY	Michel	29/09/2000	IP-CF	GLAXO SB	Symposium			
10300	MARTY	Michel	29/09/2000	IP-CF	BMS	Séminaire			
10300	MARTY	Michel	29/09/2000	VB		Toutes les précédentes			
10300	MARTY	Michel	01/01/1999	IP-EC	RPR				
10300	MARTY	Michel	01/01/1999	IP-EC	SANOFI WINTHROP				
10300	MARTY	Michel	01/01/1999	IP-EC	PHARMACIA & UPJOHN				
10300	MARTY	Michel	01/01/1999	IP-EC	GLAXO WELLCOME				
10300	MARTY	Michel	01/01/1999	IP-EC	NEXSTAR				
10300	MARTY	Michel	01/01/1999	IP-EC	ZENECA				
10300	MARTY	Michel	01/01/1999	IP-EC	BMS				
10300	MARTY	Michel	01/01/1999	IP-CF	RPR				
10300	MARTY	Michel	01/01/1999	IP-CF	ZENECA				
10300	MARTY	Michel	01/01/1999	IP-CF	SANOFI WINTHROP				
10300	MARTY	Michel	01/01/1999	IP-CF	GLAXO WELLCOME				
10300	MARTY	Michel	01/01/1999	IP-CF	SB				
10300	MARTY	Michel	01/01/1999	IP-RE	PHARMACIA & UPJOHN				
10300	MARTY	Michel	01/01/1999	IP-AC	RPR				
10300	MARTY	Michel	01/01/1999	IP-AC	SANOFI WINTHROP				
10300	MARTY	Michel	01/01/1999	IP-AC	NEXSTAR				
10300	MARTY	Michel	01/01/1998	IP-AUT	RPR				
10300	MARTY	Michel	01/01/1998	IP-AUT	Sanofi				
10300	MARTY	Michel	01/01/1998	IP-AUT	Novartis				
10300	MARTY	Michel	01/01/1998	IP-AUT	SB				
10300	MARTY	Michel	01/01/1998	IP-AUT	Pharmacia-Upjohn				
10300	MARTY	Michel	01/01/1998	IP-AUT	Roche				
10300	MARTY	Michel	01/01/1998	IP-AUT	Boerhinger				
10300	MARTY	Michel	01/01/1998	IP-AUT	Schering-Plough				
10300	MARTY	Michel	01/01/1998	IP-AUT	Baxter				
10300	MARTY	Michel	01/01/1998	IP-AUT	PFO				
10300	MARTY	Michel	01/01/1998	IP-AUT	Glaxo Wellcome				
10300	MARTY	Michel	01/01/1998	VB	Etudes cliniques : versement au GEMMM				
10301	MARZIN	Daniel	19/05/2010	LD-AR	Institut de recherche PIERRE FABRE	Conseil, expertise	Rémunération personnelle		
10301	MARZIN	Daniel	19/05/2010	EC-INV	NOVARTIS, JOLLY-JATEL, GENETHON, CEPHALON, MELLITECH, BIOPROJET, MACOPHARMA, DA VOLTERRA, PIERRE FABRE, ORPHAN, NATURA, CIBA Inc, MONACHEM, FOVEA, MAPREG, BAYER SANTE, ARKOPHARMA, ALAXIA, INNATE, ANAVEX France, SEPTEOS, DIANA Naturals, TERATECH, QUANTUM G	Etudes pré-cliniques réalisées au sein du laboratoire de l'Institut Pasteur de Lille dont je suis Chef de Service		04/2009	05/2010
10301	MARZIN	Daniel	19/05/2010	EC-CO	INTESTINAL BIOTECH DEVELOPMENT	Membre d'un comité de sécurité GEDO 507 (en cours)		02/2010	
10301	MARZIN	Daniel	19/05/2010	IP-RE	ORPHA Eu, NOVAGALI, MACOPHARMA, BIOALLIANCE Pharma, MAPREG, MAYOLY SPINDLER, SANOFI AVENTIS, NICOX, NEGMA LERADS, SPTODONT	Etudes précliniques - études précliniques réalisées au sein du laboratoire de l'Institut Pasteur de Lille dont je suis le chef de service		04/2009	05/2010
10301	MARZIN	Daniel	19/05/2010	IP-RE	Institut de recherche SERVIER, MACOPHARMA, ETHYPHARM, LFB	Etudes précliniques - études précliniques réalisées au sein du laboratoire de l'Institut Pasteur de Lille dont je suis le chef de service		01/2010	12/2010
10301	MARZIN	Daniel	19/05/2010	(Autre)	Biologie SERVIER	Bourse CIFRE d'une doctorant		01/2006	12/2009
10301	MARZIN	Daniel	19/05/2010	LD-AR	INNATE PHARMA	Conseil , expertise	rémunération personnelle		
10301	MARZIN	Daniel	30/03/2009	LD-AR	INNATE PHARMA	Expertise et conseil en Toxicologie (en cours)	rémunération personnelle	01/2004	
10301	MARZIN	Daniel	30/03/2009	LD-AR	INSTITUT DE RECHERCHE PIERRE FABRE	Expertise et conseil en Toxicologie (en cours)	rémunération personnelle	01/2004	
10301	MARZIN	Daniel	30/03/2009	IP-RE	BIOLOGIE SERVIER, LFB, FAUST PHARMACEUTICALS, NEGMA			01/2004	12/2004
10301	MARZIN	Daniel	30/03/2009	IP-RE	FOURNIER,OTL PHARMA, JOLY JATEL, SUBSTIPHARM, ADIR			01/2005	12/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10301	MARZIN	Daniel	30/03/2009	IP-RE	NEGMA LERADS, TROPHOS, FAUST PHARMACEUTICALS, LFB, ORPHAN, ANACONDA PHARMA, MAPREG			01/2008	12/2008
10301	MARZIN	Daniel	30/03/2009	IP-RE	BAXTER, NOVAGALI, NOVEXEL, NEGMA LERADS, FAUST PHARMACEUTICALS, GALDERMA, PROSTRAKAN PHARMA, ADIR			01/2007	12/2007
10301	MARZIN	Daniel	30/03/2009	IP-RE	ANACONDA PHARMA, NICOX, R ET D PHARMA, CARL ZEISS MEDITEC, IPRAD, MACO PHARMA, NOVAGALI PHARMA, ADIR, ORPHAN EUROPE, BIO ALLIANCE PHARMA, ETHYPHARM, MAPREG			01/2008	12/2008
10301	MARZIN	Daniel	30/03/2009	IP-RE	ORPHAN EUROPE, IDA INDUSTRIAL PARK			01/2009	12/2009
10301	MARZIN	Daniel	30/03/2009	(Autre)	BIOLOGIE SERVIER	Bourse CIFRE d'une doctorante		01/2006	12/2009
10301	MARZIN	Daniel	07/07/2008	LD-AR	PIERRE FABRE	Consultant	Rémunération personnelle		
10301	MARZIN	Daniel	07/07/2008	LD-AR	INNATE PHARMA	Consultant			
10301	MARZIN	Daniel	07/07/2008	RE-DE	ANACONDA BAXTER CARL ZEISS MEDITEC FAUST PHARMACEUTICALS GALDERMA MACOPHARMA NICOX NOVAGALI NOVEXELL NEGMAN ORPHAN EUROPE PROSTRAKAN	rapports experts	rémunération personnelle		
10301	MARZIN	Daniel	07/07/2008	IP-CF	SERVIER	Séminaire interne : conférence	rémunération personnelle	11/2007	11/2007
10301	MARZIN	Daniel	07/07/2008	VB	ALFACT INNOVATION, ALPHARMA, ANACONDA, ARTERIA, BIOPROJET, Centre de recherches phytothérapiques, CIBA inc, CLARINS, CEPHALON, CR phytothérapiques, DBV Technologies, DISPHAR, EUSA PHARMA, FAUST PHARMA, GENFIT, HOLDER, INNATE PHARMA, IPRAD, LFB, L'OREAL,	Etudes de toxicologie (Laboratoires ayant confié des études de toxicologie au laboratoire de toxicologie de l Institut Pasteur de Lille			
10301	MARZIN	Daniel	07/07/2008	(Autre)	SERVIER	Bourse de thèse (contrat CIFRE - 1 étudiante)		12/2006	12/2009
10301	MARZIN	Daniel	07/07/2008	RE-AUT	MACOPHARMA	Rapports d'experts	rémunération institution		
10301	MARZIN	Daniel	02/08/2007	RE-DE	GALDERMA, PROSTRAKAN, NOVAGALI PHARMA	Conseil / expertise			
10301	MARZIN	Daniel	02/08/2007	IP-AUT	IDD	Conférences			
10301	MARZIN	Daniel	02/08/2007	IP-AUT	Andrey Rey Consultant	conférences			
10301	MARZIN	Daniel	02/08/2007	VB	CLARINS, GENFIT, LFB, PIERRE FABRE MEDICAMENT, PIERRE FABRE DERMOCOSMETIQUE, IFRAD, SGS MULTILAB, MAYOLY SPINDLER, STALLERGENES	Etudes de mutagénèse réalisés dans le service de toxicologie dont j'ai la responsabilité	Institut Pasteur de Lille		
10301	MARZIN	Daniel	02/08/2007	VB	THEA, CEPHALON, L'OREAL, CIT, TROPHOS, INNATE PHARMA, ARTERIA, BIOPROJET	Etudes de mutagénèse réalisés dans le service de toxicologie dont j'ai la responsabilité	Institut Pasteur de Lille		
10301	MARZIN	Daniel	26/09/2006	LD-AR	SOCIETE ROQUETTE			01/2002	
10301	MARZIN	Daniel	26/09/2006	LD-AR	LABORATOIRES PIERRE FABRE - LABORATOIRES INNATE PHARMA - SOCIETE ROQUETTE			01/2003	
10301	MARZIN	Daniel	26/09/2006	LD-AR	LABORATOIRES PIERRE FABRE - LABORATOIRES INNATE PHARMA - SOCIETE ROQUETTE			01/2004	
10301	MARZIN	Daniel	26/09/2006	LD-AR	LABORATOIRES PIERRE FABRE - LABORATOIRES INNATE PHARMA - SOCIETE ROQUETTE			01/2005	
10301	MARZIN	Daniel	26/09/2006	LD-AR	LABORATOIRES PIERRE FABRE - LABORATOIRES INNATE PHARMA - LABORATOIRE FOURNIER - LABORATOIRES FAUST			01/2006	
10301	MARZIN	Daniel	26/09/2006	RE-DE	LFB - NEGMA - FAUST		rémunération personnelle		
10301	MARZIN	Daniel	26/09/2006	RE-DE	MACO PHARMA - STALLERGENES		rémunération institution		
10301	MARZIN	Daniel	26/09/2006	RE-AUT	RHADIA		R2MUN2RATION INSTITUTION		
10301	MARZIN	Daniel	26/09/2006	CF-INT	LABORATOIRES SERVIER	Paris (colloques interne) toxicologie	rémunération personnelle	11/2005	
10301	MARZIN	Daniel	26/09/2006	CF-AUD	LABORATOIRES SERVIER	Réunion international de mutagenèse - San francisco		09/2005	09/2005
10301	MARZIN	Daniel	26/09/2006	VB		liste des sociétés ou laboratoires ou institutions ayant passé des contrat d'études de mutagenèse avec les laboratoires de toxicologie génétique de l'institut Pasteur de Lille ayan			
10301	MARZIN	Daniel	26/09/2006	VB		liste des sociétés ou laboratoires ou institutions ayant passé des contrat d'études de mutagenèse avec les laboratoires de toxicologie généti		01/2006	
10301	MARZIN	Daniel	26/09/2006	(Autre)	LABORATOIRE SERVIER	Financement d'une thèse (contrat CIFRE) : en cours de discussion			
10301	MARZIN	Daniel	01/06/2006	CF-INT	SERVIER	sujet : Mutagenèse - Paris	aucune rémunération	11/2005	
10301	MARZIN	Daniel	01/06/2006	CF-AUD	SERVIER	Société de mutagenèse environnementale - San Francisco		09/2005	
10301	MARZIN	Daniel	01/06/2006	RE-DE	MACO PHARMA	Expertises précliniques	rémunération versée à une institution		
10301	MARZIN	Daniel	01/06/2006	RE-DE	OTL PHARMA	expertises précliniques	rémunération versée à une institution		
10301	MARZIN	Daniel	01/06/2006	LD-AR	Société ROQUETTE		Rémunération personnelle	01/2002	12/2002
10301	MARZIN	Daniel	01/06/2006	LD-AR	PIERRE FABRE		Rémunération personnelle	01/2003	12/2003
10301	MARZIN	Daniel	01/06/2006	LD-AR	INNATE PHARMA		Rémunération personnelle	01/2003	12/2003
10301	MARZIN	Daniel	01/06/2006	LD-AR	Société ROQUETTE		Rémunération personnelle	01/2003	12/2003
10301	MARZIN	Daniel	01/06/2006	LD-AR	PIERRE FABRE		Rémunération personnelle	01/2004	12/2004
10301	MARZIN	Daniel	01/06/2006	LD-AR	INNATE PHARMA		Rémunération personnelle	01/2004	12/2004
10301	MARZIN	Daniel	01/06/2006	LD-AR	société ROQUETTE		Rémunération personnelle	01/2004	12/2004
10301	MARZIN	Daniel	01/06/2006	LD-AR	PIERRE FABRE		Rémunération personnelle	01/2005	12/2005
10301	MARZIN	Daniel	01/06/2006	LD-AR	INNATE PHARMA		Rémunération personnelle	01/2005	12/2005
10301	MARZIN	Daniel	01/06/2006	LD-AR	Société ROQUETTE		Rémunération personnelle	01/2005	12/2005
10301	MARZIN	Daniel	01/06/2006	LD-AR	PIERRE FABRE		Rémunération personnelle	01/2006	12/2006
10301	MARZIN	Daniel	01/06/2006	LD-AR	INNATE PHARMA		Rémunération personnelle	01/2006	12/2006
10301	MARZIN	Daniel	01/06/2006	LD-AR	LABORATOIRES FOURNIER		Rémunération personnelle	01/2006	12/2006
10301	MARZIN	Daniel	01/06/2006	LD-AR	LABORATOIRES FAUST				
10301	MARZIN	Daniel	03/02/2006	VB	ROQUETTE, FLAMEL TECHNOLOGIE, GOEMAR, INNATE PHARMA, BIOPROJET, PANPHARMA	Activités donnant lieu à un versement au laboratoire de toxicologie dont l'assure la direction à l'Institut Paste		01/2006	

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10301	MARZIN	Daniel	03/02/2006	VB	PIERRE FABRE, MACOPHARMA, STALLERGENES, ADISSEO, SCHWARZ PHARMA, CEVA SANTé ANIMALE, EXPANSCIENCE, ADENOBIO, NUFARM, MERCK GéNéRIQUES, ADéLIE SANTé, EVOLUPHARM, TROPHOS, ESTEVE CHEMICA, CYNALTIS, TRANSPHARM, MERCK-THERAMEX,	Activités donnant lieu à un versement au laboratoire de toxicologie dont j'assure la direction à l'Institut Paste		12/2005	
10301	MARZIN	Daniel	03/02/2006	CF-AUD	SERVIER	congrès mutagenèse EMS (USA)		09/2005	
10301	MARZIN	Daniel	03/02/2006	CF-INT	SERVIER	congrès mutagenèse EMS (USA)	Rémunération personnelle	11/2005	
10301	MARZIN	Daniel	20/04/2005	LD	PIERRE FABRE	Contrat annuel		01/2006	
10301	MARZIN	Daniel	20/04/2005	IP-EC	L'OREAL	Publication		05/2005	
10301	MARZIN	Daniel	20/04/2005	IP-RE	MACOPHARMA	Solutes de perfusion (versé à l'Institut Pasteur)		02/2006	
10301	MARZIN	Daniel	20/04/2005	IP-RE	OTL PHARMA	Hydroxyurée		10/2005	
10301	MARZIN	Daniel	20/04/2005	IP-AC	INNATE PHARMA, BIOLOGIE SERVIER, LFB, NEGMA LERADS, FOURNIER	Développement préclinique	Rémunération personnelle	07/2005	
10301	MARZIN	Daniel	20/04/2005	IP-AUT	L'OREAL	Participation à un congrès		10/2004	
10301	MARZIN	Daniel	20/04/2005	VB	GENFIT, MAYOLY SPINDLER, STALLERGENES, MACOPHARMA, L'OREAL, LFB, ROCHE, PIERRE FABRE, ALPHARMA, PHARMACIE CENTRALE DES ARMEES,	Activités donnant lieu à un versement au laboratoire de toxicologie dont j'assure la direction à l'Institut Paste		06/2005	
10301	MARZIN	Daniel	20/04/2005	VB	SUBSTIPHARM, SYNTH-INNOVE, SANOFI SYNTHELABO, GALDERMA, THEA, ALLERGAN, TROPHOS, JANSSEN-CILAG, PHARMACIE CENTRALE DES HOPITAUX,	Activités donnant lieu à un versement au laboratoire de toxicologie dont j'assure la direction à l'Institut Paste		10/2005	
10301	MARZIN	Daniel	20/04/2005	VB	PROSKELIA, BAXTER, TRANSPHARM/AXISS, ORPHAN, BAUSCH & LOMB, BERKEN, THERAMEX, SERVIER, SOLVAY	Activités donnant lieu à un versement au laboratoire de toxicologie dont j'assure la direction à l'Institut Paste		12/2005	
10301	MARZIN	Daniel	06/07/2004	LD	PIERRE FABRE				
10301	MARZIN	Daniel	06/07/2004	LD	INNATE PHARMA				
10301	MARZIN	Daniel	06/07/2004	IP-RE	BAXTER				
10301	MARZIN	Daniel	06/07/2004	IP-RE	LFB				
10301	MARZIN	Daniel	06/07/2004	IP-AC	NEGMA-LERADS				
10301	MARZIN	Daniel	06/07/2004	IP-AC	FOURNIER				
10301	MARZIN	Daniel	06/07/2004	IP-AC	BIOLOGIE SERVIER				
10301	MARZIN	Daniel	06/07/2004	IP-AC	MAYOLY SPINDLER				
10301	MARZIN	Daniel	06/07/2004	VB	AVENTIS, BAXTER, BIOALLIANCE PHARMA, BIOLOGIE SERVIER, CERIA, CHEMSAGE	Laboratoires ayant effectué des versements au profit de l'Institut Pasteur de Lille			
10301	MARZIN	Daniel	06/07/2004	VB	(suite) CONJUCHEM, FAUST PHARMACEUTICALS, FOURNIER, GALDERMA, GENFIT, JANSEN, INNATE PHARMA, LFB, l'OREAL, MACCO PHARMA	Laboratoires ayant effectué des versements au profit de l'Institut Pasteur de Lille			
10301	MARZIN	Daniel	06/07/2004	VB	(suite) MAYOLY SPINDLER, NEGMA-LERADS, ORPHAN EUROPE, ORFAGEN, OTR3, PHARMACIE CENTRALE DES ARMEES, PHARMACIE CENTRALE HOPITAUX DE PARIS, PIERRE FABRE, SYNTINNETA, THEISS	Laboratoires ayant effectué des versements au profit de l'Institut Pasteur de Lille			
10301	MARZIN	Daniel	15/04/2003	LD	FOURNIER	Préclinique contrat annuel			
10301	MARZIN	Daniel	15/04/2003	LD	PIERRE FABRE	Préclinique contrat annuel			
10301	MARZIN	Daniel	15/04/2003	IP-RE	BAXTER	Préclinique			
10301	MARZIN	Daniel	15/04/2003	IP-RE	LFB	Préclinique			
10301	MARZIN	Daniel	15/04/2003	IP-AC	NEGMA LERADS	Préclinique			
10301	MARZIN	Daniel	15/04/2003	IP-CF	INSTITUT PASTEUR DE LILLE	Formation techniciens Mutagénea			
10301	MARZIN	Daniel	15/04/2003	IP-AUT	GALDERMA	Chef de service de toxicologie - Institut Pasteur de Lille Financement d'une thèse			
10301	MARZIN	Daniel	15/04/2003	VB	Voir doc. Joint	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	LD	LAFON	Consultant Toxicologie			
10301	MARZIN	Daniel	09/05/2000	LD	HOECHST MARION ROUSSEL	Consultant Toxicologie			
10301	MARZIN	Daniel	09/05/2000	IP-AC	NEGMA	Etudes préclinigues			
10301	MARZIN	Daniel	09/05/2000	IP-AC	ORPHAN Europe	Etudes préclinigues			
10301	MARZIN	Daniel	09/05/2000	IP-CF	IFIP	Nouveaux tests de mutagénèse 04/05/2000			
10301	MARZIN	Daniel	09/05/2000	VB	BAILLEUL	Institut Pasteur (Lille)			
10301	MARZIN	Daniel	09/05/2000	VB	Institut Henri BEAUFOUR	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	BESINS-ISCOVESCO	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	BIOPROJET	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	BIOVECTOR Therapeutics	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	BOEHRINGER	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	CIS BIO International	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	DAKOTA PHARM	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	DEXTER	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	Institut de Recherche PIERRE FABRE	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	FOURNIER	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	FRESENIUS	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	GALDERMA	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	Laboratoire Français du Fractionnement et des Biotechnologies	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	MERCK LIPHA	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	NEGMA	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	ORPHAN Europe	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	SCHWARZ PHARMA	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	Institut de Recherches International SERVIER	Institut Pasteur			
10301	MARZIN	Daniel	09/05/2000	VB	SMITHKLINE BEECHAM	Institut Pasteur			
10301	MARZIN	Daniel	01/01/1999	LD	LAFON				
10301	MARZIN	Daniel	01/01/1999	LD	ROUSSEL				
10301	MARZIN	Daniel	01/01/1999	IP-RE	BAYER				
10301	MARZIN	Daniel	01/01/1999	IP-RE	BESINS ISCOVESCO				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10301	MARZIN	Daniel	01/01/1999	IP-RE	IRIS SERVIER				
10301	MARZIN	Daniel	01/01/1999	IP-AC	SCHERING				
10301	MARZIN	Daniel	01/01/1999	IP-AC	NEGMA				
10301	MARZIN	Daniel	01/01/1999	IP-AC	PHARMA 2000				
10301	MARZIN	Daniel	01/01/1999	IP-AC	SKB				
10301	MARZIN	Daniel	01/01/1999	IP-AC	CIRD GALDERMA				
10301	MARZIN	Daniel	01/01/1999	IP-AC	ETHYPHARM				
10301	MARZIN	Daniel	01/01/1999	IP-AC	STALLERGENES				
10301	MARZIN	Daniel	01/01/1999	IP-AC	FOURNIER				
10301	MARZIN	Daniel	01/01/1999	IP-CF	IFIP				
10301	MARZIN	Daniel	01/01/1999	IP-CF	JOUVEINAL				
10301	MARZIN	Daniel	01/01/1999	IP-RE	BAXTER-CLINSEC				
10301	MARZIN	Daniel	01/01/1999	IP-AC	FDM PHARMA				
10301	MARZIN	Daniel	01/01/1999	IP-AC	GLAXO WELLCOME				
10301	MARZIN	Daniel	01/01/1999	IP-CF	ARC				
10301	MARZIN	Daniel	01/01/1999	VB	AGUETTANT SANTE	Pour l'Institut Pasteur de Lille			
10301	MARZIN	Daniel	01/01/1999	VB	Assistance publique des hôpitaux de Paris		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	BAYER PHARMA		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	BEAUFOUR		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	BESINS ISCOVESCO		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	THERAPLIX		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	SERVIER		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	CIBA GEIGY		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	CIRD GALDERMA		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	CIS BIO INTERNATIONAL		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	CLINTEC-BAXTER		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	DAKOTA PHARM		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	FOURNIER		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	GLAXO WELLCOME		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	GRUNENTHAL		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	GUERBET		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	HOUDE		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	INNOTHERA		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	JOUVEINAL		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	LAFON		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	MERAM		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	MERIEUX		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	NEGMA/PHARMA2000		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	NOVO NORDISK		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	PARKE DAVIS		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	PFIZER		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	PIERRE FABRE		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	SANOFI		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	SERB (Société d'Etude et de Recherches Biologiques)		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	SYNTHON		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	THERAMEX		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1999	VB	THERAPLIX		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	LD	Lafon				
10301	MARZIN	Daniel	01/01/1998	LD	Roussel				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	IBS				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Negma				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Pierre Fabre				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Servier				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Innothéra				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Clintec				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Wellcome				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Scherring				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Baxter				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Besins-Iscovesco				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Stallergènes				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	Jouveinal				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	André Rey Consultants				
10301	MARZIN	Daniel	01/01/1998	IP-AUT	IFIP				
10301	MARZIN	Daniel	01/01/1998	VB	Aguettant		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Besin		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Beaufour		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	CERB		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Cermol		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Ciba-Geigy		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Cis Bio		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Clintec		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	CNTS		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Co-Ligne/Nexis		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	CRID		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Dakota Pharm		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Debat/Fournier		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Dexter		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Galderma		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Grunenthal		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Glaxo-Wellcome		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Houdé		Institut Pasteur de Lille		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10301	MARZIN	Daniel	01/01/1998	VB	Guerbet		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	IRI Servier		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Innothéra		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Jouveinal		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Negma		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Lafon		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	LFB		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Meram		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Novo Nordisk		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Parke Davis		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Pfizer		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Pierre Fabre		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Sanofi		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Synthon		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Secma		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Théramex		Institut Pasteur de Lille		
10301	MARZIN	Daniel	01/01/1998	VB	Théraplix		Institut Pasteur de Lille		
65434	MASSARD	Sandrine	13/08/2009	PAR	SERVIER MONDE	RESPONSABLE DU DROIT DES SOCIETES	MARI	09/1997	
60184	MAUBLANT	Jean	30/06/2000	VB	SCHERING CS BIO INTERNATIONAL	Centre Jean SERVIER (CLCC).			
61839	MENTRE	France	01/11/2010	LD-AR	AMGEN	Cours de modélisation PKPD	Rémunération personnelle	01/2010	
61839	MENTRE	France	01/11/2010	VB	SANOFI-AVENTIS	Financement du salaire d'un doctorant dans l'unité de recherche plus crédits de recherche associés	Université Paris Diderot	01/2010	
61839	MENTRE	France	01/11/2010	VB	NOVARTIS	Financement du salaire d'un doctorant dans l'unité de recherche plus crédits de recherche associés	INSERM	01/2007	
61839	MENTRE	France	01/11/2010	VB	SERVIER	Financement du salaire d'un doctorant dans l'unité de recherche plus crédits de recherche associés	INSERM	01/2003	
61839	MENTRE	France	01/11/2010	LD-AR	SERVIER	Consultant en modélisation PKPD pour différents produits	Rémunération personnelle	01/2005	
61839	MENTRE	France	01/11/2010	LD-AR	SANOFI-AVENTIS	Consultant en modélisation PKPD pour différents produits	Rémunération personnelle	01/2005	
61839	MENTRE	France	01/11/2010	LD-AR	NOVARTIS	Consultant en modélisation PKPD pour différents produit	Rémunération personnelle	01/2008	
65606	MESSAS	Emmanuel	27/04/2009	LD-AR	SANOFI	Consulting / thrombose / Plavix	rémunération personnelle	01/2006	12/2008
65606	MESSAS	Emmanuel	27/04/2009	LD-AR	ASTRA ZENECA	Consulting / Athérosclérose / Crestor	rémunération personnelle	01/2008	12/2009
65606	MESSAS	Emmanuel	27/04/2009	LD-AR	SERVIER	Consulting / Angor/ Ivabradine	rémunération personnelle	01/2008	12/2009
65606	MESSAS	Emmanuel	27/04/2009	EC-CO	BAYER	C	Co-investigateur - recrutement patient	01/2008	
65606	MESSAS	Emmanuel	27/04/2009	EC-CO	LILLY		Co-investigateur - recrutement patient	01/2007	12/2008
65606	MESSAS	Emmanuel	27/04/2009	IP-AC	BMS	Présentation EPU / Plavix	rémunération personnelle	01/2008	12/2009
65606	MESSAS	Emmanuel	27/04/2009	CF-INT	BMS	Symposium - SFM Int - Plavix	rémunération personnelle	01/2008	12/2008
65606	MESSAS	Emmanuel	27/04/2009	CF-INT	ASTRA ZENECA	EPU / Association amicale / Crestor	rémunération personnelle	01/2009	12/2009
65606	MESSAS	Emmanuel	27/04/2009	CF-INT	SERVIER	Symposium / TUC / MEDEC/ Ivapradime	rémunération personnelle	01/2009	12/2009
61843	MEYER	Olivier	14/10/2009	EC-CO	ROCHE SHUGAI	Tocilizumab	co-Investigateur	01/2009	
61843	MEYER	Olivier	14/10/2009	EC-CO	WYETH	Enbrel	co-investigateur	01/2009	
61843	MEYER	Olivier	14/10/2009	EC-CO	SERONO	Atacicept	co-investigateur	01/2009	
61843	MEYER	Olivier	14/10/2009	EC-CO	PFIZER	anti-NGF	co-investigateur	01/2010	
61843	MEYER	Olivier	14/10/2009	RE-AUT	COMEDIS APHP	roactemra : admission à l'APHP	aucune rémunération	01/2009	12/2009
61843	MEYER	Olivier	14/10/2009	IP-AC	SERVIER	Safety committee	rémunération personnelle et institution	01/2000	
61843	MEYER	Olivier	14/10/2009	CF-AUD	ROCHE	Congrès de l'ACR (Philadelphie - USA)		01/2009	12/2009
61843	MEYER	Olivier	14/10/2009	CF-AUD	BMS	Congrès EULAR (Amsterdam)		01/2008	12/2008
61843	MEYER	Olivier	14/10/2009	CF-AUD	SERVIER	Congrès Français Rhumatologie Paris		01/2008	12/2008
61843	MEYER	Olivier	14/10/2009	VB	SCHERING PLOUGH	Soutien à la recherche en rhumatologie	ARDIR (loi 1901)	01/2007	
61843	MEYER	Olivier	14/10/2009	VB	ROCHE	Soutien à la recherche en rhumatologie	ARDIR (loi 1901)	01/2007	
61843	MEYER	Olivier	14/10/2009	VB	ABBOTT	Soutien à la recherche en rhumatologie	ARDIR (loi 1901)	01/2007	
61843	MEYER	Olivier	10/12/2008	IP-AC	SANOFI AVENTIS	Groupe de réflexion stratégie thérapeutique de la polyarthrite rhumatoïde (en cours)	rémunération personnelle	01/2007	12/2007
61843	MEYER	Olivier	10/12/2008	CF-AUD	ROCHE	congrès ACR annuel	ARDIR (association de recherche)	01/2007	12/2008
61843	MEYER	Olivier	10/12/2008	VB	WYETH	Acquisition d'un échographe pour le service	ARDIR (association de recherche)	01/2007	12/2008
61843	MEYER	Olivier	10/12/2008	VB	SCHERING PLOUGH	acquisition d'un échographe pour le service	rémunération personnelle	01/2000	
61843	MEYER	Olivier	10/12/2008	LD-AR	SERVIER	Président du comité de surveillance des études PHASE III PROTELOS	co-investigateur		
61843	MEYER	Olivier	10/12/2008	EC-CO	WYETH	ENBREL (en cours)	co-investigateur		
61843	MEYER	Olivier	10/12/2008	EC-CO	ROCHE	RITUXIMAB (en cours)	co-investigateur		
61843	MEYER	Olivier	10/12/2008	EC-CO	ABBOTT	HUMIRA (en cours)	co-investigateur		
61843	MEYER	Olivier	10/12/2008	EC-CO	SERONO	ATACICEPT (en cours)	co-investigateur		
61843	MEYER	Olivier	10/12/2008	EC-CO	ASPREVA	MYCOPHENOLATE (en cours)	co-investigateur		
61843	MEYER	Olivier	10/12/2008	CF-AUD	ROCHE	Congrès ACR annuel		01/2006	12/2006
61843	MEYER	Olivier	10/12/2008	CF-AUD	BMS	Congrès EULAR annuel		01/2007	12/2007
61843	MEYER	Olivier	10/12/2008	CF-AUD	BMS	Congrès EULAR annuel		01/2008	12/2008
61843	MEYER	Olivier	19/01/2008	EC-CO	WYETH	Enbrel (en cours)	co-investigateur		
61843	MEYER	Olivier	19/01/2008	EC-CO	ROCHE	Mabthera (en cours)	co-investigateur		
61843	MEYER	Olivier	19/01/2008	EC-CO	ASPREVA	Cellcept (en cours)	co-investigateur		
61843	MEYER	Olivier	19/01/2008	EC-CO	SERONO	Atacicept (en cours)	co-investigateur		
61843	MEYER	Olivier	19/01/2008	IP-AC	SERVIER	Direction du comité de Safety PROTELOS et gonarthrose (en cours)	rémunération partagée personnelle/institution		
61843	MEYER	Olivier	19/01/2008	CF-AUD	ROCHE	Réunion congrès ACR - USA		11/2007	11/2007
61843	MEYER	Olivier	19/01/2008	CF-AUD	ROCHE	Réunion congrès ACR - USA		11/2006	11/2006
61843	MEYER	Olivier	19/01/2008	CF-AUD	BMS	Réunion congrès EULAR - Barcelone		06/2007	06/2007
61843	MEYER	Olivier	19/01/2008	VB	WYETH	Echographie	ARDIR - Association Loi 1901	09/2007	01/2008
61843	MEYER	Olivier	19/01/2008	VB	SCHERING PLOUGH	Echographie - soutien à la recherche en rhumatologie -	ARDIR - Association Loi 1901	09/2007	01/2008
61843	MEYER	Olivier	19/01/2008	VB	ABBOTT	Echographie	ARDIR - Association Loi 1901	09/2007	01/2008
61843	MEYER	Olivier	19/01/2008	CF-AUD	ROCHE	congrès EULAR - Barcelone - annuel		01/2006	12/2007
61843	MEYER	Olivier	19/01/2008	CF-AUD	SERVIER	Congrès Français SFR - annuel		01/2008	12/2008
61843	MEYER	Olivier	19/01/2008	EC-CO	WYETH	Enbrel	co-Investigateur	01/1998	
61843	MEYER	Olivier	13/02/2007	EC-CO	ABBOTT	Humira	co-investigateur	01/2000	
61843	MEYER	Olivier	13/02/2007	EC-CO	ROCHE	Rituximab	co-investigateur	01/2006	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61843	MEYER	Olivier	13/02/2007	EC-CO	ASPREVA	Celicept	co-investigateur	01/2004	
61843	MEYER	Olivier	13/02/2007	IP-AC	SANOFI-AVENTIS	réflexion (STPR) sur la polyarthrite rhumatoïde	rémunération personnelle	01/2003	
61843	MEYER	Olivier	13/02/2007	IP-AC	SERVIER	Safetee committee	rémunération personnelle / institution	01/1998	
61843	MEYER	Olivier	13/02/2007	CF-AUD	ROCHE	congrès annuel Américain de Rhumatologie (ACR)		11/2006	11/2006
61843	MEYER	Olivier	13/02/2007	CF-AUD	BMS	congrès annuel Européen de Rhumatologie (EULAR)		06/2006	06/2006
61843	MEYER	Olivier	13/02/2007	VB	WYETH	subvention de recherche	Association loi 1901 - A.R.D.I.R.	01/2006	
61843	MEYER	Olivier	13/02/2007	VB	ROCHE	subvention de recherche	Association loi 1901 - A.R.D.I.R.	01/2007	
61843	MEYER	Olivier	23/12/2005	LD-AR	SERVIER	Conseil scientifique ; comité de surveillance ; évènements indésirables	rémunération personnelle / versée à une institution	01/1997	12/2003
61843	MEYER	Olivier	23/12/2005	EC-CO	WYETH	Etudes phase III Enbrel	Co-investigateur		
61843	MEYER	Olivier	23/12/2005	EC-CO	ABBOTT	Etudes Phase III Humira	Co-investigateur		
61843	MEYER	Olivier	23/12/2005	CF-AUD	WYETH, ROCHE, SCHERING PLOUGH, ABBOTT	Congrès Américain de Rhumatologie (ACR)		01/2002	12/2005
61843	MEYER	Olivier	18/01/2005	IP-EC	AVENTIS	Groupe de réflexion sur le traitement de la Polyarthrite Rhumatoïde (GESPR), groupe d'experts hospitalo universitaires			
61843	MEYER	Olivier	18/01/2005	IP-CF	ABBOTT	Compte rendu du congrès annuel ACR, sans aucune rémunération personnelle			
61843	MEYER	Olivier	18/01/2005	VB	WYETH	Essais cliniques phase III			
61843	MEYER	Olivier	18/01/2005	VB	ROCHE	Essais cliniques phase III			
61843	MEYER	Olivier	18/01/2005	VB	ABBOTT	Essais cliniques phase III			
63611	MICALLEF-ROLL	Joëlle	02/02/2010	EC-INV	TROPHOS	Etude de biodisponibilité - TRO19622	Co-investigateur	01/2010	06/2010
63611	MICALLEF-ROLL	Joëlle	02/02/2010	EC-INV	DANONE INSTITUTE	Etude impact risque cardiovasculaire	Co-investigateur	01/2010	12/2012
63611	MICALLEF-ROLL	Joëlle	14/10/2008	EC-CO	SANOFI-AVENTIS	Etude de Phase 1 - SSR103800	CO-INVESTIGATEUR	09/2008	12/2008
63611	MICALLEF-ROLL	Joëlle	14/10/2008	EC-INV	AP-HM	Essai clinique - Pravastatine/zolandronate	Co-investigateur	10/2008	12/2012
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	PIERRE FABRE	Etude Déanol PK	Co-investigateur	01/2007	12/2007
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	PIERRE FABRE	Etude de phase 1 L0014 IN 102 tanganil	Co-investigateur	01/2007	12/2007
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	SANOFI-AVENTIS	Etude phase 1 EXM 10497 Kétamine	Co-investigateur	03/2007	05/2008
63611	MICALLEF-ROLL	Joëlle	01/02/2008	CF-AUD	SERVIER	XIème séminaire de Pharmacologie	auditeur	12/2007	12/2007
63611	MICALLEF-ROLL	Joëlle	01/02/2008	CF-INT	HAS	GT Protocole de sevrage des benzodiazépines chez le sujet agé	Aucune rémunération	02/2007	12/2007
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	LACTALIS	Etude physiologique	Co-investigateur	02/2007	12/2007
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	SANOFI-AVENTIS	Etudes marqueurs physiologiques	Co-investigateur	01/2007	12/2007
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	SANOFI AVENTIS	Etude phase 1 INT 6078	Co-investigateur	01/2007	01/2008
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-CO	SANOFI AVENTIS	Etude phase 1 INT6078	co-investigateur	01/2007	01/2008
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-INV	AP-HM	Etude épidémiologique cas témoins ecstasy	Investigateur Coordonnateur	02/2003	12/2008
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-INV	AP-HM	Essai clinique Acide ascorbique	Investigateur coordonnateur	09/2005	10/2008
63611	MICALLEF-ROLL	Joëlle	01/02/2008	EC-INV	AP-HM	Essai clinique THC	investigateur coordonnateur	03/2003	10/2008
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-INV	AP-HM	Essai clinique acide ascorbique, en cours	Investigateur coordonnateur	12/2004	12/2008
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-INV	AP-HM	Etude épidémiologique cas témoin ECSTASY, en cours	Investigateur coordonnateur	11/2003	12/2008
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	SANOFI-AVENTIS	Etude phase I, Eplivanserine	Co-Investigateur	06/2005	01/2007
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	SANOFI-AVENTIS	Etude phase I, Zolpidem	Co-Investigateur	01/2003	04/2003
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	SANOFI-AVENTIS	Etude phase I M100907, en cours	Co-Investigateur	11/2006	
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	SANOFI-AVENTIS	Etude marqueurs physiologiques, en cours	Co-Investigateur	06/2007	
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	LACTALIS	Etude physiologique, en cours	Co-Investigateur	06/2007	
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	PIERRE-FABRE	Etude Structum	Co-Investigateur	01/2007	04/2007
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	PIERRE-FABRE	Etude phases Tanganil	Co-Investigateur	04/2007	06/2007
63611	MICALLEF-ROLL	Joëlle	10/07/2007	EC-CO	PIERRE-FABRE	Etude Deanol	Co-Investigateur	09/2006	12/2006
63611	MICALLEF-ROLL	Joëlle	10/07/2007	IP-AC	LASER	Etude ISP, cohorte schizophrénie (membre comité scientifique), en cours	Aucune rémunération	01/2004	
63611	MICALLEF-ROLL	Joëlle	10/07/2007	CF-INT	BMS	CD-ROOM, Etiopathogénie des schizophrénies	Rémunération personnelle	01/2004	12/2004
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	MERISTEM	Lipase	co-investigateur	01/2003	12/2004
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	SANOFI	Eplivanserine	co-investigateur	01/2006	
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	UCB	UCB 34714	co-investigateur	01/2003	12/2003
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	UCB	Seletracetam	co-investigateur	01/2005	12/2005
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	SANOFI AVENTIS	PDY 5036 (Zolpidem)	co-investigateur	01/2003	12/2003
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	IMMUNOTECH	réactil	co-investigateur	01/2003	
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	SERVIER	Pinbédil	co-investigateur	01/2003	12/2004
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	BIOPROJET	BF 2649	co-investigateur	01/2004	12/2004
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	SANOFI AVENTIS	Dépakine chronosphère	co-investigateur	01/2004	03/2005
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	AVANTAGE NUTRITION	Lycopène	co-investigateur	01/2004	12/2005
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	GRIMBERG	Diclofenac	co-investigateur	06/2005	09/2005
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	PIERRE FABRE	Deanol (étude PK)	co-investigateur	10/2005	12/2005
63611	MICALLEF-ROLL	Joëlle	08/02/2006	EC-CO	PIERRE FABRE	Deanol (étude II)	co-investigateur	01/2006	
63611	MICALLEF-ROLL	Joëlle	08/02/2006	CF-INT	LUNDBECK	Seropram - études pharmacologiques chez l'animal - Avignon -Beaunes	rémunération personnelle / versée à une institution	10/2003	11/2003
63611	MICALLEF-ROLL	Joëlle	08/02/2006	CF-INT	BMS	Etiopathogénie de la sélizopumenie (sur la schizophrénie)	rémunération personnelle / versée à une institution	11/2004	
63611	MICALLEF-ROLL	Joëlle	08/02/2006	(Autre)	SOCIETE LASER	Pr ABENHAIM - membre du comité scientifique, cohorte schizophrénie (membre comité scientifique), en cours		10/2005	
63611	MICALLEF-ROLL	Joëlle	12/05/2005	IP-EC	AVENTIS	Essais phase II			
63611	MICALLEF-ROLL	Joëlle	12/05/2005	IP-CF	LUNDBECK	Colloque, année 2003			
63611	MICALLEF-ROLL	Joëlle	12/05/2005	VB	UCB				
63611	MICALLEF-ROLL	Joëlle	12/05/2005	VB	BIOPROJET	Essai de phase II (AP-HM)			
63611	MICALLEF-ROLL	Joëlle	12/05/2005	VB	IMMUNOTECH	Essai de phase I (AP-HM)			
63611	MICALLEF-ROLL	Joëlle	29/03/2005	IP-EC	SANOFI - SYNTHELABO - PIERRE FABRE				
63611	MICALLEF-ROLL	Joëlle	29/03/2005	IP-EC	IMMUNOTECH - BIO PROJET - UCB - AVENTIS				
63611	MICALLEF-ROLL	Joëlle	29/03/2005	IP-AC	LUNDBECK	Séropram : études animales			
65671	MICHEL	Laurence	31/03/2009	LD-AR	INSERM	Expert en dermatologie, Institut thématique IHP, Immunologie hématologie dermatologie	aucune rémunération	01/2008	
65671	MICHEL	Laurence	31/03/2009	LD-AR	MERCK	Expert en dermatologie	rémunération institution	01/2007	
65671	MICHEL	Laurence	31/03/2009	EC-INV	UCB PHARMA / INSERM	RBM 05 : étude propriétés anti-cytokiniques, anti-histaminique chez 45 patients allergiques	investigateur coordonnateur	01/2005	12/2008
65671	MICHEL	Laurence	31/03/2009	EC-INV	SERONO	Pré-clinique : étude inhibiteur IKK2 sur voie NFKB de lymphocytes timoraux (ilc)	investigateur expérimentateur principal	01/2004	12/2007
65671	MICHEL	Laurence	31/03/2009	EC-INV	MERCK	Pré-clinique : études des isoformes I2-17 dans le psoriasis	investigateur expérimentateur principal	01/2007	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
65671	MICHEL	Laurence	31/03/2009	EC-CO	GENZYME	Etude des effets Biologiques du campath ex vivo dans les LCT	collaborateur expérimentateur au laboratoire	01/2005	12/2008
65671	MICHEL	Laurence	31/03/2009	EC-CO	ANR	élude d'anticoprs anti-lag 3 neutralisants dans le mélanome / le psoriasis (biotech triebel) ex vivo	partenaire projet ANR (3 partenaires) : co-expérimentateur	01/2006	12/2009
65671	MICHEL	Laurence	31/03/2009	RE-AUT	MERCK	Expertise dossier IL-17 recherche	rémunération personnelle et institution	01/2008	12/2008
65671	MICHEL	Laurence	31/03/2009	IP-AC	MERCK	Analyse données dermatologiques programme IL17 isoformes	rémunération personnelle et institution	01/2008	12/2008
65671	MICHEL	Laurence	31/03/2009	CF-INT	LIGAUD PHARM	lymphoma CTCL congress Berlin, international symposium on the Biology and immunology of cutaneas lym	rémunération institution	01/2008	01/2008
65671	MICHEL	Laurence	31/03/2009	CF-INT	SHERING PLOUGH R	World cibgress buenos aeres octobre	rémunération institution	10/2007	10/2007
65671	MICHEL	Laurence	31/03/2009	CF-AUD	SPANDIDOS PUB	Crète : spandidos publication		05/2008	05/2008
65671	MICHEL	Laurence	31/03/2009	IP-AUT	INCA	Projet développement inhibiteurs (peptides NEMO) voie NFKB dans les LTC (interaction avec Servier et Pasteur)		01/2006	12/2009
62209	MILANO	Gérard	14/09/2010	LD-AR	AMGEN	Vectibix	Rémunération personnelle	01/2006	12/2008
62209	MILANO	Gérard	14/09/2010	LD-AR	MERCK SERONO	Cetuximal	Rémunération personnelle	01/2006	12/2007
62209	MILANO	Gérard	14/09/2010	LD-AR	SANOFI AVENTIS	Taxotere	Rémunération personnelle	01/2007	12/2008
62209	MILANO	Gérard	14/09/2010	LD-AR	BIOALLIANCE	Doxorubicine - transdrug	Rémunération personnelle	01/2007	12/2008
62209	MILANO	Gérard	14/09/2010	EC-INV	ASTRA ZENECA	Etudes précliniques de laboratoire - Zactima	Expérimentateur principal	01/2006	12/2009
62209	MILANO	Gérard	14/09/2010	EC-INV	WYETH	Etudes précliniques de laboratoire - Torisel	Expérimentateur principal	01/2006	12/2009
62209	MILANO	Gérard	14/09/2010	CF-INT	JANSSEN	EPO et protection cellulaire - Troyes	Rémunération personnelle	01/2007	
62209	MILANO	Gérard	14/09/2010	CF-INT	GSK	Récepteurs Erb B et cancer du sein - 4ème congrès de gynécologie obstétrique - Nice Côte d'Azur	Rémunération personnelle	01/2007	
62209	MILANO	Gérard	14/09/2010	CF-INT	LILLY	Gemcitabine et Pemetroxed, des alliés naturels - Strasbourg - Partage d'expérience médecins et pharmacien	Rémunération personnelle	01/2007	
62209	MILANO	Gérard	14/09/2010	CF-INT	PFIZER	Thérapies multipistes - "Ouvrir des voies d'avenir"	Rémunération personnelle	01/2007	
62209	MILANO	Gérard	14/09/2010	CF-INT	JANSSEN	Pharmacogénétique des traitements anticancéreux - 4èmes rencontres Hématologie Oncologie - Biarritz	Rémunération personnelle	01/2008	
62209	MILANO	Gérard	14/09/2010	CF-INT	AMGEN	Panitumumab : anticorps 100% humain - Symposium Vectibix Paris	Rémunération personnelle	01/2008	
62209	MILANO	Gérard	27/06/2008	CF-INT	WYETH	Sympo Marseille	Rémunération personnelle	04/2008	
62209	MILANO	Gérard	27/06/2008	CF-INT	MERCK	JFPD-Paris	Rémunération personnelle	03/2008	
62209	MILANO	Gérard	27/06/2008	CF-INT	MERCK	biennales de Monaco	Rémunération personnelle	01/2008	
62209	MILANO	Gérard	27/06/2008	IP-AC	SANOFI-AVENTIS	board TPF	Rémunération personnelle	04/2008	
62209	MILANO	Gérard	27/06/2008	IP-AC	MERCK	board GETCO	Rémunération personnelle	01/2008	
62209	MILANO	Gérard	27/06/2008	IP-AC	AMGEN	boards kras et vectibix	Rémunération personnelle	01/2008	
62209	MILANO	Gérard	29/12/2000	IP-EC	SANOFI	Etudes expérimentales in vitro			
62209	MILANO	Gérard	29/12/2000	IP-EC	WYETH LEDERLE	Etudes de compatibilité in vitro			
62209	MILANO	Gérard	29/12/2000	IP-EC	BMS	Dosages enzymatiques intralumoraux			
62209	MILANO	Gérard	29/12/2000	IP-RE	SERVIER	Bilan sur fotémustine			
62209	MILANO	Gérard	29/12/2000	IP-CF	ROCHE	Conférence, congrès sur traitement anticancéreux - Paris (02/2000) - Symposium Xeloda®			
62134	MILLET	Bruno	31/03/2009	PAR	SERVIER	Directeur filière Italie	frère	01/1996	
62134	MILLET	Bruno	31/03/2009	PAR	JANSSEN	médecin régional	conjoint	11/2005	
62134	MILLET	Bruno	31/03/2009	CF-INT	BMS, JANSSEN, LILLY, LUNDBECK, ARDIX	5 à 6 fois / an	rémunération partagée personnelle/institution		
62134	MILLET	Bruno	31/03/2009	EC-INV	BMS	Aripiprazole			
62134	MILLET	Bruno	19/06/2006	LD-AR	BMS	Groupe d'expert PREST	rémunération personnelle	01/2005	12/2006
62134	MILLET	Bruno	19/06/2006	EC-INV	ORGANON-PFIZER	Azénapine	investigateur coordonnateur	11/2005	12/2006
62134	MILLET	Bruno	19/06/2006	EC-INV	BMS	Aripiprazole			
62134	MILLET	Bruno	19/06/2006	RE-DE		sauf pour l'Agence de contrôle de la publicité			
62134	MILLET	Bruno	19/06/2006	CF-INT	BMS, JANSSEN, LILLY, LUNDBECK, ARDIX	5 à 6 fois / an	rémunération partagée personnelle/institution		
62134	MILLET	Bruno	19/06/2006	CF-AUD	ARDIX	Nice - Stablon		09/2005	09/2005
62134	MILLET	Bruno	19/06/2006	VB	Société Neuro-Psychiatrie de l'Ouest (SNPO)	Congrès novembre 2005	SNPO	11/2005	11/2006
62134	MILLET	Bruno	19/06/2006	PAR	JANSSEN	médecin régional	conjoint	11/2005	
62134	MILLET	Bruno	19/06/2006	PAR	SERVIER	Directeur filière Italie	frère	01/1996	
62134	MILLET	Bruno	23/02/2004	IP-EC	LUNDBECK	Bifeprunox			
62134	MILLET	Bruno	23/02/2004	IP-EC	ORGANON	Essais cliniques Azénapine			
62134	MILLET	Bruno	23/02/2004	IP-CF		Pour tous les laboratoires impliqués dans le SNC			
62134	MILLET	Bruno	23/02/2004	VB	BMS	Club Sainte-Anne	Une subvention par le laboratoire BMS		
62134	MILLET	Bruno	24/04/2002	IP-EC		Essai clinique investigateur MK-OP69 - Protocole 065.00			
62134	MILLET	Bruno	24/04/2002	PAR	SERVIER	Frère			
62134	MILLET	Bruno	24/04/2002	PAR	PFIZER	Conjoint			
62134	MILLET	Bruno	24/04/2002	IP-EC		Essai clinique investigateur CL3296027			
65435	MITTON	David	24/06/2009	EC-INV	BIOBANK	Etudes non cliniques (biomécanique)	expérimentateur principal	01/2005	12/2009
65435	MITTON	David	24/06/2009	EC-INV	MEDIMAPS	Etude non clinique (biomécanique)	expérimentateur principal	01/2006	12/2009
65435	MITTON	David	24/06/2009	EC-CO	BIOSPACE	Etude non clinique (recherche en modélisation géométrique) / système EOS	expérimentateur non principal	01/2006	12/2008
65435	MITTON	David	24/06/2009	RE-AUT	DEVOLIM	ANR TecSan	aucune rémunération	01/2007	12/2007
65435	MITTON	David	24/06/2009	RE-AUT	SMAIO	ANR TecSan	aucune rémunération	01/2009	12/2009
65435	MITTON	David	24/06/2009	CF-INT	SERVIER	Séminaire qualité osseuse / composition de l'os cortical et implications biomécaniques / aucun produit - Pari	rémunération personnelle	01/2007	12/2007
65435	MITTON	David	24/06/2009	CF-AUD	SERVIER	Séminaire qualité osseuse / contrainte mécanique et qualité osseuse : de la cellule à l'organe - aucun produit - Paris		01/2009	12/2009
65435	MITTON	David	24/06/2009	IP-AUT	BIOSPACE	Co-inventeur de brevet associé au système EOS		01/2000	12/2008
65607	MODINE	Thomas	25/03/2009	EC-INV	CHRU LILLE	EPICAR	investigateur coordonnateur	09/2005	09/2008
65607	MODINE	Thomas	25/03/2009	EC-INV	CHRU LILLE	COGCAR	investigateur principal	02/2008	
65607	MODINE	Thomas	25/03/2009	EC-CO	CHRU LILLE	CABAT	co-investigateur	01/2004	12/2006
65607	MODINE	Thomas	25/03/2009	CF-AUD	ST JUDE MEDICAL	PCR 2008 - Barcelone		05/2008	05/2008
65607	MODINE	Thomas	25/03/2009	CF-AUD	SERVIER MEDICAL	SFC Paris		01/2009	01/2009
61727	MONTALESCOT	Gilles	14/08/2009	LD-AR	BMS - ELI LILLY - SANOFI-AVENTIS - THE MEDICINES COMPANY - CORDIS - SCHERING-PLOUGH - GLAXOSMITHKLINE - MERCK SHARPE & DOHME	Conseil - Enseignement Post-Universitaire	Rémunération personnelle	01/2008	
61727	MONTALESCOT	Gilles	12/08/2009	VB	SANOFI-AVENTIS - ELI LILLY	Bourses de recherche	ACTION - AIDERAT - NEB - INSERM - AP-HP	01/2008	
61727	MONTALESCOT	Gilles	12/08/2009	EC-INV	SANOFI-AVENTIS - BMS - ELI LILLY - SERVIER	Essais cliniques/enoxaparin/clopidogrel/prasugrel/AntiX/TRA/neseritide	Investigateur coordinateur	07/2008	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61727	MONTALESCOT	Gilles	12/08/2009	LD-AR	BMS - SANOFI-AVENTIS - ELI LILLY - GUERBET MEDICAL - MEDTRONIC - BOSTON SCIENTIFIC - CORDIS - STAGO - CENTOCOR - FONDATION DE FRANCE - INSERM - FED FRANCAISE DE CARDIOLOGIE - SOCIETE FRANCAISE DE CARDIOLOGIE	Recherche	Rémunération institution	01/2008	12/2009
61727	MONTALESCOT	Gilles	23/05/2008	LD-AR	SANOFI - BMS -ELI LILLY - MEDICINES COMPANY - GSK - MSD - SCHERING- DAIICHI	Consultant - orateur dans symposium (en cours)	rèmunération personnelle	01/2008	12/2009
61727	MONTALESCOT	Gilles	23/05/2008	EC-INV	SANOFI AVENTIS - BMS - LILLY - STAGO	recherche clinique (en cours)	investigateur ou coordinateur		
61727	MONTALESCOT	Gilles	23/05/2008	EC-CO		Multiples études cliniques de laboratoire ou société de service (en cours)	investigateur		
61727	MONTALESCOT	Gilles	23/05/2008	CF-INT	SANOFI - BMS - LILLY - SCHERING - GSK - MSD - DAIICHI	Symposium - orateur	rémunération personnelle		
61727	MONTALESCOT	Gilles	23/05/2008	VB	SANOFI - BMS - LILLY - GUERBET - GSK - MSD - DAIICHI - MEDTRONIC - CORDIS- STAGO - BOSTON	Recherche (en cours)	INSERM U856 Association ACTION - Association AIDERAT		
10312	MONTASTRUC	Jean-Louis	01/12/2010	Néant					
10312	MONTASTRUC	Jean-Louis	08/02/2010	Néant					
10312	MONTASTRUC	Jean-Louis	16/02/2009	EC-CO	THERABEL LABORATOIRE ET HELSSIN (SUISSE)	Etude pharmacoépidémiologique des effets indésirables hépatiques, cutanés, digestifs, cardiovasculaires et	co-investigateur	06/2007	11/2007
10312	MONTASTRUC	Jean-Louis	12/09/2008	Néant					
10312	MONTASTRUC	Jean-Louis	01/10/2007	EC-INV	THERABEL	Etude sur les effets indésirables des AINS	Rémunération versée à une Association loi 1901	07/2007	09/2007
10312	MONTASTRUC	Jean-Louis	12/06/2007	PAR	PIERRE FABRE	Fille : service jundique (CDI)		05/2007	03/2008
10312	MONTASTRUC	Jean-Louis	12/06/2007	IP-EC	THERABEL	Etude de pharmacoépidémiologie concernant le risque comparé de l'atteinte hépatique avec les différents AINS			
10312	MONTASTRUC	Jean-Louis	02/01/2007	PAR	PIERRE FABRE	Stage dans le cadre de la thèse de droit à l'université des sciences sociales de Toulouse (contrat CIFRE)	Fille	05/2004	05/2007
10312	MONTASTRUC	Jean-Louis	18/01/2006	IP-AC	PIERRE FABRE MEDICAMENT	Avis de pharmacovigilance sur un produit en développement	rémunération versée à une institution	07/2005	09/2005
10312	MONTASTRUC	Jean-Louis	18/01/2006	IP-AC	NOVARTIS SANTE FAMILIALE	Expertise sur les effets indésirables du Diclofenac	rémunération versée à une institution	01/2005	12/2005
10312	MONTASTRUC	Jean-Louis	18/01/2006	PAR	PIERRE FABRE	Stage dans le cadre de la thèse de droit à l'université des sciences sociales de Toulouse (contrat CIFRE)	Fille	05/2004	05/2007
10312	MONTASTRUC	Jean-Louis	15/09/2005	IP-AC	NOVARTIS SANTE FAMILIALE	Revue des effets indésirables hépatiques du Diclofenac	rémunération versée à une institution	01/2005	07/2005
10312	MONTASTRUC	Jean-Louis	15/09/2005	IP-AC	PIERRE FABRE MEDICAMENT	Revue de pharmacovigilance d'un médicament en développement clinique	rémunération versée à une institution	07/2005	07/2005
10312	MONTASTRUC	Jean-Louis	15/09/2005	PAR	PIERRE FABRE MEDICAMENT	Fille étudiant en thèse d'université de droit. Contrat CIFRE (mi-temps université et mi-temps industrie) le financement vient en grande majori		05/2004	05/2007
10312	MONTASTRUC	Jean-Louis	24/11/2004	VB		Membre du conseil scientifique de l'étude EULEV (Leviracetam Keppra) depuis fin 2004			
10312	MONTASTRUC	Jean-Louis	24/11/2004	PAR	UNIVERSITE DES SCIENCES SOCIALES	Fille faisant une thèse de droit depuis mai 2004 - mi temps			
10312	MONTASTRUC	Jean-Louis	24/11/2004	PAR	PIERRE FABRE	Fille faisant une thèse de droit depuis mai 2004 - mi temps, dans le cadre d'une bourse CIFRE			
10312	MONTASTRUC	Jean-Louis	14/09/2004	IP-CF	SANOFI	Formation obésité, octobre 2004			
10312	MONTASTRUC	Jean-Louis	14/09/2004	PAR		Fille réalisant une these de droit dans le cadre d'une bourse Sivke, contrat université des sciences sociales de toulouse + le laboratoire Pierre Fabre			
10312	MONTASTRUC	Jean-Louis	10/03/2004	Néant					
10312	MONTASTRUC	Jean-Louis	27/11/2003	IP-RE	PIERRE FABRE	Effets indésirables milnacipram			
10312	MONTASTRUC	Jean-Louis	27/11/2003	IP-RE	UCB	Rapport Nootropyl pour la commission de la transparence - 2003			
10312	MONTASTRUC	Jean-Louis	21/10/2002	VB	SANOFI	Rapport d'expertise en 2002			
10312	MONTASTRUC	Jean-Louis	21/10/2002	VB	MERABEL	Essai clinique			
10312	MONTASTRUC	Jean-Louis	27/09/2001	VB	LILLY	Essai de Pharmacologie clinique - Association Régionale pour le développement de la Recherche Biomédicale			
10312	MONTASTRUC	Jean-Louis	27/09/2001	VB	TEVA	Essai de Pharmacologie clinique - Association Régionale pour le développement de la Recherche Biomédicale			
10312	MONTASTRUC	Jean-Louis	15/01/2000	VB	NOVARTIS ; ROCHE ; SERVIER ; SKB ; LILLY ; THERAPHARM	Participation à essais cliniques : versements à Association			
10312	MONTASTRUC	Jean-Louis	15/01/2000	VB	NOVARTIS ; ROCHE ; SERVIER ; SKB ; LILLY ; THERAPHARM	Interventions dans colloques : Association			
10312	MONTASTRUC	Jean-Louis	01/01/2000	VB	NOVARTIS	Essais cliniques donnant lieu à versement à association loi 1901			
10312	MONTASTRUC	Jean-Louis	01/01/2000	VB	ROCHE	Essais cliniques donnant lieu à versement à association loi 1901			
10312	MONTASTRUC	Jean-Louis	01/01/2000	VB	SERVIER	Essais cliniques donnant lieu à versement à association loi 1901			
10312	MONTASTRUC	Jean-Louis	01/01/1999	IP-EC	NOVARTIS				
10312	MONTASTRUC	Jean-Louis	01/01/1999	VB	ROCHE	Versé au budget de l'Association Régionale pour la Recherche Biomédicale			
10312	MONTASTRUC	Jean-Louis	01/01/1998	IP-AUT	Sandoz				
10312	MONTASTRUC	Jean-Louis	01/01/1998	VB	Sandoz		Essais cliniques et suivi de pharmacoépidémiologie		
10312	MONTASTRUC	Jean-Louis	01/01/1998	VB	Roche		Essais cliniques et suivi de pharmacoépidémiologie pour		
10313	MOORE	Nicholas	07/11/2008	CF-INT	LUNDBECK	Prague WPA/Berlin investigator's meeting/ Barcemone ECNP/ présentation des résultats de SCOPDD	Rémunération personnelle	01/2008	12/2008
10313	MOORE	Nicholas	07/11/2008	IP-AC	OTSUKA US	Participation à un comité de sécurité	Rémunération personnelle	01/2003	12/2007
10313	MOORE	Nicholas	07/11/2008	IP-AC	PROCTOR ET GAMBLE US	participation à un comité de sécurité	Rémunération personnelle	01/2004	
10313	MOORE	Nicholas	07/11/2008	RE-AUT	RECKITT-BENCISER	analyse des données de sécurité/Ibuprofene-paracetamol	Rémunération personnelle	07/2008	10/2008
10313	MOORE	Nicholas	07/11/2008	EC-CO	LUNDBECK	etude Scop; responsable comité de sécurité	responsable comité de sécurité	01/2002	12/2008
10313	MOORE	Nicholas	08/06/2004	IP-EC	TOUS LABORATOIRES				
10313	MOORE	Nicholas	08/06/2004	RE-AUT	BOOTS	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-DE	PFIZER	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-DE	TAKEDA	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-AUT	BAXTER	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-AUT	ASTRA ZENECA	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-DE	VIATRIS	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-AUT	HELSINN	Expertises			
10313	MOORE	Nicholas	08/06/2004	RE-AUT	DIVERS LABORATOIRES	Expertises	Idem Laboratoires cités pour les rapports d'expertise		
10313	MOORE	Nicholas	08/06/2004	IP-AC	TOUS LABORATOIRES	Sécurité des médicaments, pharmacoépidémiologie ...			
10313	MOORE	Nicholas	08/06/2004	CF-INT	BOOTS	Sécurité des médicaments, pharmacoépidémiologie ...			
10313	MOORE	Nicholas	08/06/2004	CF-INT	PFIZER	Sécurité des médicaments, pharmacoépidémiologie ...			
10313	MOORE	Nicholas	08/06/2004	CF-INT	ASTRA ZENECA	Sécurité des médicaments, pharmacoépidémiologie ...			
10313	MOORE	Nicholas	08/06/2004	CF-INT	SELON DEMANDE	Sécurité des médicaments, pharmacoépidémiologie ...			
10313	MOORE	Nicholas	08/06/2004	VB	MERCK	Essais cliniques, études épidémiologiques			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10313	MOORE	Nicholas	08/06/2004	VB	PFIZER	Essais cliniques, études épidémiologiques			
10313	MOORE	Nicholas	08/06/2004	VB	BOOTS	Essais cliniques, études épidémiologiques			
10313	MOORE	Nicholas	08/06/2004	VB	VIATRIS	Essais cliniques, études épidémiologiques			
10313	MOORE	Nicholas	08/06/2004	VB	DIVERS	Essais cliniques, études épidémiologiques			
10313	MOORE	Nicholas	01/01/1999	IP-EC	BOOTS HEALTHCARE				
10313	MOORE	Nicholas	01/01/1999	IP-EC	IPSOR				
10313	MOORE	Nicholas	01/01/1999	IP-EC	SERVIER				
10313	MOORE	Nicholas	01/01/1999	IP-RE	BAYER				
10313	MOORE	Nicholas	01/01/1999	IP-RE	RHONE POULENC RORER				
10313	MOORE	Nicholas	01/01/1999	IP-RE	BOOTS HEALTHCARE				
10313	MOORE	Nicholas	01/01/1999	IP-AC	LIPHA				
10313	MOORE	Nicholas	01/01/1999	IP-AC	BAYER				
10313	MOORE	Nicholas	01/01/1999	IP-AC	RHONE POULENC RORER				
10313	MOORE	Nicholas	01/01/1999	IP-AC	BOOTS HEALTHCARE				
10313	MOORE	Nicholas	01/01/1999	IP-CF	BAYER				
10313	MOORE	Nicholas	01/01/1999	IP-CF	RHONE POULENC RORER				
10313	MOORE	Nicholas	01/01/1999	IP-EC	MERCK				
10313	MOORE	Nicholas	01/01/1999	VB		Taxe professionnelle : pas en 1997.			
10313	MOORE	Nicholas	01/01/1998	IP-AUT	Synthélabo				
10313	MOORE	Nicholas	01/01/1998	IP-AUT	Servier				
10313	MOORE	Nicholas	01/01/1998	IP-AUT	R.P.R				
10313	MOORE	Nicholas	01/01/1998	IP-AUT	Boots				
10313	MOORE	Nicholas	01/01/1998	IP-AUT	Bayer				
10313	MOORE	Nicholas	01/01/1998	VB	Byk		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
10313	MOORE	Nicholas	01/01/1998	VB	Synthélabo		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
10313	MOORE	Nicholas	01/01/1998	VB	Sandoz		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
10313	MOORE	Nicholas	01/01/1998	VB	Servier		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
10313	MOORE	Nicholas	01/01/1998	VB	Knoll		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
10313	MOORE	Nicholas	01/01/1998	VB	Sanofi		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
10313	MOORE	Nicholas	01/01/1998	VB	R.P.R		Essais cliniques versés à Naturalia, Biologia ou Arepehn		
61848	MOULIN	Philippe	30/12/2010	VB	SANOFI	bourse de recherche	ezus lyon 1	01/2009	12/2010
61848	MOULIN	Philippe	30/12/2010	CF-AUD	SERVIER	EASD			
61848	MOULIN	Philippe	30/12/2010	CF-AUD	LILLY/MSD	EASD			
61848	MOULIN	Philippe	30/12/2010	CF-AUD	MSD	ALFEDIAM-SFD			
61848	MOULIN	Philippe	30/12/2010	CF-AUD	ASTRA ZENECA /MSD/ASTRA ZENECA MSD /	AHA			
61848	MOULIN	Philippe	30/12/2010	CF-INT	NOVARTIS	epu regional lescol aliskiren	Rémunération personnelle	01/2009	01/2009
61848	MOULIN	Philippe	30/12/2010	IP-AC	LILLY	developpement inhibiteur CETP	Rémunération personnelle	01/2010	12/2010
61848	MOULIN	Philippe	30/12/2010	IP-AC	NOVO NORDISK	developpement liraglutide	Rémunération personnelle	01/2010	12/2010
61848	MOULIN	Philippe	30/12/2010	RE-DE	SERVIER	resultat essai benfluorex versus placebo transprence	Rémunération institution	01/2005	12/2006
61848	MOULIN	Philippe	30/12/2010	LD-AR	ASTRA ZENECA BMS	advisory board saxagliptine	Rémunération personnelle	01/2009	12/2010
61848	MOULIN	Philippe	30/12/2010	LD-AR	SANOFI REGENREON	advisory board	Rémunération institution	06/2010	06/2010
61848	MOULIN	Philippe	30/12/2010	EC-INV	LILLY	invest registre HYPOCS	co invest	01/2005	
61848	MOULIN	Philippe	30/12/2010	EC-INV	BMS-ASTRA	invest essai SAVOR saxa vs placebo□□remunération exclusivement via institution ezus LYON1	co invest	01/2010	
61848	MOULIN	Philippe	30/12/2010	EC-INV	MSD	invest essai TECOS januvia vs placebo□□remunération exclusivement via institution ezus LYON1	co invest	01/2010	
61848	MOULIN	Philippe	30/12/2010	EC-INV	GSK	invest essai STABILITY dapladib vs placebo□□remunération exclusivement via institution ezus LYON1	co invest	01/2010	
61848	MOULIN	Philippe	30/12/2010	EC-INV	SERVIER	benfluorex coordination scientifique internationale regulate trial □□remunération exclusivement via institution	investigateur principal	01/2005	12/2010
61848	MOULIN	Philippe	30/12/2010	LD-AR	AMT	advisoru board glybera	Rémunération institution	07/2010	
61848	MOULIN	Philippe	30/12/2010	LD-AR	GSK	advisory board darapladib	Rémunération personnelle	01/2010	
61848	MOULIN	Philippe	30/12/2010	LD-AR	ASTRA ZENECA	advisory board rosuvastatine	Rémunération institution	01/2005	01/2010
61848	MOULIN	Philippe	30/12/2010	LD-ODE	NéANT				
61848	MOULIN	Philippe	30/12/2010	IF	NéANT		<5000 € ou <5% du capital		
61848	MOULIN	Philippe	25/06/2010	Néant					
61848	MOULIN	Philippe	01/07/2009	LD-AR	ASTRAZENECA	Advisory board Rosuvastatine	rémunération institution	01/2004	12/2007
61848	MOULIN	Philippe	01/07/2009	EC-INV	SERVIER	Essai clinique, Regulate, Benfluorex vs Pia - essai international	investigateur principal - rémunération institution	01/2004	12/2010
61848	MOULIN	Philippe	01/07/2009	EC-CO	SANOFI	Acomplia	co-investigateur	01/2008	12/2009
61848	MOULIN	Philippe	01/07/2009	EC-CO	SANOFI	EFC 10841	co-investigateur	01/2008	12/2009
61848	MOULIN	Philippe	01/07/2009	EC-CO	GSK	Darapladib	co-investigateur	01/2005	12/2015
61848	MOULIN	Philippe	01/07/2009	RE-DE	SERVIER	Benfluorex AMM	rémunération institution	01/2007	
61848	MOULIN	Philippe	01/07/2009	IP-AC	ASTRAZENECA	Board Rosuvastatine - Etude Jupiter	rémunération institution	01/2009	
61848	MOULIN	Philippe	01/07/2009	IP-AC	BMS - ASTRAZENECA	Board scientifique	rémunération personnelle/institution	01/2009	
61848	MOULIN	Philippe	01/07/2009	CF-INT	ASTRAZENECA	Symposium avancées cardio	rémunération institution	01/2008	12/2008
61848	MOULIN	Philippe	01/07/2009	CF-INT	GSK	EPU	rémunération institution	01/2008	12/2008
61848	MOULIN	Philippe	01/07/2009	CF-INT	GSK	EPU	rémunération institution	01/2009	12/2009
61848	MOULIN	Philippe	01/07/2009	CF-AUD	PFIZER	ALFEDIAM		01/2009	12/2009
61848	MOULIN	Philippe	01/07/2009	CF-AUD	SERVIER	EASD		01/2008	12/2008
61848	MOULIN	Philippe	01/07/2009	CF-AUD	MSD	AHA		01/2008	12/2008

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61848	MOULIN	Philippe	01/07/2009	CF-AUD	FOURNIER	AHA		01/2009	12/2009
61848	MOULIN	Philippe	01/07/2009	CF-AUD	ASTRA ZENECA	AHA		01/2007	12/2007
61848	MOULIN	Philippe	01/07/2009	CF-AUD	NOVARTIS	EASD		01/2007	12/2007
61848	MOULIN	Philippe	01/07/2009	VB	SANOFI	Bourse de recherche	Université Lyon 1 EZUS	01/2009	
61848	MOULIN	Philippe	12/03/2009	LD-AR	ASTRA ZENECA	consulting-advisory board, rosuvastatine	rémunération institution	01/2004	12/2007
61848	MOULIN	Philippe	12/03/2009	LD-AR	ASTRA ZENECA	consulting-advisory board / saxagliptine	rémunération institution	01/2008	
61848	MOULIN	Philippe	12/03/2009	EC-INV	SERVIER IRIS	essais régulate en cours . Benfluorex	investigateur principal	01/2004	
61848	MOULIN	Philippe	12/03/2009	EC-CO	MSD	sitagliptine	co-investigateur	01/2007	12/2008
61848	MOULIN	Philippe	12/03/2009	EC-CO	MSD	SITAGLIPINE	co investigateur	01/2007	12/2008
61848	MOULIN	Philippe	12/03/2009	EC-CO	SANOFI	rimonabant	co-investigateur	01/2006	12/2008
61848	MOULIN	Philippe	12/03/2009	EC-CO	SANOFI	EFC 10 841	co-investigateur	01/2008	12/2008
61848	MOULIN	Philippe	12/03/2009	EC-CO	GSK	LPL 100 GOI	co-investigateur	01/2009	12/2009
61848	MOULIN	Philippe	12/03/2009	EC-CO	NOVO	NN 2116 liraglutide	co-investigateur	01/2009	12/2009
61848	MOULIN	Philippe	12/03/2009	EC-CO	SERVIER	S 18 886	co-investigateur	01/2004	12/2008
61848	MOULIN	Philippe	12/03/2009	IP-RE	SERVIER IRIS	AMM transparence / benfluorex	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	IP-AC	ASTRA ZENECA	reflexion autour Jupiter : étude Cester	rémunération institution	01/2008	
61848	MOULIN	Philippe	12/03/2009	CF-INT	GSK	EPU régionaux et radicaux	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	CF-INT	TAKEDA	EPU régionaux et radicaux	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	CF-INT	MSD	EPU régionaux et radicaux	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	CF-INT	TAKEDA	EPU régionaux et radicaux	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	CF-INT	ASTRA ZENECA	EPU régionaux et radicaux	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	CF-INT	PFIZER	EPU régionaux et radicaux	rémunération institution		
61848	MOULIN	Philippe	12/03/2009	CF-AUD	MSD	AHA		01/2008	
61848	MOULIN	Philippe	12/03/2009	CF-AUD	SERVIER	EASD		01/2008	
61848	MOULIN	Philippe	12/03/2009	VB	CF SUPRA		EZUS Lyon 1		
61848	MOULIN	Philippe	12/03/2009	VB	SANOFI	non rétribué - recherche vieillissement artériel	EZUS Lyon 1	01/2009	12/2009
61848	MOULIN	Philippe	19/09/2008	LD-AR	DANONNE	ADVISORY BOARD	rémunération institution	01/2007	12/2007
61848	MOULIN	Philippe	19/09/2008	LD-AR	ASTRAZENECA	ADVISORY BOARD	rémunération institution	01/2007	12/2007
61848	MOULIN	Philippe	19/09/2008	EC-INV	SERVIER	essai clinique	investigateur principal	01/2004	12/2010
61848	MOULIN	Philippe	19/09/2008	EC-INV	MSD - TAKEDA - SANOFI - SERVIER	co-investigateur : essais cliniques			
61848	MOULIN	Philippe	19/09/2008	RE-DE	SERVIER	BENFLUOREX conseil pour la firme transparence	rémunération institution		
61848	MOULIN	Philippe	19/09/2008	CF-INT	PFIZER - GSK - SERVIER - TAKEDA - MSD - LILLY	EPU multiples : universités lors de - jamais de perception directe d'honoraire	rémunération institution		
61848	MOULIN	Philippe	19/09/2008	CF-AUD	NOVARTIS	AHA			
61848	MOULIN	Philippe	19/09/2008	CF-AUD	SERVIER	EASD			
61848	MOULIN	Philippe	19/09/2008	CF-AUD	MSD	ALFEDIAM			
61848	MOULIN	Philippe	19/09/2008	VB	ASTRAZENECA	2 bourses de recherches (GELAGE L 191 - E ZUS)		01/2005	12/2006
61848	MOULIN	Philippe	26/11/2007	IP-AUT	EN 2007: GSK,SANOFI,MERK, ROCHE, ...	epu	pas de rémunération personnelle□ versement institution ezus lyon 1 systématique		
61848	MOULIN	Philippe	26/11/2007	IP-AC	ASTRA ZENECA	advisory board	Rémunération institution		01/2007
61848	MOULIN	Philippe	26/11/2007	RE-DE	IRIS	benfluorex transparence	Rémunération institution	04/2008	
61848	MOULIN	Philippe	26/11/2007	EC-INV	IRIS SERVIER	essais clinique internationaux benfluorex	investigateur principal coordination essais clinique ointernationaux benfluorex□ pas de rémunération perso: compte recherche ezus lyon1 >=5000 € ou >=5% du capital	04/2002	12/2006
61848	MOULIN	Philippe	26/11/2007	IF	SANOFI		HCL	01/2003	
61848	MOULIN	Philippe	07/03/2007	VB	SERVIER	Echographe	prise en charge ponctuelle des frais de déplacement et de l'inscription		
61848	MOULIN	Philippe	07/03/2007	CF-AUD	SERVIER, LILLY, NOVARTIS,	congrès annuels EASD	<5000 € ou <5% du capital	01/2000	
61848	MOULIN	Philippe	07/06/2006	IF	SANOFI	Action	rémunération institution	01/2002	01/2007
61848	MOULIN	Philippe	07/06/2006	LD-AR	ASTRA ZENECA	Consultant Board cardio vasculaire	coordonnateur principal	01/2002	
61848	MOULIN	Philippe	07/06/2006	EC-INV	SERVIER IRIS	Essais cliniques Benfluorex	co-investigateur	01/2005	
61848	MOULIN	Philippe	07/06/2006	EC-CO	SANOFI	Rimonabant	co-investigateur		12/2004
61848	MOULIN	Philippe	07/06/2006	EC-CO	TAKEDA	Pioglitazone	co-investigateur		12/2005
61848	MOULIN	Philippe	07/06/2006	EC-CO	LILLY	Raloxifène	co-investigateur	01/2006	
61848	MOULIN	Philippe	07/06/2006	EC-CO	MSD		rémunération institution		12/2005
61848	MOULIN	Philippe	07/06/2006	RE-DE	SERVIER IRIS	Benfluorex	rémunération institution		
61848	MOULIN	Philippe	07/06/2006	CF-INT	SERVIER, SANOFI-AVENTIS, MSD, GSK, PFIZER, MERCK LIPHA	EPU divers		01/2006	12/2006
61848	MOULIN	Philippe	07/06/2006	CF-AUD	NOVARTIS	EASD		01/2005	12/2005
61848	MOULIN	Philippe	07/06/2006	CF-AUD	TAKEDA	AHA		01/2005	12/2005
61848	MOULIN	Philippe	07/06/2006	CF-AUD	SERVIER	EASD			
61848	MOULIN	Philippe	02/01/2006	EC-INV	SERVIER	Benfluorex - 2 essais cliniques	Investigateur principal - rémunération versée sur un compte universitaire	01/2002	12/2007
61848	MOULIN	Philippe	02/01/2006	EC-CO	TAKEDA	Actos	Co-investigateur		
61848	MOULIN	Philippe	02/01/2006	EC-CO	SANOFI-AVENTIS		Co-investigateur	01/2005	12/2005
61848	MOULIN	Philippe	02/01/2006	EC-CO	LILLY	Raloxifene	Co-investigateur	01/2005	12/2005
61848	MOULIN	Philippe	02/01/2006	RE-AUT	SERVIER	Benfluorex	Rémunération versée à une institution	01/2005	
61848	MOULIN	Philippe	02/01/2006	IP-AC	ASTRA-ZENECA	Crestor	Rémunération versée à une institution	01/2000	01/2007
61848	MOULIN	Philippe	02/01/2006	CF-INT	MERCK, LIPHA, MSD, SANOFI-AVENTIS, PFIZER, ETC...	Inombrables	Rémunération versée à 80 % à une institution et 20%personnelle prise en charge ponctuelle des frais de déplacement et de l'inscription		
61848	MOULIN	Philippe	02/01/2006	CF-AUD		Congrès annuels AHA (American Heart Congress) + congrès annuel EASD			
61848	MOULIN	Philippe	02/01/2006	IF	SANOFI	Action (épouse). Peut être vendues en 2005	>5000€ ou à 5% du capital	01/2000	12/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61848	MOULIN	Philippe	02/01/2006	CF-AUD	EASD	congrès annuel			
61848	MOULIN	Philippe	04/07/2005	IP-AC	ASTRA ZENECA France	Advisory Board (sans rémunération directe - EZUS Université Lyon 1)			
61848	MOULIN	Philippe	04/07/2005	IP-EC	SERVIER	Benfluorex			
61848	MOULIN	Philippe	04/07/2005	IP-EC	LILLY	Erista			
61848	MOULIN	Philippe	04/07/2005	IP-EC	TAKEDA	Pro activ			
61848	MOULIN	Philippe	04/07/2005	IP-EC	TAKEDA				
61848	MOULIN	Philippe	04/07/2005	IP-EC	SERVIER	S-18886			
61848	MOULIN	Philippe	04/07/2005	IP-EC	GLAXO				
61848	MOULIN	Philippe	04/07/2005	IP-RE	SERVIER	Benfluorex			
61848	MOULIN	Philippe	04/07/2005	IP-CF	SERVIER	EASD (2005)			
61848	MOULIN	Philippe	04/07/2005	IP-CF	SANOFI	Symposium interne SM			
61848	MOULIN	Philippe	04/07/2005	IP-CF	SERVIER	EASD			
61848	MOULIN	Philippe	04/07/2005	IP-CF	ASTRA ZENECA	AHA			
61848	MOULIN	Philippe	04/07/2005	IP-CF	TAKEDA	AHA			
61848	MOULIN	Philippe	04/07/2005	VB	FOURNIER, PFIZER, MERCK, MSD, ASTRA ZENECA, SERVIER, LILLY, NOVO				
61848	MOULIN	Philippe	04/07/2005	{Autre}	Nouvelle Société Française d'Athérosclérose	CA			
61848	MOULIN	Philippe	04/07/2005	{Autre}		Advisory Board - à compter de septembre 2005			
61848	MOULIN	Philippe	15/06/2004	IP-EC	SERVIER				
61848	MOULIN	Philippe	15/06/2004	IP-AC	ASTRA ZENECA	Board			
61848	MOULIN	Philippe	15/06/2004	IP-CF	ASTRA ZENECA, MERCK SHARP & DOHME, PFIZER, SANDOZ, SERVIER, AVENTIS				
61848	MOULIN	Philippe	15/06/2004	VB	ASTRA ZENECA, MERCK SHARP & DOHME, PFIZER, SANDOZ, SERVIER, AVENTIS				
61848	MOULIN	Philippe	26/06/2003	IP-EC	SERVIER	Coordinateur essai multicentrique			
61848	MOULIN	Philippe	26/06/2003	IP-AC	ASTRA ZENECA	Conseil scientifique			
61848	MOULIN	Philippe	26/06/2003	IP-AC	SHERING	Conseil scientifique			
61848	MOULIN	Philippe	26/06/2003	IP-CF	MERCK SHARP DHOME	2003			
61848	MOULIN	Philippe	26/06/2003	IP-CF	ASTRA ZENECA	2003			
61848	MOULIN	Philippe	26/06/2003	IP-CF	LIPHA MERCK	< 2003			
61848	MOULIN	Philippe	26/06/2003	IP-CF	BAYER	< 2003			
61848	MOULIN	Philippe	26/06/2003	IP-CF	GLAXO SMITHKLINE	2003			
61848	MOULIN	Philippe	26/06/2003	IP-CF	BMS	< 2003			
61848	MOULIN	Philippe	26/06/2003	IP-CF	PARKE DAVIS	< 2003			
61848	MOULIN	Philippe	26/06/2003	IP-AUT		Prise en charge déplacement congrès : idem			
61848	MOULIN	Philippe	26/06/2003	VB	ASTRA ZENECA	EZUS Lyon 1			
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	ROCHE	Réunions nationales/AVASTIN	Rémunération personnelle	01/2008	12/2008
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	PFIZER	réunions nationales	Rémunération personnelle	01/2008	12/2008
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	ABBOTT	réunions nationales	Rémunération personnelle	06/2009	06/2009
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	BOEHRINGER	reunion locale	Rémunération personnelle	05/2009	05/2009
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	IPSEN	réunions nationales	Rémunération personnelle	01/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	NOVARTIS		Rémunération personnelle	01/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	THERVAL	plusieurs réunions nationales, regionales	Rémunération personnelle	01/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	CF-INT	ASTRA ZENECA	plusieurs réunions nationales et regionales	Rémunération personnelle	12/2008	
62135	MOURAD	Jean- Jacques	05/05/2009	IP-AC	DAIICHI SANKYO	conseil/Olmetec/sevikar	Rémunération personnelle	12/2008	
62135	MOURAD	Jean- Jacques	05/05/2009	IP-AC	ABBOTT	conseil/Tarka	Rémunération personnelle	02/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	IP-AC	NOVARTIS	Conseil/Rasilez	Aucune rémunération	01/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	IP-AC	BAYER	Conseil/Telmisartan	Rémunération personnelle	01/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	EC-INV	TAKEDA	coordonnateur d'une enquête/Kenzen		04/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	LD-AR	ARDIX/THERVAL	consultant/HTA/Preterax	Rémunération personnelle	01/2009	
62135	MOURAD	Jean- Jacques	05/05/2009	LD-AR	SERVIER	consultant/HTA/Perindopril	Rémunération personnelle	01/2009	
62135	MOURAD	Jean- Jacques	17/06/2008	IP-CF	TAKEDA		Rémunération personnelle		
62135	MOURAD	Jean- Jacques	17/06/2008	CF-INT	ARDIX		Aucune rémunération		
62135	MOURAD	Jean- Jacques	17/06/2008	CF-INT	WYETH		Aucune rémunération		
62135	MOURAD	Jean- Jacques	17/06/2008	CF-INT	MSD		Aucune rémunération		
62135	MOURAD	Jean- Jacques	17/06/2008	CF-INT	ASTRA ZENECA		Aucune rémunération	03/2008	05/2008
62135	MOURAD	Jean- Jacques	17/06/2008	IP-AC	NOVARTIS		Aucune rémunération	01/2008	12/2008
62135	MOURAD	Jean- Jacques	17/06/2008	IP-AC	PFIZER		Rémunération personnelle	01/2008	12/2008
62135	MOURAD	Jean- Jacques	17/06/2008	IP-AC	SERVIER		Rémunération personnelle	01/2008	12/2008
62135	MOURAD	Jean- Jacques	17/06/2008	IP-AC	THERVAL		rémunération personnelle	01/2006	12/2008
62135	MOURAD	Jean- Jacques	17/06/2008	IP-AC	THERVAL	Consultant / PRETERAX®	rémunération personnelle	01/2005	12/2008
62135	MOURAD	Jean- Jacques	14/06/2008	LD-AR	PFIZER	Groupe d'expert - AMLOR® / CADUET®	rémunération personnelle	01/2005	12/2008
62135	MOURAD	Jean- Jacques	14/06/2008	LD-AR	SERVIER	Groupe d'expert - PRETERAX®	Coordonnateur	01/2007	12/2008
62135	MOURAD	Jean- Jacques	14/06/2008	IP-EC	MSD		rémunération personnelle	03/2008	03/2008
62135	MOURAD	Jean- Jacques	14/06/2008	CF-INT	TAKEDA	Environnement épidémiologique sur l' HTA	rémunération personnelle	05/2008	05/2008
62135	MOURAD	Jean- Jacques	14/06/2008	CF-INT	ASTRA ZENECA	Environnement HTA	rémunération personnelle	01/2006	12/2008
62135	MOURAD	Jean- Jacques	14/06/2008	IP-AC	THERVAL	Consultant PRETERAX®		06/2006	12/2007
62135	MOURAD	Jean- Jacques	25/02/2007	EC-INV	THERVAL MEDICAL	coordonateur d'étude/ Preterax		06/2007	09/2007
62135	MOURAD	Jean- Jacques	26/02/2007	CF-AUD	SERVIER	European society hypertension / european society of cardiology	Rémunération personnelle	12/2006	12/2006
62135	MOURAD	Jean- Jacques	26/02/2007	IP-AC	NOVARTIS	Membre d'un board de reflexion international/ Aliskiren	Rémunération personnelle	12/2006	12/2006
62135	MOURAD	Jean- Jacques	26/02/2007	IP-AC	BAYER	Membre d'un board de reflexion international/ Telmisartan	Rémunération personnelle	02/2007	02/2007
62135	MOURAD	Jean- Jacques	26/02/2007	IP-AC	DAIICHI SANKYO	membre d'un board international/ association olmetec-amlodipine		05/2006	05/2006
62135	MOURAD	Jean- Jacques	30/03/2006	CF-AUD	ASTRA-ZENECA	marrakech/syndrome métabolique	Rémunération personnelle	03/2006	12/2006
62135	MOURAD	Jean- Jacques	30/03/2006	CF-INT	PFIZER	epidemiologie d.el'HTA/risque cardiovasculaire/Amlor/Tahor/caduet	Rémunération personnelle	03/2006	04/2006
62135	MOURAD	Jean- Jacques	30/03/2006	CF-INT	IPSEN	Observance thérapeutique/Nisis	Rémunération personnelle	01/2006	01/2007
62135	MOURAD	Jean- Jacques	30/03/2006	LD-AR	THERVAL MEDICAL	conseil sur l'HTA et la microcirculation/Preterax	AMIS93	05/2005	06/2005
62135	MOURAD	Jean- Jacques	25/10/2005	VB	BMS	contribution à l'achat d'un matériel de recherche clinique		05/2006	05/2006
62135	MOURAD	Jean- Jacques	25/10/2005	CF-AUD	ASTRA ZENECA	syndrome métabolique	rémunération personnelle	07/2005	12/2005
62135	MOURAD	Jean- Jacques	25/10/2005	IP-AC	BOEHRINGER	Conseil dans l'HTA			
62135	MOURAD	Jean- Jacques	25/10/2005	EC-CO	SANKYO	OLMESARTAN	investigateur d'une étude internationale multicentrique prospective	06/2005	10/2007

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62135	MOURAD	Jean- Jacques	25/10/2005	EC-INV	SANOFI	APROVEL	MEMBRE CONSEIL SCIENTIFIQUE	10/2004	03/2006
62135	MOURAD	Jean- Jacques	25/10/2005	EC-INV	NOVARTIS	COORDONATEUR d'étude phase 4 environnement de l'HTA	coordonateur	10/2004	10/2005
62135	MOURAD	Jean- Jacques	06/04/2005	IP-AC	BOEHRINGER INGELHEIM	Conseil auprès du médical cardiovasculaire depuis Mars 2005	Rémunération personnelle	03/2005	
62135	MOURAD	Jean- Jacques	28/01/2004	LD-AR	THERVAL MEDICAL	Consultant	moi	09/2003	10/2006
62135	MOURAD	Jean- Jacques	28/01/2004	EC-CO	PIERRE FABRE	Essai de phase IV, coordonateur	moi	10/2004	01/2005
62135	MOURAD	Jean- Jacques	28/01/2004	EC-CO	BMS	Essai de phase IV, maitre du scientifique (Plavix)	moi	10/2004	06/2005
62135	MOURAD	Jean- Jacques	28/01/2004	IP-AC	BEAUFOUR IPSEN	Conseil dans l'HTA	Vous	10/2004	10/2006
62135	MOURAD	Jean- Jacques	28/01/2004	IP-AC	PFIZER	Conseil dans l'HTA	Vous	10/2004	10/2006
62135	MOURAD	Jean- Jacques	28/04/2003	LD	THERVAL	Consultant puur la microcirculation			
62135	MOURAD	Jean- Jacques	28/04/2003	IP-EC	BRISTOL MYERS SQUIBB	Membre du conseil scientifique, enquête ATTEST - artérite			
62135	MOURAD	Jean- Jacques	28/04/2003	IP-AC	PFIZER	Réalisation d'enquêtes			
62135	MOURAD	Jean- Jacques	28/04/2003	IP-AC	BEAUFOUR-IPSEN	Réalisation d'outils pédagogiques			
62135	MOURAD	Jean- Jacques	28/04/2003	IP-CF	THERVAL	HTA - Microcirculation			
62135	MOURAD	Jean- Jacques	28/04/2003	IP-CF	PFIZER, BRISTOL MYERS SQUIBB, SANOFI	HTA			
62135	MOURAD	Jean- Jacques	11/03/2002	LD	THERVAL MEDICAL	Consultant			
62135	MOURAD	Jean- Jacques	11/03/2002	IP-AC	BEAUFOUR IPSEN	Elaboration brochure HTA			
62135	MOURAD	Jean- Jacques	11/03/2002	IP-AC	NOVARTIS	Membre conseil scientifique enquête MG			
62135	MOURAD	Jean- Jacques	11/03/2002	IP-AC	PFIZER	Membre conseil scientifique enquête MG			
62135	MOURAD	Jean- Jacques	11/03/2002	IP-CF	MSD	Participation conférence			
62135	MOURAD	Jean- Jacques	11/03/2002	IP-CF	BMS	Participation conférence			
60736	NETTER	Patrick	06/02/2009	VB		Actuellement Directeur de l'Institut des Sciences Biologiques du CNRS			
60736	NETTER	Patrick	06/02/2009	IP-AUT	BIO IBERICA (Espagne)	Co-détenteur de 2 brevets (2002 et 2003)		01/2008	12/2013
60736	NETTER	Patrick	09/01/2003	IF	PFIZER	Actions			
60736	NETTER	Patrick	09/01/2003	IF	AVENTIS	Actions			
60736	NETTER	Patrick	09/01/2003	IP-CF	SERVIER	7ème séminaire annuel de formation en pharmacologie expérimentale et clinique : "Les nouveaux défis de l'ostéoporose" à Vaux de Cernay			
60736	NETTER	Patrick	09/01/2003	VB	AVENTIS	UHP, Nancy 1 et CNRS			
60736	NETTER	Patrick	09/01/2003	VB	SERVIER	UHP, Nancy 1			
60736	NETTER	Patrick	09/01/2003	VB	RODHIA	UHP, Nancy 1			
60736	NETTER	Patrick	09/01/2003	VB	THERAPLIX	UHP, Nancy 1			
60736	NETTER	Patrick	05/02/2001	IP-CF	SEARLE	OARSI (Barcelone) : Anti Cox2 en clinique			
60736	NETTER	Patrick	05/02/2001	VB	AVENTIS	UHP, Nancy 1 et CNRS			
60736	NETTER	Patrick	05/02/2001	VB	NEGMA	UHP, Nancy 1			
60736	NETTER	Patrick	05/02/2001	VB	SERVIER	UHP, Nancy 1			
60736	NETTER	Patrick	05/02/2001	VB	GUERBET	UHP, Nancy 1			
60736	NETTER	Patrick	05/02/2001	VB	SEARLE	UHP, Nancy 1			
60736	NETTER	Patrick	05/02/2001	VB	RHODIA	UHP, Nancy 1			
60736	NETTER	Patrick	05/02/2001	VB	THERAMEX	UHP, Nancy 1			
60736	NETTER	Patrick	25/04/2000	IF	AVENTIS, NOVARTIS, PFIZER, SANOFI, MERCK	Actions.			
60736	NETTER	Patrick	25/04/2000	VB	BOEHRINGER	Au titre du laboratoire de pharmacologie de l'UMR 7561 CNRS UHP Nancy 1 et du service de pharmacologie clinique et toxicologie.			
60736	NETTER	Patrick	25/04/2000	VB	SERVIER	UHP Nancy 1			
60736	NETTER	Patrick	25/04/2000	VB	GUERBET	UHP Nancy 1 et CHU Nancy.			
60736	NETTER	Patrick	25/04/2000	VB	SEARLE	UHP Nancy 1 et CHU Nancy.			
60736	NETTER	Patrick	25/04/2000	VB	AVENTIS	UHP Nancy 1 et CNRS.			
62802	NONY	Patrice	29/01/2010	IP-AC	MERCK	Losartan - plan de développement pédiatrique	rémunération institution	01/2008	01/2010
62802	NONY	Patrice	29/01/2010	EC-CO	BMS	Etude ADOPT	Membre du comité d'évènements critiques	01/2008	12/2011
62802	NONY	Patrice	29/01/2010	EC-CO	BMS	Etude ADOPT	Membre du comité d'évènements critiques	01/2008	12/2010
62802	NONY	Patrice	29/01/2010	EC-CO	SERVIER	Procoralan (Ivabradine)	développement d'un modèle in silico	01/2007	12/2008
62802	NONY	Patrice	29/01/2010	EC-CO	BMS	Essai ADOPT : Apixaban Dosing to Optimize Protection from Thrombosis	membre du comité d'évènements critiques	01/2008	12/2010
62802	NONY	Patrice	12/12/2008	EC-CO	BMS	Etude ADOPT	Membre du comité d'évènements critiques	01/2008	12/2010
62802	NONY	Patrice	12/12/2008	VB	SERVIER	Modélisation	UCBL	01/2006	12/2008
62802	NONY	Patrice	12/12/2008	VB	AFRETH	Expertise	UCBL	01/2008	12/2008
62802	NONY	Patrice	28/10/2008	EC-CO	BMS	Etude ADOPT	Membre du comité d'évènements critiques	01/2008	12/2010
62802	NONY	Patrice	28/10/2008	VB	CNAMTS	Modélisation	UCBL	01/2005	12/2008
62802	NONY	Patrice	28/10/2008	VB	SERVIER	Modélisation	UCBL	01/2006	12/2008
62802	NONY	Patrice	28/10/2008	VB	AFRETH	Expertise	UCBL	01/2008	12/2008
62802	NONY	Patrice	03/01/2008	EC-CO	BMS	Essai ADOPT : Apixaban Dosing to Optimize Protection from Thrombosis	membre du comité d'évènements critiques	01/2008	12/2010
62802	NONY	Patrice	03/01/2008	EC-CO	SERVIER	Procoralan (Ivabradine)	développement d'un modèle in silico	01/2007	12/2010
62802	NONY	Patrice	03/01/2008	IP-AC	MERCK	Losartan - plan de développement pédiatrique	rémunération institution	01/2008	
62802	NONY	Patrice	03/01/2008	CF-INT	AFRETH	Congrès annuel thermalisme - 2006	rémunération institution	01/2006	12/2006
62802	NONY	Patrice	12/03/2007	(Autre)		membre suppléant de la commission de Transparence			12/2008
62802	NONY	Patrice	14/09/2005	IP-AUT	CNAMTS	Contrat de recherche en cours avec la CNAMTS			
62802	NONY	Patrice	27/04/2004	(Autre)	ANAES	Expertise			
62802	NONY	Patrice	29/03/2004	Néant					
62802	NONY	Patrice	10/04/2003	IP-RE	Union Européenne	Divers (6° PCRD)			
62802	NONY	Patrice	10/04/2003	VB	PHRC	N°98.071 - Hospices civils de Lyon			
62802	NONY	Patrice	10/04/2003	VB	Afssaps	Subvention (contrat D2843) - Hospices civils de Lyon			
61051	NUSS	Philippe	03/11/2008	LD-AR	JANSSEN	Groupe d'expert sur les anti psychotropes	rémunération personnelle	01/2008	12/2009
61051	NUSS	Philippe	03/11/2008	EC-INV	SANOFI	Etude clinique Saredutant	Coordinateur France	01/2008	12/2008
61051	NUSS	Philippe	03/11/2008	RE-DE	BAYER SANTE FAMILIALE	Demande d'évaluation du bénéfice en clinique d'un traitement phytothérapeutique de l'anxiété	rémunération personnelle	01/2007	12/2008
61051	NUSS	Philippe	03/11/2008	IP-AC	JANSSEN	Avis sur la notion de rémission dans la psychose	rémunération personnelle	01/2006	12/2007
61051	NUSS	Philippe	03/11/2008	CF-INT	JANSSEN	Schizophrenia Research conference (Venise)	aucune rémunération		
61051	NUSS	Philippe	03/11/2008	CF-INT	LILLY	American Psychiatric Association (Washington)	aucune rémunération		
61051	NUSS	Philippe	03/11/2008	CF-INT	SERVIER	European Conference Psychiatry (Munich)	aucune rémunération		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61051 NUSS		Philippe	03/11/2008	CF-AUD	JANSSEN	Schizophrenia Research conference (Venise)	aucune rémunération		
61051 NUSS		Philippe	03/11/2008	CF-AUD	LILLY	American Psychiatric Association (Washington)	aucune rémunération		
61051 NUSS		Philippe	03/11/2008	CF-AUD	SERVIER	European Conference Psychiatry (Munich)	aucune rémunération		
61051 NUSS		Philippe	06/11/2002	IP-EC	BMS	Actuel : étude ouverte aripiprazole : 8 patients			
61051 NUSS		Philippe	06/11/2002	IP-EC	LUNDBECK	Actuel : étude ouverte Serdolect : 8 patients			
61051 NUSS		Philippe	06/11/2002	IP-AC	GSK	Lamictal			
61051 NUSS		Philippe	06/11/2002	IP-CF	SANOFI	Conférences			
61051 NUSS		Philippe	06/11/2002	IP-CF	GSK	Conférences			
61051 NUSS		Philippe	06/11/2002	IP-CF	LUNDBECK	Conférences			
61051 NUSS		Philippe	12/10/2002	IP-EC	SERVIER	Sulbutiamine symptômes négatifs de schizophrénie			
61051 NUSS		Philippe	12/10/2002	IP-EC	PFIZER	Mémoire autobiographique dans le PTSD			
61051 NUSS		Philippe	12/10/2002	IP-EC	BMS	Efficacité tolérance aripiprazole			
61051 NUSS		Philippe	12/10/2002	IP-RE	ANAES	Relecture des recommandations pour le traitement du trouble anxieux généralisé et du trouble post-traumatique			
61051 NUSS		Philippe	12/10/2002	IP-AC		Contacts informels avec l'industrie pharmaceutique sur l'évolution des besoins en psychiatrie + module de formation continue			
61051 NUSS		Philippe	12/10/2002	IP-CF	Toutes sociétés pharmaceutiques	Participation à de nombreux symposiums nationaux et internationaux sur les pathologies psychiatriques dans le cadre de symposiums scientifiques sponsorisés par l'industrie au			
61051 NUSS		Philippe	21/04/2000	LD	BRISTOL MYERS SQUIBB	1999-2000 : Advisory Board			
61051 NUSS		Philippe	21/04/2000	IP-EC	BOEHRINGER INGELHEIM	Essai Fibanserine (investigateur)			
61051 NUSS		Philippe	21/04/2000	IP-AC	AVENTIS	Conseil ponctuel			
61051 NUSS		Philippe	21/04/2000	IP-CF	SMITH KLINE BEECHAM	Dépression			
61051 NUSS		Philippe	21/04/2000	IP-CF	LUNDBECK	Psychose au quotidien - suicide			
61051 NUSS		Philippe	21/04/2000	IP-CF	SANOFI SYNTHELABO	Amisulpiride			
61051 NUSS		Philippe	21/04/2000	IP-CF	JANSSEN CILAG	Réhabilitation S Z			
61051 NUSS		Philippe	21/04/2000	IP-CF	UCB	Anxiété			
61051 NUSS		Philippe	21/04/2000	IP-AUT	SKB	Ouvrage collectif dépression			
10325 OLIE		Jean-Pierre	24/11/2005	EC-INV	IRIS	Agomélatine	Coordonateur	01/2004	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	EC-INV	BMS	Aripiprazole	Coordonateur	01/2004	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	EC-INV	LILLY	Duloxétine	Investigateur	01/2004	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	IP-AC	IRIS	Conseil pour psychotropes	rémunération personnelle	01/2003	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	IP-AC	JANSSEN	Conseil pour psychotropes	Rémunération personnelle	01/2003	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	CF-INT	SERVIER	Chine : rencontres médicales franco-chinoises	Aucune rémunération	09/2005	09/2005
10325 OLIE		Jean-Pierre	24/11/2005	CF-INT	LILLY	Porto (janvier 2005) - Edimbourg (janvier 2006)	Aucune rémunération	01/2005	01/2006
10325 OLIE		Jean-Pierre	24/11/2005	VB	SANOFI	Soutien structure. Centre de recherches	Delegat Recherche Hopital Ste-Anne	01/2004	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	VB	PIERRE FABRE	Soutien structure Centre de recherches		01/2004	12/2005
10325 OLIE		Jean-Pierre	24/11/2005	VB	LILLY	Soutien structure Centre de recherches		01/2004	12/2005
10325 OLIE		Jean-Pierre	23/04/2004	IP-EC	SERVIER	Coordination étude 042 - Agomélatine			
10325 OLIE		Jean-Pierre	23/04/2004	IP-RE	PFIZER	Enquête sur le dépistage de la démence chez le psychiatre			
10325 OLIE		Jean-Pierre	23/04/2004	IP-AC	SERVIER	Agomélatine			
10325 OLIE		Jean-Pierre	23/04/2004	IP-CF	LILLY	FMC			
10325 OLIE		Jean-Pierre	23/04/2004	IP-CF	PIERRE FABRE	FMC			
10325 OLIE		Jean-Pierre	23/04/2004	IP-CF	BMS	Edition séminaire psychiatrie biologique			
10325 OLIE		Jean-Pierre	20/01/2004	IP-EC	SERVIER	Coordination etude 042 Agomélatine® (Servier)			
10325 OLIE		Jean-Pierre	20/01/2004	IP-RE	PFIZER	Enquête sur démence financée par PFIZER			
10325 OLIE		Jean-Pierre	20/01/2004	IP-AC	SERVIER	Agomelatine®			
10325 OLIE		Jean-Pierre	20/01/2004	IP-CF	LILLY ; PIERRE FABRE	FMC			
10325 OLIE		Jean-Pierre	20/01/2004	IP-CF	BRISTOL MYERS SQUIBB	Edition séminaire psychiatrie			
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	RHONE POULENC	Coordination d'une étude Lithium + Anafranil versus Placebo + Anafranil chez les déprimés.			
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	KNOLL	Coordination d'une étude phase II pour un nouvel antipsychotique.			
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	LILLY	Rédaction du rapport pour la demande d'enregistrement européen pour Olanzapine.			
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	LUNDBECK	Rédaction du rapport pour la demande d'enregistrement du Citalopram injectable.			
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	SMITHKLINE BEECHAM L				
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	JANSSEN	Participation à un comité de rédaction de "House Organe" : Halopsy.			
10325 OLIE		Jean-Pierre	01/01/1999	IP-EC	ORGANON	Participation à un comité de rédaction de "House Organe" : Humeurs.			
61196 ORGOGOZO		Jean-Marc	04/11/2002	IP-EC		Nombreux et diversifiés			
61196 ORGOGOZO		Jean-Marc	04/11/2002	IP-AC		Nombreux et diversifiés			
61196 ORGOGOZO		Jean-Marc	04/11/2002	IP-CF		Nombreux et diversifiés			
61196 ORGOGOZO		Jean-Marc	04/11/2002	(Autre)	BAYER, NOVARTIS, SANOFI SYNTHELABO, MSD, BMS, SERVIER, BOEHRINGER INGELHEIM, GSK, AVENTIS, LUNDBECK, EISAI, PFIZER, JANSSEN CILAG, ELAN, WYETH, PIERRE FABRE, BEAUFOUR IPSEN, ROCHE...	Laboratoires concernés : rubriques essais cliniques, activités de conseil, conférences			
63645 PACI		Angelo	01/08/2010	CF-AUD	CHUGAI	American Association for Cancer Research Congress		04/2010	05/2010
63645 PACI		Angelo	01/08/2010	RE-AUT	PIERRE FABRE	ETUDE DE STABILITE DU BUSILVEX	Rémunération personnelle/institution	08/2010	03/2011
63645 PACI		Angelo	01/08/2010	EC-CO	PIERRE FABRE ONCOLOGIE	Busilvex	expérimentateur non principal	04/2009	04/2011
63645 PACI		Angelo	16/09/2008	IP-AC	INTSEL CHIMOS	Conseils pour développement d'une gamme générique	Rémunération personnelle	07/2008	10/2008
63645 PACI		Angelo	16/09/2008	CF-INT	MSD	ASCO 2008	Aucune rémunération	05/2008	06/2008
63645 PACI		Angelo	16/09/2008	EC-CO	KEOCYT	en développement	expérimentateur non principal	09/2008	08/2011
63645 PACI		Angelo	03/09/2007	IP-AC	SANDOZ	Conseils pour développement d'une gamme générique	Rémunération personnelle	03/2007	05/2008
63645 PACI		Angelo	09/06/2006	LD-AR	INTSEL CHIMOS	Elaboration du dossier destiné aux pharmaciens hospitaliers de divers produits de cancérologie	rémunération personnelle	03/2006	06/2006
63645 PACI		Angelo	09/06/2006	EC-CO	JANSSEN CILAG/ORTHOBIOTECH	développement de dosages de principes actifs anesthésiques ou antalgiques pour analyse plasmatique - etc	expérimentateur non principal	08/2005	08/2006
63645 PACI		Angelo	09/06/2006	CF-INT	PIERRE FABRE	Espagne - présentation d'une étude pédiatrique de l'utilisation du Busilvex (Busulfan IV)	rémunération personnelle	04/2006	04/2006
63645 PACI		Angelo	09/06/2006	CF-INT	PIERRE FABRE	Espagne. Présentation d'une étude pédiatrique de l'utilisation du busilvex ® (Busulfan IV)	rémunération personnelle	04/2006	04/2006
63645 PACI		Angelo	14/02/2005	LD	LABORATOIRE SERVIER	Internat Pharmacie			
63645 PACI		Angelo	14/02/2005	(Autre)		Microparticules à visée diagnostique et thérapeutiques			
63645 PACI		Angelo	14/02/2005	VB	INSTITUT GUSTAVE ROUSSY	Participation aux activités de recherche de nombreux laboratoires pharmaceutiques au sein de l'institut de recherche			
63645 PACI		Angelo	14/02/2005	IP-AUT	EUROPEAN SOCIETY OF CLINICAL PHARMACY	Membre			
63645 PACI		Angelo	14/02/2005	IP-AUT	ASSOCIATION EUROPEENNE DE FORMATION POUR LES PHARMACIENS	Membre et fondateur			
63645 PACI		Angelo	10/02/2005	IP-AC	SERVIER	Veille tehnologique mono??			
63645 PACI		Angelo	10/02/2005	IP-CF	AVENTIS	European Society of Clinical Pharmacy		11/2007	11/2007
63405 PAGES		Jean-Christophe	08/05/2008	IP-AUT	SERVIER	Conseil classement de vecteurs			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63405 PAGES		Jean-Christophe	08/05/2008	IP-AUT	VECTALYS	Conseil classement de vecteurs (en cours)		06/2006	
63405 PAGES		Jean-Christophe	04/12/2007	CF-INT	SERVIER	Centre de Recherche de Croissy	Aucune rémunération	11/2007	11/2007
63405 PAGES		Jean-Christophe	20/06/2006	Néant					
61141 PASQUIER		Florence	11/05/2009	LD-ODE	MINISTERE DE L'ENSEIGNEMENT SUPERIEUR	Co-directive de l'équipe d'accueil EA 2691 (Université Lille-Nord de France)	Contrat quadriennal, renouvelé	01/2003	12/2010
61141 PASQUIER		Florence	11/05/2009	LD-AR	JANSSEN-CILAG	Coordination nationale d'une étude multicentrique internationale évaluant la galantamine chez des patients a	Rémunération: institution	01/2003	12/2004
61141 PASQUIER		Florence	11/05/2009	LD-AR	NOVARTIS	PI d'une Etude multicentrique internationale en double aveugle comparant la rivastigmine et le donepezil chr	Rémunération: institution	01/2001	12/2005
61141 PASQUIER		Florence	11/05/2009	LD-AR	NOVARTIS	PI d'une Etude multicentrique internationale en double aveugle contre le placebo de la rivastigmine dans la (	Rémunération: institution	01/2001	12/2005
61141 PASQUIER		Florence	11/05/2009	LD-AR	EISAI	PI d'une Etude multicentrique internationale en double aveugle contre placebo du donepezil dans la maladie	Rémunération: institution	01/2003	12/2005
61141 PASQUIER		Florence	11/05/2009	LD-AR	SANOFI-SYNTHELABO	PI d'une Etude multicentrique internationale en double aveugle contre placebo du SR57667B dans la maladi	Rémunération: institution	01/2003	12/2004
61141 PASQUIER		Florence	11/05/2009	LD-AR	IRIS-SERVIER	PI d'une Etude multicentrique international en double aveugle contre placebo du SR18986 dans le MCI (étuc	Rémunération: institution	01/2004	12/2005
61141 PASQUIER		Florence	11/05/2009	LD-AR	BEAUFOUR-IPSEN	Co-investigateur de l'étude multicentrique internationale en double aveugle contre placebo de l'EGb 761 dan	Rémunération: institution	01/2002	
61141 PASQUIER		Florence	11/05/2009	LD-AR	DEBIO CLINIC	PI d'une étude multicentrique internationale en duble aveugle contre placebo du DEB-ZT-201 dans la maladi	Rémunération: institution	01/2003	12/2006
61141 PASQUIER		Florence	11/05/2009	LD-AR	AMERSHAM HEALTH GE HEALTHCARE	PI d'une Etude multicentrique internationale du DaTSCAN	Rémunération: institution	01/2004	12/2006
61141 PASQUIER		Florence	11/05/2009	LD-AR	NEUROCHEM	PI d'une Etude multicentrique international en double aveugle contre placebo de l'Homotaurine dans la mala	Rémunération: institution	01/2005	12/2007
61141 PASQUIER		Florence	11/05/2009	LD-AR	ELAN/WYETH	PI de l'étude multicentrique internationale du suivi des patients ayant participé à l'étude d'immunisation activ	Rémunération: institution	01/2006	12/2006
61141 PASQUIER		Florence	11/05/2009	LD-AR	GLAXO-SMITHKLINE	PI d'une étude multicentrique internationale en double aveugle contre placebo de la rosiglitazone dans la ma	Rémunération: institution	01/2006	12/2009
61141 PASQUIER		Florence	11/05/2009	LD-AR	LUNDBECK	PI d'une étude multicentrique nationale en double aveugle contre placebo de la mémantine sur l'astrophie cé	Rémunération: institution	01/2006	12/2008
61141 PASQUIER		Florence	11/05/2009	LD-AR	SCHARTZ-BIOPROJET	Initiation et Coordination nationale d'un essai multicentrique évaluant le BF.2.649 dans la maladie à corps de	Rémunération: institution	01/2005	
61141 PASQUIER		Florence	11/05/2009	LD-AR	EISAI	PI d'une étude multicentrique nationale en double aveugle contre placebo du donepezil dans le MCI amnésic	Rémunération: institution	01/2007	
61141 PASQUIER		Florence	11/05/2009	LD-AR	WYETH	PI d'une Etude multicentrique internationale en double aveugle contre placebo de l'ACC-001 (immunisation :	Rémunération: institution	01/2008	
61141 PASQUIER		Florence	11/05/2009	LD-AR	WYETH	PI d'une Etude multicentrique internationale en double aveugle contre placebo du bapineuzumab (immunisa	Rémunération: institution	01/2009	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PIERRE FABRE	PI d'une Etude multicentrique nationale en double aveugle contre placebo du V0191 dans le MCI en cours)	Rémunération: institution	01/2008	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Investigateur principal de l'étude des facteurs prédictifs de la survie, de l'évolution cognitive et de l'entrée en	Rémunération: institution	01/2002	12/2004
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-Investigateur de l'étude PLASA- Plan des soins et d'aides dans la maladie d'Alzheimer.	Rémunération: institution	01/2003	12/2006
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude Paradigme Parkinson-Alzheimer's disease: impact of gene metabolism and envir	Rémunération: institution	01/2003	12/2007
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude de confirmation neuropathologique de la maladie d'Alzheimer.	Rémunération: institution	01/2003	12/2007
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude sur la fin de vie dans la maladie d'Alzheimer.	Rémunération: institution	01/2004	12/2008
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude des Greffes de neurones foetaux dans la maladie de Huntington (en cours)	Rémunération: institution	01/2001	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude du polysulfate de pentosan dans la maladie de Creutzfeldt-Jakob	Rémunération: institution	01/2006	12/2009
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude SIGAL (système IGF-1 et maladie d'Alzheimer) - (en cours)	Rémunération: institution	01/2007	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC + MILDT	Co-investigateur de l'étude Korsakol (sur les patients alcooliques chroniques avec ou sans syndrome de Kor	Rémunération: institution	01/2007	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude de la doxycycline dans la maladie de Creutzfeldt-Jakob (en cours)	Rémunération: institution	01/2008	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Co-investigateur de l'étude sur les mutations du gène de la Progranuline (en cours)	Rémunération: institution	01/2009	
61141 PASQUIER		Florence	11/05/2009	LD-AR	PHRC	Investigateur principal de l'étude sur l'influence du contrôle des facteurs de risque vasculaire sur l'évolution c	Rémunération: institution	01/2009	
61141 PASQUIER		Florence	11/05/2009	LD-AR	ANR	Co-investigateur de l'étude de liaison génétique dans les DFT et les DFT-SLA (en cours)	Rémunération: institution	01/2007	
61141 PASQUIER		Florence	11/05/2009	LD-AR	DRC Lille	Investigateur principal de l'étude de Reconnaissance implicite et explicite des objets et des visages chez le si	Rémunération: aucune	01/2005	
61141 PASQUIER		Florence	11/05/2009	LD-AR	DRC Lille	Investigateur principal de l'étude Mild cognitive impairment facteurs diagnostiques, pronostiques et évolutifs	Rémunération: aucune	01/2004	
61141 PASQUIER		Florence	11/05/2009	IP-AC	ADIR (SERVIER)	Membre du comité scientifique et d'adjudication des cas de démence dans l'étude PERFORM (en cours)	Rémunération: institution (ADRINORD)	01/2006	
61141 PASQUIER		Florence	11/05/2009	IP-AC	SANOFI-AVENTIS	Recommandations et conseils sur les essais cliniques nécessaires pour optimiser la communication sur le P	Rémunération: institution (ADRINORD)	10/2006	10/2006
61141 PASQUIER		Florence	11/05/2009	IP-AC	EISAI	Intervention au cours des "rencontres autour du cerveau et de la maladie d'Alzheimer avec exposition itinéra	Rémunération: institution (ADRINORD)	02/2007	02/2007
61141 PASQUIER		Florence	11/05/2009	IP-AC	ASTRA-ZENECA	Expertise scientifique, réunion relative à l'AZD 3480	Rémunération: institution (ADRINORD)	02/2008	05/2008
61141 PASQUIER		Florence	11/05/2009	IP-AC	GENFIT	Expertise pour des programmes de recherche portant sur le développement de médicament ou l'identificatio	Rémunération: institution (ADRINORD)	01/2009	12/2009
61141 PASQUIER		Florence	11/05/2009	IP-AC	INSERM	Expertise collective de l'Inserm sur la maladie d'Alzheimer.	Rémunération: institution (ADRINORD)	05/2007	12/2007
61141 PASQUIER		Florence	11/05/2009	IP-AC	ALZHEIMER'S RESEARCH TRUST	Expertise de projets de recherche.	Rémunération: aucune	01/2008	12/2008
61141 PASQUIER		Florence	11/05/2009	IP-AC	EUROPEAN COMMISSION	Expert pour les projets du 7th Framework Programme (FP7)	Rémunération: personnelle	01/2007	12/2007
61141 PASQUIER		Florence	11/05/2009	IP-AC	ANR	Expert pour les projets TecSan.	Rémunération: aucune	01/2005	12/2007
61141 PASQUIER		Florence	11/05/2009	IP-AC	MINISTERE DE LA SANTE	Comité national du PHRC.	Rémunération: personnelle	01/2008	12/2010
61141 PASQUIER		Florence	11/05/2009	IP-AC	AFSSAPS	Expert ponctuel au sujet du méprobamate des inhibiteurs d'acétylcholinestérase.	Rémunération: aucune	01/2007	12/2008
61141 PASQUIER		Florence	11/05/2009	IP-AC	HAS	Membre de la commission de transparence sur les traitements anti-Alzheimer.	Rémunération: aucune	01/2006	12/2006
61141 PASQUIER		Florence	11/05/2009	IP-AC	HAS	Présidente du groupe de travail sur les recommandations sur le diagnostic et la prise en charge de la maladi	Rémunération: personnelle	01/2007	12/2008
61141 PASQUIER		Florence	11/05/2009	IP-AC	INPES	Membre de comités scientifiques ponctuels concernant des actions sur la maladie d'Alzheimer (en cours)	Rémunération: personnelle	01/2003	
61141 PASQUIER		Florence	11/05/2009	IP-AC	DGS	Membre du comité d'experts mandaté par la DGS auprès de l'Inserm, la CNAMTS et les laboratoires Lundbe	Rémunération: aucune	01/2002	12/2006
61141 PASQUIER		Florence	11/05/2009	IP-AC	ANESM	Membre du conseil scientifique (en cours)	Rémunération: aucune	01/2007	
61141 PASQUIER		Florence	11/05/2009	IP-AC	EISAI	Membre du comité scientifique Hippocampe (en cours)	Rémunération: personnelle	01/2007	
61141 PASQUIER		Florence	11/05/2009	IP-AC	IPSEN-BEAUFOUR	Membre du comité scientifique de l'étude Guidage (en cours)	Rémunération: personnelle	01/2002	
61141 PASQUIER		Florence	11/05/2009	IP-AC	JANSSEN	Membre du comité scientifique (en cours)	Rémunération: personnelle	01/2008	
61141 PASQUIER		Florence	11/05/2009	IP-AC	PHARMACO-GIENS	Participation aux rencontres de Pharmaco-Giens.	Rémunération: aucune	06/2008	06/2008
61141 PASQUIER		Florence	11/05/2009	IP-AC	GE HEALTHCARE	Membre du conseil consultatif en neuroimagerie des démences.	Rémunération: personnelle	01/2006	12/2008
61141 PASQUIER		Florence	11/05/2009	IP-AC	SERVIER	Membre du Scientific advisory board (sur les programmes de recherche en cours Neurologie).	Rémunération: personnelle	10/2007	10/2007
61141 PASQUIER		Florence	11/05/2009	IP-AC	SANOFI-AVENTIS	Comité scientifique de l'étude S-AGES (en cours)	Rémunération: personnelle	01/2008	
61141 PASQUIER		Florence	11/05/2009	IP-AC	EISAI INTERNATIONAL	Advisory board, steering committee meeting sur la démence parkinsonienne et la démence à corps de Lewy	Rémunération: personnelle	01/2007	01/2007
61141 PASQUIER		Florence	11/05/2009	IP-AC	BAYER INTERNATIONAL	Advisory Board international pour un traceur en développement.	Rémunération: personnelle	01/2009	01/2009
61141 PASQUIER		Florence	05/11/2002	IP-AC	NOVARTIS	Comité scientifique			
61141 PASQUIER		Florence	05/11/2002	IP-AC	EISAI	Comité scientifique			
61141 PASQUIER		Florence	05/11/2002	IP-AC	JANSSEN CILAG	Comité scientifique			
61141 PASQUIER		Florence	05/11/2002	IP-CF	EISAI	Plusieurs colloques			
61141 PASQUIER		Florence	05/11/2002	IP-CF	NOVARTIS	Plusieurs colloques			
61141 PASQUIER		Florence	05/11/2002	IP-CF	JANSSEN CILAG	Plusieurs colloques			
61141 PASQUIER		Florence	05/11/2002	VB	AVENTIS	Essai Riluzole			
61141 PASQUIER		Florence	05/11/2002	VB	BEAUFOUR IPSEN	Essai Ginkgo Biloba			
61141 PASQUIER		Florence	05/11/2002	VB	NOVARTIS	Essai Rivastiquine			
61141 PASQUIER		Florence	05/11/2002	VB	EISAI	Essai Orpeperil			
61141 PASQUIER		Florence	26/06/2000	IP-EC		5 à 6 essais cliniques/an			
61141 PASQUIER		Florence	26/06/2000	IP-RE	AVENTIS	Comité scientifique de l'évaluation Riluzol dans la maladie de Huntington (2000)			
61141 PASQUIER		Florence	26/06/2000	VB		Dans le cadre des essais thérapeutiques seulement			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64218 PATHAK		Atul	10/07/2006	IP	SANOFI AVENTIS	Actions - 17 actions			
64218 PATHAK		Atul	10/07/2006	LD-AR	PIERRE FABRE	Participation à un conseil indépendant de sécurité (Safety Board) pour un produit en développement	rémunération versée à une institution	06/2006	06/2007
64218 PATHAK		Atul	10/07/2006	LD-AR	FERTIZIN	Participation à un conseil indépendant de sécurité (Safety Board) pour un produit en développement	rémunération versée à une institution	07/2004	10/2005
64218 PATHAK		Atul	10/07/2006	EC-INV	SANKYO	Etude observationnelle de phase 4	conseil scientifique	10/2006	10/2007
64218 PATHAK		Atul	10/07/2006	EC-CO	SANKYO	Participation à la réalisation d'essais cliniques - Olmesartan	co-investigateur	01/2006	01/2008
64218 PATHAK		Atul	10/07/2006	CF-INT	BMS, MSD, SANOFI, PFIZER, ASTRA ZENECA, SOLVAY, SERVIER	Plusieurs réunions	rémunération partagée personnelle / institution		
64218 PATHAK		Atul	10/07/2006	CF-AUD	BMS, MSD, SANOFI, PFIZER, ASTRA ZENECA, SOLVAY, SERVIER	Participation aux différents congrès scientifiques			
61059 PELISSIER-LANGBORT		Clara	29/11/2007	EC-INV	IPRAD	Etude Secnidazole versus metronidazole	elaboration protocole - réunion investigateurs - suivi	01/2007	12/2007
61059 PELISSIER-LANGBORT		Clara	29/11/2007	CF-INT	SERVIER	Protelos - co-modérateur du symposium - Servier Médical "ostéoporose = rationnel du choix thérapeutique (	rémunération personnelle	01/2007	01/2007
61059 PELISSIER-LANGBORT		Clara	29/11/2007	CF-INT	GRUNENTHAL INTERNATIONAL	Chairmanship du symposium Grunenthal (Belara) lors du 7ème congrès de la Société Européenne de Gyné	rémunération personnelle	10/2007	10/2007
61059 PELISSIER-LANGBORT		Clara	20/02/2006	LD-AR	AVENTIS	expert	rémunération personnelle	01/2002	12/2004
61059 PELISSIER-LANGBORT		Clara	20/02/2006	LD-AR	AVENTIS	expert d'unboard	rémunération personnelle	07/2005	10/2005
61059 PELISSIER-LANGBORT		Clara	20/02/2006	LD-AR	BAYER SANTE FAMILIALE	consultant	rémunération personnelle	11/2005	
61059 PELISSIER-LANGBORT		Clara	20/02/2006	LD-AR	BIODIM	expertise scientifique sur progestatifs	rémunération personnelle	09/2005	03/2006
61059 PELISSIER-LANGBORT		Clara	20/02/2006	LD-AR	ADECA 75	conseil scientifique et éthique	aucune rémunération	01/2003	01/2006
61059 PELISSIER-LANGBORT		Clara	20/02/2006	IP-AC	PFIZER	groupe de travail neurologues - gynécologues (migraine)		01/2005	12/2006
61059 PELISSIER-LANGBORT		Clara	20/02/2006	CF-INT	GRUNENTHAL	Nice : 22ème journées de FME du collège de gynécologie médicale du Sud Est - l'Acetate de chlormadinone	aucune rémunération	02/2006	02/2006
61059 PELISSIER-LANGBORT		Clara	20/02/2006	CF-INT	WYETH	Amicale 17ème - Paris "Contraception en 2005 : actualités"		11/2005	11/2005
61059 PELISSIER-LANGBORT		Clara	28/02/2004	IP-EC	SERVIER	Essai clinique en 2003			
61059 PELISSIER-LANGBORT		Clara	28/02/2004	IP-AC	AVENTIS	Activités de conseil			
61059 PELISSIER-LANGBORT		Clara	28/02/2004	IP-CF	AVENTIS	FMC : tout médical endométriose			
61059 PELISSIER-LANGBORT		Clara	28/02/2004	IP-CF	THERAMEX	1 article sur les progestatifs			
61059 PELISSIER-LANGBORT		Clara	10/03/2003	IP-EC	SERVIER	Essai clinique sur Aerodiol			
61059 PELISSIER-LANGBORT		Clara	10/03/2003	IP-EC	THERAMEX MERCK	Article Annales d'endocrinologie sur les lipides et l'acétate de nomegertrol (sous presse)			
61059 PELISSIER-LANGBORT		Clara	10/03/2003	IP-AC	AVENTIS	Conseil sur la gynécologie			
61059 PELISSIER-LANGBORT		Clara	10/03/2003	IP-CF	SCHERING-PLOUGH, SERVIER, AVENTIS, etc.	Présidente de symposiums			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-RE	ORGANON	Etude Livial			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-EC	SERVIER	Etude Aerodiol			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-EC	FABRE	Etude Menopause patch et progestatif patch			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-EC	SOLYMES	Etude thrombose, Hôtel Dieu			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-AC	FABRE	1999			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-AC	SOLYMES	1999			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	IP-CF	SOLVAY, PHARMA, SERVIER, SOLYMES	Congrès			
61059 PELISSIER-LANGBORT		Clara	28/01/2000	(Autre)		Présidente de la Société Française de Gynécologie - Secrétaire de la Société Européenne de Gynécologie - Présidente de l'AMGOP (Amicale des Gynécologues et Obstétriciens			
62710 PELISSOLO		Antoine	25/01/2010	CF-INT	LILLY ET BOEHRINHER	Board d'experts sur la dépression et la Duloxétine (en cours)	Aucune rémunération	01/2008	06/2009
62710 PELISSOLO		Antoine	25/01/2010	CF-INT	UCB PHARMA	Participation au CREA (Cercle de Recherche et d'Etude sur l'Anxiété) comme expert sur les troubles anxieu	Aucune rémunération	01/2008	06/2009
62710 PELISSOLO		Antoine	25/01/2010	CF-INT	LUNDBECK	Congres de l'Encéphale; intervention sur les dépressions sévères	Rémunération personnelle	01/2010	01/2010
62710 PELISSOLO		Antoine	25/01/2010	CF-INT	LUNDSECK	Congrès Français de Psychiatrie (Nice); intervention sur les dépressions récurrentes	Rémunération personnelle	12/2009	12/2009
62710 PELISSOLO		Antoine	25/01/2010	EC-CO	SIGMA-TAU	Etude controlée du sevrage de l'alprazolam et du prazépam	Membre du comité scientifique	06/2007	
62710 PELISSOLO		Antoine	25/01/2010	EC-CO	LYNAPHARM	Etude controlée du sevrage de l'alprazolam et du prazépam	Membre du comité scientifique	06/2007	12/2008
62710 PELISSOLO		Antoine	15/09/2008	CF-INT	SERVIER	Animateur du séminaire "Valoriser votre Recherche" destiné à de jeunes psychiatres	Rémunération personnelle	01/2008	01/2008
62710 PELISSOLO		Antoine	15/09/2008	EC-CO	LYNAPHARM	Etude controlée du sevrage de l'alprazolam et du prazépam	Membre du comité scientifique	06/2007	12/2008
62710 PELISSOLO		Antoine	15/09/2008	CF-INT	WYETH	Conférence dans le cadre d'un séminaire interne de formation des visiteurs médicaux sur la dépression (Bar	Rémunération personnelle	08/2008	08/2008
62710 PELISSOLO		Antoine	27/06/2008	IP-AUT	LUNDBECK	Rédaction d'un article de synthèse sur les effets de l'escitalopram dans les troubles anxieux		01/2008	07/2008
62710 PELISSOLO		Antoine	27/06/2008	CF-INT	BIOCODEX	Participation comme orateur à une journée scientifique sur le trouble de l'adaptation	Rémunération personnelle	03/2008	03/2008
62710 PELISSOLO		Antoine	27/06/2008	CF-INT	LILLY ET BOEHRINHER	Board d'experts sur la dépression et la Duloxétine (en cours)	Rémunération personnelle	01/2008	
62710 PELISSOLO		Antoine	27/06/2008	CF-INT	UCB PHARMA	Participation au CREA (Cercle de Recherche et d'Etude sur l'Anxiété) comme expert sur les troubles anxieu	Rémunération personnelle	01/2008	06/2009
62710 PELISSOLO		Antoine	27/06/2008	EC-CO	LUNDBECK	Essai clinique multicentrique comparant Escitalopram et Duloxetine dans la dépression majeure (en cours)	Coordonnateur pour la France	01/2005	12/2007
62710 PELISSOLO		Antoine	25/06/2007	CF-AUD	SANOFI-SYNTHELABO	Congrès de la Société Franco-Algérienne de psychiatrie, Montpellier		06/2007	06/2007
62710 PELISSOLO		Antoine	25/06/2007	CF-INT	WYETH	Académie de neuropsychopharmacologie, Dubai	Aucune rémunération	02/2007	02/2007
62710 PELISSOLO		Antoine	25/06/2007	CF-INT	SERVIER	Animation d'un séminaire de formation sur la recherche en psychiatrie (« Valoriser votre recherche »), 3 jour	Rémunération personnelle	01/2007	01/2007
62710 PELISSOLO		Antoine	25/05/2006	LD-AR	UCB PHARMA	Participation au CREA (Cercle de Recherche et d'Etude sur l'Anxiété) comme expert sur les troubles anxieu	rémunération personnelle	01/2001	
62710 PELISSOLO		Antoine	25/05/2006	LD-AR	PFIZER	Board d'experts sur l'anxiété généralisée et la Prégabaline (en cours)	rémunération personnelle	01/2005	
62710 PELISSOLO		Antoine	25/05/2006	LD-AR	LILLY	Board d'experts sur la dépression et la Duloxétine (en cours)	rémunération personnelle	01/2005	
62710 PELISSOLO		Antoine	25/05/2006	EC-INV	LUNDBECK SA	Essai clinique multicentrique comparant Escitalopram et Duloxetine dans la dépression majeure (en cours)	investigateur coordonnateur pour la France	06/2005	
62710 PELISSOLO		Antoine	25/05/2006	EC-CO	GSK	Etude épidémiologique nationale sur la phobie sociale en psychiatrie (étude "phoenix")	membre du comité scientifique	01/2001	12/2004
62710 PELISSOLO		Antoine	25/05/2006	EC-CO	GSK	Etude épidémiologique nationale sur la prescription de la paroxetine dans le trouble anxiété généralisé (obs	membre du comité scientifique	01/2003	
62710 PELISSOLO		Antoine	25/05/2006	EC-CO	PFIZER	Etude nationale sur la dépression récurrente en psychiatrie libérale (étude "ECLAIR")	membre du comité scientifique	01/2003	12/2005
62710 PELISSOLO		Antoine	25/05/2006	IP-AC	LUNDBECK SA	Participation comme expert à une réunion sur les risques suicidaires associés aux traitements antidépresse	rémunération personnelle	10/2003	10/2003
62710 PELISSOLO		Antoine	25/05/2006	IP-AC	BMS	Participation à un groupe de travail sur les effets neuropsychiatriques de l'Efavirenz	rémunération personnelle	01/2002	12/2003
62710 PELISSOLO		Antoine	25/05/2006	CF-INT	GSK	Conférence destinée aux médecins généralistes sur les émotions - Mulhouse	rémunération personnelle	05/2004	05/2004
62710 PELISSOLO		Antoine	25/05/2006	CF-INT	LYNAPHARM	Conférence destinée aux médecins sur la prescription des benzodiazépines (Produit du laboratoire : Lysanxi	rémunération personnelle		
62710 PELISSOLO		Antoine	25/05/2006	CF-INT	SERVIER	Animation d'un séminaire de formation sur la recherche en psychiatrie ("Valoriser votre recherche"), 3 journ	rémunération personnelle	03/2004	03/2004
62710 PELISSOLO		Antoine	25/05/2006	CF-INT	SERVIER	Animation d'un séminaire de formation sur la recherche en psychiatrie ("Valoriser votre recherche"), 3 journ	rémunération personnelle	03/2005	03/2005
62710 PELISSOLO		Antoine	25/05/2006	CF-INT	SERVIER	Animation d'un séminaire de formation sur la recherche en psychiatrie ("Valoriser votre recherche"), 3 journ	rémunération personnelle	03/2006	03/2006
62710 PELISSOLO		Antoine	25/05/2006	CF-AUD	GSK	Congrès international de l'ECNP, psychopharmacologie - Amsterdam	aucune rémunération	10/2005	10/2005
62710 PELISSOLO		Antoine	25/05/2006	IP-AUT	LYNAPHARM	Co-rédaction d'un guide sur les Benzodiazépines destiné aux généralistes		01/2004	12/2004
62710 PELISSOLO		Antoine	20/05/2006	CF-INT	SERVIER	Séminaire "valoriser votre recherche"	rémunération personnelle	01/2003	12/2006
62710 PELISSOLO		Antoine	20/05/2006	EC-CO	GSK	Etude Epidémiologique PHOENIX (Phobies Sociales)	comité scientifique	01/2002	12/2006
62710 PELISSOLO		Antoine	20/05/2006	LD-AR	UCB-PHARMA	Participation au CREA (Cercle de Recherche et d'Etudes sur l'Anxiété)	rémunération personnelle	01/2001	12/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62710	PELISSOLO	Antoine	20/05/2006	EC-INV	LUNDBECK	Essai clinique de phase IV comparaison Escitalopram / Duloxetine dans la dépression majeure	coordonnateur	01/2005	12/2006
62710	PELISSOLO	Antoine	20/05/2006	EC-CO	GSK	Etude observationnelle alternative (Prescription Déroxat)	comité scientifique	01/2003	12/2006
62710	PELISSOLO	Antoine	20/05/2006	EC-CO	PFIZER	Etude épidémiologique ECLAIR	comité scientifique	01/2002	12/2005
62710	PELISSOLO	Antoine	20/05/2006	IP-AC	PFIZER	Participation à un groupe d'expert sur la Prégabaline	rémunération personnelle		
62710	PELISSOLO	Antoine	20/05/2006	CF-INT	LYNAPHARM	Prescription de Benzodiazépines	rémunération personnelle	02/2006	02/2006
62710	PELISSOLO	Antoine	20/05/2006	IP-AC	LILLY	Participation à un groupe de travail sur la Dosulépine	rémunération personnelle	01/2005	12/2006
62710	PELISSOLO	Antoine	02/09/2005	EC-CO	PFIZER	Etude nationale sur la dépression récurrente en psychiatrie libérale (étude "ECLAIR") - Membre du comité scientifique		01/2003	12/2005
62710	PELISSOLO	Antoine	02/09/2005	IP-AC	LUNDBECK SA	participation comme expert à une réunion sur les risques suicidaires associés aux traitements antidépresseu	Rémunération personnelle	10/2003	10/2003
62710	PELISSOLO	Antoine	02/09/2005	IP-AC	BMS	Participation à un groupe de travail sur les effets neuropsychiatriques de l'éfavirenz	Rémunération personnelle	01/2002	12/2003
62710	PELISSOLO	Antoine	02/09/2005	CF-INT	GSK	Conférence destinée aux médecins généralistes sur les émotions (Mulhouse)	Rémunération personnelle	05/2004	05/2004
62710	PELISSOLO	Antoine	02/09/2005	IP-AUT	LYNAPHARM	Co-rédaction d'un guide sur les benzodiazépines destinés aux généralistes		01/2004	12/2004
62710	PELISSOLO	Antoine	23/06/2005	IP-CF		Exposés en FMC et préparation d'articles			
62710	PELISSOLO	Antoine	26/02/2003	IP-EC	GLAXO SMITHKLINE	Coordination étude Phoenix			
62710	PELISSOLO	Antoine	26/02/2003	IP-EC	UCB	Groupe scientifique CREA			
62710	PELISSOLO	Antoine	26/02/2003	IP-CF	ROCHE NICKOLES	réunions FMC sur stress et anxiété			
64200	PETIT	Alain	02/04/2010	LD	TECHNOLOGIE SERVIER	Responsable service analytique	CDI	06/1982	
64200	PETIT	Alain	04/02/2009	LD	TECHNOLOGIE SERVIER	Responsable service analytique	CDI	06/1982	
64200	PETIT	Alain	16/11/2007	LD	TECHNOLOGIE SERVIER	Responsable service analytique	CDI	06/1982	
64200	PETIT	Alain	30/03/2006	LD	TECHNOLOGIE SERVIER	Responsable service analytique	CDI	06/1982	
62844	PHILIPPE	François	23/01/2008	EC-CO	ASTRAZENECA	Co-investigateur essai PLATO (anti-agrégant AZD)	co-investigateur	01/2007	12/2008
62844	PHILIPPE	François	23/01/2008	CF-INT	PFIZER	Symposium VIAGRA - Strasbourg 2008	Rémunération personnelle		
62844	PHILIPPE	François	24/01/2007	EC-CO	ASTRA ZENECA	Etude PLATO phase IV (Antiagrégant vs Clopidogrel)	co-investigateur	01/2007	12/2007
62844	PHILIPPE	François	24/01/2007	EC-CO	LILLY	Registre APTOR (suivi post Angioplastie) (1er Trim 2007 / 2e Trim 2007)	co-investigateur	01/2007	06/2007
62844	PHILIPPE	François	24/01/2007	CF-INT	BRISTOL-MYERS-SQUIBB	Symposium Francais PRAVADUAL (courant 2006)	rémunération personnelle	01/2006	12/2007
62844	PHILIPPE	François	24/01/2007	CF-INT	SANOFI AVENTIS	Conférence syndrome Coronaire Aigu - PLAVIX (courant 2006)	Rémunération personnelle		12/2008
62844	PHILIPPE	François	24/01/2007	CF-INT	ASTRAZENECA	Conférence symposium Dyslipidémie CRESTOR international (courant 2007)	rémunération personnelle		12/2008
62844	PHILIPPE	François	24/01/2007	CF-AUD	SERVIER	ACC 2007 - New Orléans		03/2007	03/2007
62844	PHILIPPE	François	23/03/2006	EC-CO	LILLY	étude TIMI 38 - TRITON - Prasugrel vs Clopidogrel dans les syndromes coronaires aigus avec angioplastie	co-investigateur	09/2005	06/2006
62844	PHILIPPE	François	23/03/2006	EC-CO	(GRACE) AVENTIS	registre international des syndromes coronaires aigus GRACE	co-investigateur	01/2002	12/2006
62844	PHILIPPE	François	23/03/2006	IP-AC	DRASS-IF	réorganisation Cardiologie interventionnelle	aucune rémunération	01/2004	12/2004
62844	PHILIPPE	François	23/03/2006	IP-AC	CNAM	refonte de la nomenclature des actes classants en Cardiologie	rémunération personnelle	01/2002	12/2003
62844	PHILIPPE	François	23/03/2006	CF-INT	BMS	série EPV (Bretagne/nord) sur la mise à jour des recommandations AFSSAPS 2005 sur la prise en charge d	rémunération personnelle	01/2005	12/2006
62844	PHILIPPE	François	23/03/2006	CF-INT	ASTRA ZENECA	orateur à symposia "Lower is better" (rosuvastatine)	rémunération personnelle	01/2006	12/2006
62844	PHILIPPE	François	06/12/2005	EC-CO	LILLY	Etude TRITON TIMI 18 - Prasugrel : essai phase III	co-investigateur	06/2005	05/2006
62844	PHILIPPE	François	06/12/2005	IP-CF	BMS	EPU en France/ prévention cardiovasculaire/ Pravastatine et clopidogrel (courant 2005)	rémunération personnelle		
62844	PHILIPPE	François	06/12/2005	IP-CF	ASTRA ZENECA	EPU en France / recommandation AFSSAPS 2005/ Rosuvastatine (courant 2005)			
62844	PHILIPPE	François	06/12/2005	CF-INT	PFIZER	EPU en France / dysfonction érectile et cœur/ Sildenafil (courant 2005)	rémunération personnelle		
62844	PHILIPPE	François	08/09/2003	IP-EC	AVENTIS	Registre international GRACE sur les syndrômes coronaires aigus			
62844	PHILIPPE	François	08/09/2003	IP-EC	CORDIS	TYPHOON : stent sirolimus dans l'infarctus du myocarde aigu			
62844	PHILIPPE	François	08/09/2003	IP-AC	BRISTOL MYERS SQUIBB (Division cardiovasculaire)	Pravastatine en prévention cardiovasculaire			
62844	PHILIPPE	François	08/09/2003	IP-CF	BRISTOL MYERS SQUIBB	Conférence et formation "Statines en prévention"			
62844	PHILIPPE	François	08/09/2003	IP-CF	PFIZER	Vialink ; formation Sildénafil et cœur			
65787	PICAUD	Serge	01/04/2010	LD-ODE	FOVEA PHARMA	(Filiale de Sanofi). Consultant (en cours)		05/2005	
65787	PICAUD	Serge	01/04/2010	LD-AR	SERVIER	Collaboration scientifique préclinique (en cours)	Aucune rémunération	01/2007	
65787	PICAUD	Serge	01/04/2010	LD-AR	ESSILOR	Collaboration scientifique préclinique	Aucune rémunération	01/2008	
65787	PICAUD	Serge	01/04/2010	EC-INV	TARGEON	Vigabatrin	Conseiller scientifique	01/2011	
65787	PICAUD	Serge	01/04/2010	IP-AUT	INSERM	Brevets sur le Vigabatrin et la Taurine			
10339	PIETTE	François	16/04/2008	LD-AR	SERVIER	Conseil médical	rémunération personnelle	01/1995	12/2009
10339	PIETTE	François	16/04/2008	IP-AC	IPSEN	Etude GuidAge TANAKAN	aucune rémunération	01/2000	12/2010
10339	PIETTE	François	16/04/2008	CF-INT	ETABLISSEMENTS THERMAUX	Paris : Plan des établissements thermaux dans la prévention chez les sujets âgés	rémunération personnelle	01/2007	12/2007
10339	PIETTE	François	16/04/2008	CF-INT	MEDEC	Paris : La consultation de prévention à 70 ans	rémunération personnelle	01/2007	12/2007
10339	PIETTE	François	16/04/2008	VB	MEDIALIS - AGEIS	Convention pour un partenariat hôpital - entreprise : technologie pour personne âgée	APHP	01/2007	
10339	PIETTE	François	18/01/2006	LD	IRIS (SERVIER)	Conseiller	versement honoraires	01/1994	
10339	PIETTE	François	18/01/2006	LD-AR	IPSEN/BEAUFOUR	Expert étude GUIDAGE (Tanakan) 2003	Rémunération personnelle		
10339	PIETTE	François	18/01/2006	EC-INV	AB SCIENCE	AB 0424	investigateur principal	01/2006	01/2007
10339	PIETTE	François	18/01/2006	CF-INT	Association Gérontologiques Sud 77	Formation Médicale Continue - Melun - "CRP et sujet agé"	rémunération personnelle		
10339	PIETTE	François	01/01/1999	LD	Société ADIR/ SERVIER				
10339	PIETTE	François	01/01/1999	IP-AC	EISAI				
10339	PIETTE	François	01/01/1999	IP-AUT	PARKE DAVIS				
10339	PIETTE	François	01/01/1999	VB	PROCTER & GAMBLE	Association REGATES, Essai thérapeutique.			
10339	PIETTE	François	01/01/1999	VB	SYNTHELABO				
10339	PIETTE	François	01/01/1999	VB	LILLY				
10339	PIETTE	François	01/01/1999	VB	LAFON	Financement d'une bourse de recherche.			
10339	PIETTE	François	01/01/1999	VB	LOGEAIS JACQUES				
10339	PIETTE	François	01/01/1999	VB	IPSEN				
10339	PIETTE	François	01/01/1999	VB	UCB				
10339	PIETTE	François	01/01/1999	VB	GLAXO				
10339	PIETTE	François	01/01/1999	VB	JANSSEN				
10339	PIETTE	François	01/01/1998	LD	SERVIER				
10339	PIETTE	François	01/01/1998	IP-AUT	Institut Aster		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	LILLY France		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	PFIZER		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	Procter et Gamble		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	Searle		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	PARKE DAVIS		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	UCB		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	Lafon		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	GLAXO WELLCOME		pour l'association REGATES		
10339	PIETTE	François	01/01/1998	VB	SPECIA		pour l'association REGATES		
63045	PIETTE	Jean Charles					bénévolat	01/2009	01/2012
62051	PINGET	Michel	04/01/2010	LD-ODE	ASDIA EST	Comité de surveillance	rémunération personnelle	01/2009	01/2010
62051	PINGET	Michel	04/01/2010	LD-AR	MEDTRONIC	Consultant			

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62051 PINGET		Michel	04/01/2010	LD-AR	ROCHE DIAGNOSTICS	Consultant	rémunération personnelle	01/2006	01/2010
62051 PINGET		Michel	04/01/2010	LD-AR	NOVO NORDISK	Consultant	rémunération personnelle	01/2008	01/2010
62051 PINGET		Michel	04/01/2010	LD-AR	YPSOMED	Consultant	rémunération personnelle	01/2007	01/2010
62051 PINGET		Michel	04/01/2010	EC-INV	SANOFI AVENTIS	Divestigateur principal au niveau international (avc 2010)	investigateur principal	01/2008	12/2011
62051 PINGET		Michel	04/01/2010	IP-RE	MEDTRONIC	MIP 2007	aucune rémunération	01/2007	12/2007
62051 PINGET		Michel	04/01/2010	IP-RE	SANOFI AVENTIS	Consultant	aucune rémunération	01/2007	12/2007
62051 PINGET		Michel	04/01/2010	IP-AC	ROCHE DIAGNOSTICS	Advisory board (protocole diapurt)	rémunération personnelle	01/2008	12/2009
62051 PINGET		Michel	04/01/2010	IP-AC	NOVO NORDISK	Advisory board (insuline Siga)	rémunération personnelle	01/2008	12/2010
62051 PINGET		Michel	04/01/2010	CF-INT	NOVO NORDISK	Le diabète de type 2 et les insulines (Maroc, Algérie, Tunisie)	rémunération personnelle	01/2008	12/2009
62051 PINGET		Michel	04/01/2010	CF-AUD	NOVARTIS	EASD 2009		01/2009	
62051 PINGET		Michel	04/01/2010	VB	ABBOTT	Soutien à la recherche	XXX	01/2006	12/2011
62051 PINGET		Michel	01/12/2009	LD-ODE	ASDIA EST	Comité de surveillance	Bénévolat	01/2009	01/2012
62051 PINGET		Michel	01/12/2009	LD-AR	MEDTRONIC	Consultant	Rémunération personnelle	01/2009	01/2010
62051 PINGET		Michel	01/12/2009	LD-AR	ROCHE DIAGNOSTIC	Consultant	Rémunération personnelle	01/2006	01/2010
62051 PINGET		Michel	01/12/2009	LD-AR	NOVO NORDISK	Consultant	Rémunération personnelle	01/2008	01/2010
62051 PINGET		Michel	01/12/2009	LD-AR	YPSOMED	Consultant	Rémunération personnelle	01/2007	01/2010
62051 PINGET		Michel	01/12/2009	EC-INV	SANOFI AVENTIS	Investigateur principal au niveau international (avc 2010)	Investigateur principal	01/2008	12/2011
62051 PINGET		Michel	01/12/2009	IP-RE	MEDTRONIC	MIP 2007	Aucune rémunération	01/2007	12/2007
62051 PINGET		Michel	01/12/2009	IP-RE	SANOFI AVENTIS	Insuplant	Aucune rémunération	01/2007	12/2007
62051 PINGET		Michel	01/12/2009	IP-AC	ROCHE DIAGNOSTIC	Advisory Board (protocole DIAPORT)	Rémunération personnelle	01/2008	12/2009
62051 PINGET		Michel	01/12/2009	IP-AC	NOVO NORDISK	Advisory Board (insulin Sica)	Rémunération personnelle	01/2008	12/2010
62051 PINGET		Michel	01/12/2009	CF-INT	NOVO NORDISK	Le diabète de type 2 et les insulines (Maroc, Algérie, Tunisie)	Rémunération personnelle	01/2008	12/2009
62051 PINGET		Michel	01/12/2009	CF-AUD	NOVARTIS	EASD 2009		01/2009	
62051 PINGET		Michel	01/12/2009	VB	ABBOTT	Soutien à la recherche	XXX	01/2006	12/2011
62051 PINGET		Michel	19/10/2009	LD-ODE	ASDA EST	Comité de surveillance	Bénévolat	01/2009	01/2012
62051 PINGET		Michel	19/10/2009	LD-AR	MEDTRONIC	Consultant	Rémunération personnelle	01/2009	01/2010
62051 PINGET		Michel	19/10/2009	LD-AR	ROCHE DIAGNOSTIC	Consultant	Rémunération personnelle	01/2006	01/2010
62051 PINGET		Michel	19/10/2009	LD-AR	NOVO NORDISK	Consultant	Rémunération personnelle	01/2008	01/2010
62051 PINGET		Michel	19/10/2009	LD-AR	YPSOMED	Consultant	Rémunération personnelle	01/2007	01/2010
62051 PINGET		Michel	19/10/2009	EC-INV	SANOFI AVENTIS	Investigateur principal au niveau international (avc 2010)	Investigateur principal	01/2008	12/2011
62051 PINGET		Michel	19/10/2009	IP-RE	MEDTRONIC	MIP 2007	Aucune rémunération	01/2007	12/2007
62051 PINGET		Michel	19/10/2009	IP-RE	SANOFI AVENTIS	Consultant	Aucune rémunération	01/2007	12/2007
62051 PINGET		Michel	19/10/2009	IP-AC	ROCHE DIAGNOSTIC	Advisory Board (protocole Diaport)	Rémunération personnelle	01/2008	12/2009
62051 PINGET		Michel	19/10/2009	IP-AC	NOVO NORDISK	Advisory Board (insulin Siga)	Rémunération personnelle	01/2008	12/2011
62051 PINGET		Michel	19/10/2009	CF-INT	NOVO NORDISK	Le diabète de tyoe 2 et les insulines (Maroc, Algérie, Tunisie)	Rémunération personnelle	01/2008	12/2009
62051 PINGET		Michel	19/10/2009	CF-AUD	NOVARTIS	EASD 2009		01/2009	
62051 PINGET		Michel	19/10/2009	VB	ABBOTT	Soutien à la recherche	Centre Européen Etude du diabète - CEED -	01/2006	12/2011
62051 PINGET		Michel	06/04/2008	EC-INV	PFIZER	Exubera type 1	investigateur	01/2006	12/2008
62051 PINGET		Michel	06/04/2008	EC-INV	PFIZER	Exubera type 2	Investigateur - coordonateur	01/2006	12/2008
62051 PINGET		Michel	06/04/2008	EC-INV	ELI LILLY	Byetta type 2	Co-investigateur	01/2007	12/2009
62051 PINGET		Michel	06/04/2008	RE-DE	MEDTRONIC	Pompe implantée MIP 2007	Aucune rémunération		
62051 PINGET		Michel	06/04/2008	IP-AC	NOVO NORDISK		rémunération personnelle	01/2007	12/2008
62051 PINGET		Michel	06/04/2008	IP-AC	MEDTRONIC		rémunération personnelle	01/2004	12/2007
62051 PINGET		Michel	06/04/2008	IP-AC	ROCHE		rémunération personnelle	01/2003	12/2008
62051 PINGET		Michel	06/04/2008	IP-AC	YPSOMED		rémunération personnelle	01/2005	12/2008
62051 PINGET		Michel	06/04/2008	CF-INT	NOVO NORDISK	sujets divers / Alfediam	rémunération personnelle	01/2007	12/2008
62051 PINGET		Michel	06/04/2008	CF-INT	ELI LILLY	Présidence des journées Lilly en diabétologie	rémunération personnelle	01/2008	12/2008
62051 PINGET		Michel	06/04/2008	VB	ABBOTT	Soutien à la recherche		01/2004	12/2009
62051 PINGET		Michel	06/04/2008	VB	SERVIER	Soutien à la recherche		01/2002	12/2003
62051 PINGET		Michel	06/04/2008	VB	ELI LILLY	Partenariat recherche		01/2006	12/2009
62051 PINGET		Michel	06/04/2008	RE-DE	PROSTRAKAN	Insuline insuplant	aucune rémunération		
62051 PINGET		Michel	08/01/2007	LD-AR	PFIZER-AVENTIS	International advisory Board - Insuline EXUBERA	rémunération personnelle	01/2000	
62051 PINGET		Michel	08/01/2007	EC-CO	MEDTRONIC	Essai pompe	co-investigateur	01/1998	
62051 PINGET		Michel	08/01/2007	RE-DE	ABBOTT	Dosage cétonémie	aucune rémunération		
62051 PINGET		Michel	08/01/2007	RE-AUT	AVENTIS	Insuplant pour pompe	rémunération personnelle	01/2000	
62051 PINGET		Michel	08/01/2007	IP-AC	MEDTRONIC	pompe à insuline	rémunération personnelle	01/2002	12/2005
62051 PINGET		Michel	08/01/2007	IP-AC	ROCHE	pompe + lecteur	rémunération personnelle	01/2003	12/2005
62051 PINGET		Michel	08/01/2007	IP-AC	YPSOMED	aiguilles	rémunération personnelle	01/2004	12/2005
62051 PINGET		Michel	08/01/2007	CF-INT	PFIZER - ASTRA-ZENECA - SCHERING PLOUGH	Dyslipidémie	rémunération personnelle	01/2003	12/2005
62051 PINGET		Michel	08/01/2007	CF-INT	SERVIER	Diabète type 2	rémunération personnelle	01/2003	12/2004
62051 PINGET		Michel	08/01/2007	IP-AC	MEDTRONIC	pompe à insuline	rémunération personnelle	01/2006	
62051 PINGET		Michel	05/12/2005	LD-AR	PFIZER AVENTIS	Insuline Exubera - International Advisory Board (depuis 2000)	rémunération personnelle		
62051 PINGET		Michel	05/12/2005	EC-CO	MEDTRONIC	Essai pompe (depuis 1998)	co-investigateur	01/1998	
62051 PINGET		Michel	05/12/2005	RE-DE	ABBOTT	Dosage cétonémie	aucune rémunération		
62051 PINGET		Michel	05/12/2005	RE-AUT	AVENTIS	Insuplant pour pompe	rémunération personnelle	01/2000	12/2003
62051 PINGET		Michel	05/12/2005	IP-AC	MEDTRONIC	Pompe insuline	rémunération personnelle	01/2002	12/2005
62051 PINGET		Michel	05/12/2005	IP-AC	ROCHE	pompe + lecteur	rémunération personnelle	01/2003	12/2005
62051 PINGET		Michel	05/12/2005	IP-AC	YPSOMED	Aiguilles	rémunération personnelle	01/2004	12/2005
62051 PINGET		Michel	05/12/2005	CF-INT	PFIZER, ASTRA ZENECA, SCHERING PLOUGH	Dyslipidémie	rémunération personnelle	01/2003	12/2005
62051 PINGET		Michel	05/12/2005	CF-INT	SERVIER	Diabète type 2	rémunération personnelle	01/2003	12/2003
62051 PINGET		Michel	05/12/2005	CF-INT	SERVIER	Diabète de type 2	rémunération personnelle	01/2004	12/2004
62051 PINGET		Michel	12/06/2004	IP-EC	GSK, TAKEDA, AVENTIS, NOVO NORDISK	Protocole médicament			
62051 PINGET		Michel	12/06/2004	IP-RE	AVENTIS	Insuline			
62051 PINGET		Michel	12/06/2004	IP-RE	PFIZER				
62051 PINGET		Michel	12/06/2004	IP-AC	MEDTRONIC	??			
62051 PINGET		Michel	12/06/2004	IP-AC	ROCHE DIAGNOSTIC France	??			
62051 PINGET		Michel	12/06/2004	IP-CF	PFIZER				
62051 PINGET		Michel	12/06/2004	IP-AC	ASTRA ZENECA	??			
62051 PINGET		Michel	12/06/2004	IP-CF	NOVO NORDISK	??			
62051 PINGET		Michel	12/06/2004	IP-CF	AVENTIS	??			
62051 PINGET		Michel	11/03/2003	LD	MEDTRONIC	Consultant scientifique			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62051	PINGET	Michel	11/03/2003	LD	DISETRONIC	Consultant scientifique			
65055	PIOT	Olivier	10/08/2010	EC-INV	MEDTRONIC	Etude PREFER-MVP / PM ou DAI avec fonction MVP	Comité de pilotage	01/2006	12/2011
65055	PIOT	Olivier	10/08/2010	EC-INV	MEDTRONIC	Etude PRESERVES / PM ou DAI avec fonction MVP	Investigateur principal	01/2010	12/2011
65055	PIOT	Olivier	10/08/2010	EC-INV	MEDTRONIC	Etude TRIV resynchronisation	Investigateur principal	01/2010	12/2014
65055	PIOT	Olivier	10/08/2010	EC-INV	MEDTRONIC	Etude V3 resynchronisation	Comité de pilotage	01/2010	12/2014
65055	PIOT	Olivier	10/08/2010	EC-INV	SORIN	Etude BITAC Défibrillateurs double chambre	Investigateur principal	01/2009	12/2011
65055	PIOT	Olivier	10/08/2010	EC-INV	SORIN	Etude FIRST registre défibrillateur	Coordonnateur France	01/2008	12/2011
65055	PIOT	Olivier	10/08/2010	EC-INV	SORIN	Etude TUTOR Défibrillateurs avec fonction PHD	Investigateur principal	01/2010	12/2013
65055	PIOT	Olivier	10/08/2010	EC-CO	BOSTON	Etude OPTIMIND PM Altrua	Co-investigateur	01/2010	12/2013
65055	PIOT	Olivier	10/08/2010	EC-CO	BOSTON	Etude SEPTAL CRT resynchronisation	Co-investigateur	01/2009	12/2012
65055	PIOT	Olivier	10/08/2010	EC-CO	SAINT JUDE MEDICAL	Etude OPTIWAVE et OPTIWAVE II défibrillateurs	Co-investigateur	01/2008	12/2010
65055	PIOT	Olivier	10/08/2010	IP-AC	SORIN	Analyse des produits en développement et des études cliniques en cours	Rémunération personnelle	05/2010	12/2010
65055	PIOT	Olivier	10/08/2010	IP-AC	MEDTRONIC	Groupe de travail scientifique sur les innovations	Rémunération personnelle	01/2009	12/2010
65055	PIOT	Olivier	10/08/2010	IP-AC	BIOTRONIK	Conseil sur télécardiologie et stimulation / défibrillation cardiaque	Rémunération personnelle	01/2010	12/2011
65055	PIOT	Olivier	10/08/2010	CF-INT	MEDTRONIC	Journées européennes SFC / Paris / Stimulateur cardiaque IRM compatible	Rémunération personnelle	01/2010	01/2010
65055	PIOT	Olivier	10/08/2010	CF-INT	BIOTRONIK	Cardiostim 2010 / Nice / Présentation Gamme Evia	Rémunération personnelle	06/2010	06/2010
65055	PIOT	Olivier	10/08/2010	CF-INT	SORIN	Cardiostim 2010 / Nice / Résultats scientifiques étude FIRST	Aucune rémunération	06/2010	06/2010
65055	PIOT	Olivier	10/08/2010	CF-AUD	MEDTRONIC	Congrès HRS, Boston		01/2009	12/2009
65055	PIOT	Olivier	10/08/2010	CF-AUD	BIOTRONIK	Journées J. Toresani (DIU stimulation cardiaque), Strasbourg		04/2010	04/2010
65055	PIOT	Olivier	10/08/2010	CF-AUD	SORIN	Congrès ESC, Stockholm		08/2010	08/2010
65588	PIOT	Christophe	06/01/2010	EC-INV	CHU MONTPELLIER	EPO dans infarctus aigu du myocarde	investigateur coordonateur	01/2008	12/2010
65588	PIOT	Christophe	06/01/2010	EC-CO	CHU LYON	Cyclosporine dans infarctus aigu du myocarde	co-investigateur	01/2006	12/2008
65588	PIOT	Christophe	06/01/2010	EC-CO	CHU LYON	Postconditionnement dans infarctus aigu du myocarde	co-investigateur	01/2006	12/2010
65588	PIOT	Christophe	06/01/2010	CF-AUD	BIOTRONIK	TCT - San Francisco		09/2009	09/2009
65588	PIOT	Christophe	06/01/2010	CF-AUD	SERVIER	AHA - Orlando		11/2009	11/2009
65588	PIOT	Christophe	06/01/2010	CF-AUD	CORDIS	New York		02/2010	02/2010
65055	PIOT	Olivier	07/04/2008	EC-INV	MEDTRONIC	Etude randomisée - produit ADAPTA DR	investigateur principal	01/2006	12/2009
65055	PIOT	Olivier	07/04/2008	EC-INV	SORIN	registre sur le mode de réglage et les thérapies délivrées par des défibrillateurs	investigateur principal	01/2007	12/2008
65055	PIOT	Olivier	07/04/2008	EC-CO	MEDTRONIC	Etude observationnelle SENSE-HF / produit : fonction OptiVol	co-investigateur	01/2007	12/2011
65055	PIOT	Olivier	07/04/2008	EC-CO	SAINT JUDE	Etude randomisée sur optimisation forme du choc / produit : défibrillateur	co-investigateur	01/2008	12/2008
65055	PIOT	Olivier	07/04/2008	CF-INT	SORIN	Journées Européennes de la SFC - symposium Sorin - sujet : xxxx - pas de produit particulier - Paris	aucune rémunération	01/2008	01/2008
65055	PIOT	Olivier	07/04/2008	CF-INT	GUIDANT	EUROPACE " Long term performance of xxx pacing leads " produit : électrodes GUIDANT 4473-4459 - Lisb	aucune rémunération	08/2007	06/2007
65055	PIOT	Olivier	07/04/2008	CF-AUD	BIOTRONIK	Congrès " Europace" 2007 - Lisbonne		06/2007	06/2007
65055	PIOT	Olivier	07/04/2008	CF-AUD	BIOTRONIK	Congrès "World congress on cardiac pacing and Electrophysiology " 2007 - Rome		12/2007	12/2007
65055	PIOT	Olivier	07/04/2008	CF-AUD	MEDTRONIC	European Congress of European Society of Cardiology - 2007 - Vienne		09/2007	09/2007
63365	POIRIER	Jean-Yves	12/02/2007	EC-CO	CHU RENNES (CISBIO INTERNATIONAL)	Evaluation de trousses de dosage de l'IGF1 chez des témoins et patients acromégales	collaborateur	01/2005	01/2007
63365	POIRIER	Jean-Yves	12/02/2007	VB	CEDE	Centre d'étude Diabétologie Endocrinologie - association loi 2001 domiciliée au CHU et dont je suis le Présk			
63365	POIRIER	Jean-Yves	12/02/2007	VB	MEDTRONIC - CEDE	Subvention (virement direct : 250)		08/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	REACH - CEDE	virement honoraires étude (350)		10/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	Novo Nordisk - CEDE	étude ARAMIS (CIC n° 523400) - 200		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	MSD - CEDE	Subvention (BNP n° 44970) - 1 000		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	Servier - CEDE	Honoraires D MAUGENDRE vidéo conférence (BNP n°271224) -- 600		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	BMS - CEDE	Subvention (CITYBANK n° 6298463) - 375		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	LVL MED - CEDE	Subvention (congrès pompe) (CL n° 9187766) - 300		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	ROCHE - CEDE	Subvention stand Congrès pompe (Natexis n° 9067481) - 450		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	VITAL AIR - CEDE	Subvention (congrès pompe) (BNP n° 4258453) - 800		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	MEDISENSE - CEDE	Subvention (congrès pompe) (BNP n°410949) - 500		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	ORTHO CLINICAL - CEDE	Subvention (congrès pompe) (BNP n°3390362) - 300		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	SMITHS MEDICAL - CEDE	Subvention Cosmo (congrès pompe) (BNP n°6721580) - 300		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	NOVO - CEDE	Subvention (congrès pompe) (ABN AMRO n° 903345) - 250		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	MEDTRONIC CEDE	Subvention (congrès pompe) (Virement direct) - 1 400		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	GENERIMED - CEDE	Subvention (congrès pompe) (Virement direct) : 450		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	AIR - CEDE	Subvention (congrès pompe) (Virement direct : 1 500)		12/2004	
63365	POIRIER	Jean-Yves	12/02/2007	VB	AM LEGUERRIER - CEDE	Honoraires étude observatoire pompes à insuline (CIC 0619 695) - 210		05/2005	
63365	POIRIER	Jean-Yves	12/02/2007	VB	LABORATOIRE SERVIER - CEDE	Subvention (BNP 028 7183) - 200		01/2005	
63365	POIRIER	Jean-Yves	12/02/2007	VB	AVENTIS PHARMA - CEDE	Virement honoraires AM leguerrier étude GALATEEHONO - 1 420		09/2005	
63365	POIRIER	Jean-Yves	12/02/2007	VB	MEDTRONIC - CEDE	Virement remboursement déplacement I Guilhem EVADIAC - 800		12/2005	
63365	POIRIER	Jean-Yves	12/02/2007	VB	BMS - CEDE	Subvention pour étude IPS antériopathie diabétique (CityBank n° 031410155) - 600		01/2006	
63365	POIRIER	Jean-Yves	12/02/2007	VB	AML - CEDE	Virement honoraires étude REACH - 630		07/2006	
63365	POIRIER	Jean-Yves	12/02/2007	VB	AML - CEDE	Honoraires étude ADAPT (chèque BNP n° 0031212) - 1 584,70		09/2006	
63365	POIRIER	Jean-Yves	12/02/2007	VB	NOVARTIS PHARMA - CEDE	Virement honoraires étude immunosuppression / diabète greffe hépatique - 5 000		09/2006	
60288	POIRIER	Marie-France	01/03/2006	EC-CO	LILLY	Subvention gérée par CH St Anne, U796 INSERM/Centre de Recherche Clinique	membre comité de pilotage	06/2005	06/2008
60288	POIRIER	Marie-France	01/03/2006	VB	BMS	protocole de "détection de facteurs de risque biologiques et génétiques de troubles métaboliques induits par	CH St Anne (Réseau METAB), promoteur de l'étude multicentrique dont je suis le coordonnateur	09/2005	08/2008
60288	POIRIER	Marie-France	01/03/2006	EC-CO	SERVIER	Subvention gérée par CH St Anne, U796INSERM/ Centre de Recherche Clinique	(membre comité de pilotage)	08/2005	06/2008
60288	POIRIER	Marie-France	01/03/2006	EC-CO	FABRE	Subvention gérée par CH St Anne, U796 INSERM/Centre de Recherche Clinique	(membre comité de pilotage □ □	06/2005	06/2008
60288	POIRIER	Marie-France	01/03/2006	EC-CO	SANOFI	Subvention gérée par CH St Anne, U796 INSERM/Centre de Recherche Clinique	(membre comité de pilotage)	06/2005	06/2008
60288	POIRIER	Marie-France	21/02/2006	EC-INV	SERVIER	Agomélatine	Je ne perçois aucun avantage personnel		12/2005
60288	POIRIER	Marie-France	21/02/2006	EC-INV	SOLVAY	DU 127090 (phase II)		01/2000	12/2001
60288	POIRIER	Marie-France	21/02/2006	EC-CO	JANSSEN	Risperdal dans les mouvements oculaires (rapport en 2005)	Je ne perçois aucun avantage financier personnel	01/2001	12/2004
60288	POIRIER	Marie-France	21/02/2006	CF-INT	APA	Syndrome métabolique induit par les antipsychotiques/prise en charge Sanofi		05/2005	05/2005
60288	POIRIER	Marie-France	21/02/2006	VB	SERVIER, FABRE, SANOFI, LILLY	CHU St Anne, E 117 INSERM - Centre de Recherche Clinique (membre comité de pilotage)			12/2008
60288	POIRIER	Marie-France	21/02/2006	VB	PFIZER	Projet Cabanis - CH Ste Anne / E 117 / INSERM-SHU (étude génétique dans les schizophrénies)			12/2008
60288	POIRIER	Marie-France	21/02/2006	VB	PFIZER	TMS et Depression/SHU, CRHM			12/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60288	POIRIER	Marie-France	21/02/2006	(Autre)	BMS	Négociation encours pour subvention BMS d'un protocole de détection de facteurs de risques biologiques et financier personnel	Subvention auprès du CH St Anne qui est promoteur de l'étude multicentrique dont je suis le coordonateur. Je ne perçois aucun avantage		
63365	POIRIER	Jean-Yves	01/02/2006	(Autre)		aucun		02/2006	
63365	POIRIER	Jean-Yves	01/02/2006	IP-AUT		aucune		02/2006	
60288	POIRIER	Marie-France	01/07/2004	IP-EC	JANSSEN	Etude fonctions attentionnelles et oculaires des schizophrène avant et après risperidone (recherche sans BID)			
60288	POIRIER	Marie-France	01/07/2004	IP-CF	BMS	Metabolic syndrome et diabète II - congrès Marrakech mai 2004			
60288	POIRIER	Marie-France	01/07/2004	IP-CF	BMS	CINP - Paris juin 2004			
60288	POIRIER	Marie-France	01/07/2004	VB	PFIZER	CH St Anne "projet Cabanis Pfizer" étude génétique dans la schizophrénie			
60288	POIRIER	Marie-France	02/06/2004	IP-EC	SERVIER	Essai Agomelatine (terminé) - pas de rémunération			
60288	POIRIER	Marie-France	02/06/2004	IP-EC	JANSSEN	Etude des fonctions attentionnelles et préparation à l'action chez des schizophrènes avant et après risperidone - pas de rémunération			
60288	POIRIER	Marie-France	02/06/2004	IP-CF	BRISTOL MYERS SQUIBB	Ile Symposium sur le syndrome métabolique et le diabète de type II			
60288	POIRIER	Marie-France	02/06/2004	VB	PFIZER	Stimulation magnétique transcranienne et dépression : Association CRHM			
63365	POIRIER	Jean-Yves	05/05/2004	IP-EC		Quelques essais cliniques			
63365	POIRIER	Jean-Yves	05/05/2004	IP-CF		Actions ponctuelles de FMC parfois "sponsorisé" par une firme			
63365	POIRIER	Jean-Yves	05/05/2004	VB	CENTRE D'ETUDES EN DIABèTOLOGIE ET ENDOCRINOLOGIE	Association "loi 1901" domiciliée au CHU, dont je suis président		11/1999	
60288	POIRIER	Marie-France	21/08/2003	IP-EC	JANSSEN	Fonctions attentionnelles et oculomotricité avant et après rispendone dans la schizophrénie			
60288	POIRIER	Marie-France	21/08/2003	IP-EC	SERVIER	Efficacité et acceptabilité de l'Agomélatine dans dépression majeure			
60288	POIRIER	Marie-France	21/08/2003	IP-CF	FABRE	Entretiens CARLA			
60288	POIRIER	Marie-France	21/08/2003	IP-AUT	European Commission	Expert-Evaluateur FP6			
60288	POIRIER	Marie-France	15/10/2002	VB	SERVIER	Essai Agonélative (investigateur) - Association CRHM - CH Sainte-Anne Paris			
60288	POIRIER	Marie-France	15/10/2002	VB	JANSSEN	Etude fonction attentionnelle et préparation de l'action chez schizophrène, avant et après TT par resperidone - Association CRHM			
60288	POIRIER	Marie-France	15/10/2002	IP-AC	LOB Conseil	Conseil sur formation - information en Psychiatrie			
60288	POIRIER	Marie-France	15/10/2002	VB	PFIZER	Association CRHM			
60288	POIRIER	Marie-France	17/07/2000	IP-EC	SOLVAY	Coordonnateur essai clinique			
60288	POIRIER	Marie-France	17/07/2000	IP-EC	SERVIER	Investigateur essai clinique			
60288	POIRIER	Marie-France	17/07/2000	IP-EC	LILLY France	Coordonnateur recherche fondamentale			
60288	POIRIER	Marie-France	17/07/2000	IP-EC	PFIZER	Coordonnateur recherche génétique			
60288	POIRIER	Marie-France	17/07/2000	IP-CF	LILLY France	CINP			
60288	POIRIER	Marie-France	17/07/2000	IP-CF	SERVIER	Symposium / Schizophrenies (Chicago)			
60288	POIRIER	Marie-France	17/07/2000	IP-CF	AVENTIS	Mission programme génétique - Tunisie			
60288	POIRIER	Marie-France	17/07/2000	VB	PFIZER	Partenariat Sainte-Anne / Pfizer : CH Sainte-Anne			
60288	POIRIER	Marie-France	17/07/2000	VB	LILLY France	Partenariat Lilly France / SHU - CRHM (association) CH Sainte-Anne			
60261	PONCELET	Pascal	27/07/2010	CF-AUD	IPSEN	congrès cncf paris			10/2009
60261	PONCELET	Pascal	27/07/2010	CF-AUD	CHIESI	st remy de provence cncf			06/2009
60261	PONCELET	Pascal	27/07/2010	CF-AUD	IPSEN	congres cncf cannes			05/2009
60261	PONCELET	Pascal	27/07/2010	CF-AUD	SANKYO	bruxelles sympo sur le contole pa population			04/2009
60261	PONCELET	Pascal	27/07/2010	CF-AUD	BIF	esc			09/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	IPSEN	boulogne/mer niveau de tl de la pa et niveau de la mer à marée basse	Aucune rémunération		12/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	BIF	ontarget board paris	Rémunération personnelle		06/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	RECORDATI	baucampa(59) place des calciques	Rémunération personnelle		11/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	BAYER	lac majeur stresa revue année hta diabète	Rémunération personnelle		12/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	SANKYO	raguse, sympo bithérapie	Rémunération personnelle		11/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	SANKYO	paris board trithérapie	Rémunération personnelle		11/2009
60261	PONCELET	Pascal	27/07/2010	EC-INV	SANKYO	etude sevicaptypologie de prescription	investigateur principal	10/2009	
60261	PONCELET	Pascal	27/07/2010	CF-INT	SANKYO	nancy frais déplacement congrés coeur et sport	Rémunération personnelle		11/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	SANKYO	symposium hta persistance journées hta paris 2008 et paris 2006	Rémunération personnelle		10/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	SANKYO	paris , board sevikar plurithérapie	Rémunération personnelle		11/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	NOVARTIS	paris, decembre 2008 board rasilez	Rémunération personnelle		09/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	IPSEN	paris, board ontarget rasilez trithérapie	Rémunération personnelle		08/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	IPSEN	evian hta approche population vs approche personnelle	Rémunération personnelle		07/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	MERCK	algérie conférences sur beta- et hta	Rémunération personnelle		06/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	NOVARTIS	nancy 2008, symposium congres coeur et sport hta et risques	Rémunération personnelle		05/2009
60261	PONCELET	Pascal	27/07/2010	IP-AC	BOEHRINGER INGELHEIM FRANCE BIF	paris board ontarget	Rémunération personnelle		06/2009
60261	PONCELET	Pascal	27/07/2010	CF-AUD	SANKYO	deplacement journées hta paris 2008			04/2008
60261	PONCELET	Pascal	27/07/2010	CF-INT	SERVIER	noeux les mines hta personne agé hyvett	Rémunération personnelle		04/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	RECORDATI	cambrai saga des calciques	Rémunération personnelle		04/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	IPSEN	nice fmc local hta diabète	Rémunération personnelle		04/2009
60261	PONCELET	Pascal	27/07/2010	EC-INV	SANKYO	etude olmegam étude des rotation thérapeutiques persistance	board		04/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	SERVIER	noeux les mines hta personne agé	Rémunération personnelle		01/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	SERVIER	compte rendu congrés temps fort hta	Rémunération personnelle		01/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	IPSEN	hta et diabète	Rémunération personnelle		02/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	SERVIER	arles(62) en collaboration avec SFHTA,HTA sujet agé	Rémunération personnelle		01/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	SERVIER	symposium advance au CNCF	Rémunération personnelle		01/2009
60261	PONCELET	Pascal	27/07/2010	CF-INT	SERVIER	avion(62) en collaboration avec SFHTA,HTA sujet agé	Rémunération personnelle		01/2009
60261	PONCELET	Pascal	27/07/2010	EC-CO	NOVARTIS	essais sur la PA centrale exforge	expérimentateur		12/2009
60261	PONCELET	Pascal	27/01/2009	IP-AUT	BAYER	symposium Leipzig tl hta et diabète	rémunération personnelle	09/2008	09/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	IPSEN	fmc Boulogne s/ Mer tl hta diabète	rémunération personnelle		
60261	PONCELET	Pascal	27/01/2009	IP-AUT	RECORDATI	fmc place des diurétiques	rémunération personnelle	06/2008	06/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	NOVARTIS	board régional alliklrene	rémunération personnelle	07/2008	07/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	EUTHERAPIE	fmic hyvet indapamide	rémunération personnelle	11/2008	11/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	BOEHRINGER INGELHEIM	fmc ontarget telmisartan	rémunération personnelle	04/2008	04/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	BOEHRINGER INGELHEIM	board ontarget 3 réunions	rémunération personnelle	12/2007	03/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	IPSEN	board expert Valsartan	rémunération personnelle	06/2008	06/2008
60261	PONCELET	Pascal	27/01/2009	EC-CO	MENARINI	observatoire tl de l'insuffisance cardiaque en cardiologie libérale□étude devenir	rémunération personnelle	12/2007	12/2009
60261	PONCELET	Pascal	27/01/2009	IP-AUT	IPSEN	présentation congrès ACC	rémunération personnelle	03/2008	04/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	NOVARTIS	board régional rasilez	rémunération personnelle	04/2008	04/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	IPSEN	fmc Strasbourg	rémunération personnelle	06/2008	06/2008

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60261	PONCELET	Pascal	27/01/2009	CF-INT	MENARINI	congrès club cardiologie du sport Nancy symposium pas de tt	Rémunération personnelle	09/2008	09/2008
60261	PONCELET	Pascal	27/01/2009	CF-INT	NOVARTIS	congrès CCS Nancy symposium sur le risque	Rémunération personnelle	09/2008	09/2008
60261	PONCELET	Pascal	27/01/2009	IP-AUT	NOVARTIS	aliskirene et âge Lille	rémunération personnelle	12/2007	12/2007
60261	PONCELET	Pascal	27/01/2009	IP-AUT	SERVIER	vidéo transmission AHA	rémunération personnelle	11/2007	11/2007
60261	PONCELET	Pascal	27/01/2009	IP-AUT	NOVARTIS	hta résistante Lille	rémunération personnelle	12/2007	12/2007
60261	PONCELET	Pascal	27/01/2009	EC-CO	NOVARTIS	exforge	mesure de la rigidite artérielle, rôle purement technique	05/2008	02/2009
60261	PONCELET	Pascal	27/01/2009	CF-INT	DAIICHY SANKYO	sihta Paris olmetec étude des doses prescrites par rapport aux doses recommandées	Aucune rémunération	12/2008	12/2008
60261	PONCELET	Pascal	27/01/2009	CF-INT	IPSEN	AHA Nouvelle-Orléans rapport du congres pas de tt	Rémunération personnelle	11/2008	11/2008
60261	PONCELET	Pascal	27/01/2009	CF-AUD	DAIICHY SANKYO	ESC Munich		08/2008	09/2008
60261	PONCELET	Pascal	27/01/2009	CF-AUD	SERVIER	ESH Berlin		06/2008	06/2008
60261	PONCELET	Pascal	27/01/2009	CF-AUD	BOEHRINGER INGELHEIM	ACC Chicago ontarget telmisartan		03/2008	03/2008
60261	PONCELET	Pascal	26/11/2007	CF-AUD	BMS	ESH MILAN		06/2007	06/2007
60261	PONCELET	Pascal	26/11/2007	CF-AUD	NOVARTIS	ESC VIENNE		09/2007	09/2007
60261	PONCELET	Pascal	26/11/2007	CF-INT	CHIESI	journée Beaune CNCF	Rémunération personnelle	03/2007	03/2007
60261	PONCELET	Pascal	26/11/2007	IP-AC	MSD	étude HTA FA	Rémunération personnelle	11/2007	
60261	PONCELET	Pascal	26/11/2007	CF-INT	MENARINI	Paris réunion coeur et sport	Rémunération personnelle	06/2007	06/2007
60261	PONCELET	Pascal	26/11/2007	CF-INT	BIF	Québec canada congrès réadaptation	Rémunération personnelle	06/2007	06/2007
60261	PONCELET	Pascal	26/11/2007	IP-AC	IPSEN	board Paris	Rémunération personnelle	07/2007	07/2007
60261	PONCELET	Pascal	26/11/2007	CF-INT	MSD	Paris profil tensionnelle d'effort	Rémunération personnelle	04/2007	04/2007
60261	PONCELET	Pascal	26/11/2007	CF-INT	SCHERING	CNCF Nantes	Rémunération personnelle	10/2006	10/2006
60261	PONCELET	Pascal	26/11/2007	CF-INT	BOEHRINGER INGELHEIM FRANCE; BIF	board ONTARGET Paris	Rémunération personnelle	03/2007	05/2007
60261	PONCELET	Pascal	25/11/2007	CF-INT	MENARINI	congrès EUROPREVENT PARIS	Rémunération personnelle	03/2007	03/2007
60261	PONCELET	Pascal	25/11/2007	CF-INT	IPSEN	réunions en province sur les grands essais en cardio	Rémunération personnelle	01/2007	01/2007
60261	PONCELET	Pascal	25/11/2007	CF-INT	SANOFI	Paris groupe expert Rimonabant	Rémunération personnelle	12/2006	12/2006
60261	PONCELET	Pascal	25/11/2007	CF-INT	PFIZER	Nantes congrès du CNCF	Rémunération personnelle	10/2006	10/2006
60261	PONCELET	Pascal	25/11/2007	IP-AC	PFIZER ET CNCF	étude "CARDIC"	Rémunération personnelle		11/2006
60261	PONCELET	Pascal	25/11/2007	IP-AUT	MSD ET CNCF	KIT DE DIAPORAMA	rémunération personnelle	06/2006	12/2006
60261	PONCELET	Pascal	25/11/2007	CF-INT	RECORDATI	Présentation régionale programme "perso"	Rémunération personnelle	09/2006	11/2006
60261	PONCELET	Pascal	25/11/2007	CF-INT	MSD	MEDEC Paris	Rémunération personnelle	03/2006	03/2006
60261	PONCELET	Pascal	25/11/2007	CF-INT	GSK		Aucune rémunération		
60261	PONCELET	Pascal	25/11/2007	IP-AC	SOLVAY	étude PRETACT	Rémunération personnelle	11/2004	12/2005
60261	PONCELET	Pascal	25/11/2007	IP-AC	GSK	étude MAPA-automesure	Rémunération personnelle	01/2001	10/2008
60261	PONCELET	Pascal	25/11/2007	CF-AUD	SANKYO MERCK	Paris JHTA		12/2007	12/2007
60261	PONCELET	Pascal	25/11/2007	CF-AUD	IPSEN	Paris projet therapeutique de l'hypertendu		11/2007	11/2007
60261	PONCELET	Pascal	25/11/2007	CF-AUD	SERVIER	Paris congrès du CNCHG		11/2007	11/2007
60261	PONCELET	Pascal	15/02/2007	CF-INT	IPSEN	whats up - Marcq	Aucune rémunération	05/2006	05/2006
60261	PONCELET	Pascal	15/02/2007	CF-INT	PFIZER	Quotidien du Medecin coeur et diabète	Rémunération personnelle	02/2006	02/2006
60261	PONCELET	Pascal	15/02/2007	CF-INT	MSD ET SP	associations TT Cannes	Rémunération personnelle	04/2006	04/2006
60261	PONCELET	Pascal	15/02/2007	CF-INT	NOVARTIS	symposium aux JHTA 2005	Rémunération personnelle	01/2006	01/2006
60261	PONCELET	Pascal	15/02/2007	CF-INT	IPSEN	projet thérapeutique	Rémunération personnelle	01/2006	01/2006
60261	PONCELET	Pascal	15/02/2007	CF-INT	PFIZER	MEDEC	Rémunération personnelle	03/2006	03/2006
60261	PONCELET	Pascal	15/02/2007	IP-AC	M SANTE	flecaine	Rémunération personnelle		01/2006
60261	PONCELET	Pascal	15/02/2007	IP-AC	3 M	idem	Rémunération personnelle		01/2006
60261	PONCELET	Pascal	15/02/2007	IP-AC	3 M SANTE	fin etude Flecaine LP simple expérimentateur	Aucune rémunération		12/2005
60261	PONCELET	Pascal	05/06/2006	EC-CO	GSK	EPIDEMIOLOGIE	Expert	06/2002	
60261	PONCELET	Pascal	05/06/2006	CF-INT	IPSEN	ESC what's up - congres guide	Rémunération personnelle	09/2005	
60261	PONCELET	Pascal	05/06/2006	EC-CO	SANOFI AVENTIS	Etude épidemiologique risque et HTA	expert	01/2004	12/2005
60261	PONCELET	Pascal	05/06/2006	CF-INT	MENARINI	SFC Paris nebivalol	Rémunération personnelle	10/2005	
60261	PONCELET	Pascal	05/06/2006	IP-AC	PFIZER	Etude ASCOT- ESH (produit CADUET)	Rémunération personnelle	09/2005	
60261	PONCELET	Pascal	05/06/2006	CF-INT	MENARINI	controverse sport et HTA	Rémunération personnelle	06/2006	
60261	PONCELET	Pascal	05/06/2006	CF-INT	BMS	coeur et sport performance et traitement HTA - Valencia	Rémunération personnelle	05/2005	
60261	PONCELET	Pascal	05/06/2006	IP-AC	SANOFI AVENTIS	conseil prise en charge HTA (SFHTA-CNCF) Collège National des Cardiologues Français	Rémunération personnelle	06/2005	
60261	PONCELET	Pascal	05/06/2006	CF-INT	MENARINI	SFC - Lyon - Nebivolol	Rémunération personnelle	06/2005	
60261	PONCELET	Pascal	05/06/2006	CF-INT	MEDIQUID	cardiologie pratique HTA	Rémunération personnelle	03/2005	
60261	PONCELET	Pascal	05/06/2006	EC-CO	MSD SP	observatoire epidemiologie lipides - etudes duo	expert	09/2004	
60261	PONCELET	Pascal	05/06/2006	CF-INT	PFIZER	MEDEC - HTA	Rémunération personnelle	03/2005	
60261	PONCELET	Pascal	05/06/2006	CF-INT	IPSEN	AHA Dallas 2005 - what's up guide congres	Rémunération personnelle	11/2005	
60261	PONCELET	Pascal	05/06/2006	CF-INT	IPSEN	symposium projet therapeutique HTA paris	Rémunération personnelle	11/2005	11/2005
60261	PONCELET	Pascal	05/06/2006	CF-INT	IPSEN	what's up - Lille les essais	Rémunération personnelle	01/2006	
60261	PONCELET	Pascal	05/06/2006	CF-AUD	MENARINI	congrès CNCF Lyon		10/2005	10/2005
60261	PONCELET	Pascal	05/06/2006	EC-INV	JOURNAL CONSENSUS CARDIO	comite de rédaction - rédacteur		06/2004	
60261	PONCELET	Pascal	05/06/2006	EC-INV	ELSEVIER - LES ANNALES DE CARDIOLOGIES	comite de rédaction - rédacteur		01/2002	
60261	PONCELET	Pascal	05/06/2006	EC-INV	SANOFI AVENTIS	coordonateur - épidemio HTA		06/2003	11/2005
60261	PONCELET	Pascal	05/06/2006	LD-AR	RECORDATI	board conseil - pas encore formalisé	Rémunération personnelle		
60261	PONCELET	Pascal	05/06/2006	EC-CO	NOVARTIS	epidemiologie formation - valnorm	collaborateurs expert	01/2005	12/2005
60261	PONCELET	Pascal	05/06/2006	EC-CO	RECORDATI	epidemiologie formation	collaborateur expert	01/2006	
60261	PONCELET	Pascal	05/06/2006	LD-AR	IPSEN	board conseil	Rémunération personnelle	01/2004	
60261	PONCELET	Pascal	05/06/2006	LD-AR	LIPHA SANKYO	board conseil olmesartan	Rémunération personnelle	01/2004	
60261	PONCELET	Pascal	04/06/2006	CF-INT	QUOTIDIEN DU MEDECIN	coeur et diabète	Rémunération personnelle	01/2006	01/2006
60261	PONCELET	Pascal	04/06/2006	IP-AC	SANKYO LIPHA	conference de presse co-olmetec - Paris	Rémunération personnelle	06/2006	06/2006
60261	PONCELET	Pascal	04/06/2006	CF-INT	PFIZER	Paris - MEDEC stratégie traitement des sujets à haut risque	Rémunération personnelle	03/2006	03/2006
60261	PONCELET	Pascal	04/06/2006	CF-INT	MEDIQUID	revue consensus cardio comité de rédaction	Rémunération personnelle	03/2006	03/2006
60261	PONCELET	Pascal	04/06/2006	CF-AUD	LIPHA	Journées de l'HTA - Paris		12/2005	12/2005
60261	PONCELET	Pascal	04/06/2006	CF-AUD	NOVARTIS	congrès coeur et sport - Monachil (Espagne)		01/2006	01/2006
60261	PONCELET	Pascal	04/06/2006	CF-AUD	IPSEN	AHA 2005 - Dallas		11/2005	11/2005
60261	PONCELET	Pascal	04/06/2006	IP-AC	SANKYO LIPHA	board olmesartan	Rémunération personnelle	01/2006	01/2006
60261	PONCELET	Pascal	04/06/2006	CF-INT	MSD-CHIBRET, SCHERRING-PLOUGH	ACP place des associations HTA	Rémunération personnelle	02/2006	02/2006
60261	PONCELET	Pascal	04/06/2006	CF-INT	GSK	congres CNCF Lyon□□prise en charge du diabete	Rémunération personnelle	10/2005	10/2005
60261	PONCELET	Pascal	04/06/2006	CF-INT	SALON DE CARDIOLOGIE PRATIQUE MEDIQUID	references HAS HTA	Rémunération personnelle	03/2006	03/2006
60261	PONCELET	Pascal	04/06/2006	CF-INT	NOVARTIS	Journées de l'HTA - Paris	Rémunération personnelle	12/2005	12/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60261	PONCELET	Pascal	04/06/2006	CF-INT	BOEHRINGER DMSANTE	coeur et performance	Rémunération personnelle	10/2005	10/2005
60261	PONCELET	Pascal	04/06/2006	CF-INT	DM SANTE	DVD imagerie HTA	Rémunération personnelle	10/2005	10/2005
60261	PONCELET	Pascal	04/06/2006	EC-INV	SOLVAY	étude pretact eprosartan	coordonnateur 4570 euros	01/2003	04/2005
60261	PONCELET	Pascal	08/04/2005	IP-AC	PFIZER	Consultant, étude CV@goal : prévention cardiovasculaire (2003)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	PFIZER	Consultant, essais Intima-media (Immédiat), pas de traitement (2003)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	PFIZER	Scénario film : les 10 ans d'AMLOR (2003)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	PFIZER	Brochure HTA et Sport (2003)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	PFIZER	Fin CV@goal (2004)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	IPSEN	Consultant Valsartan (2004)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	SANKYO	Conseil scientifique Olmesartan (2004)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	SANOFI AVENTIS	Consultant étude ORCHESTRE, pas de traitement (2004)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	SANOFI AVENTIS	Consultant étude HTA Cardiologie libérale, pas de Traitement (2004)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	SANOFI AVENTIS	Consultant étude Echographie et Cardiologie libérale, pas de Traitement (2004)	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	IP-AC	RECORDATI	Consultation étude AGATE - Publication (2003-2004), Comité de Pilotage 2002	Aucune rémunération		
60261	PONCELET	Pascal	08/04/2005	CF-INT	MENARINI	Symposium HTA et Sport - Strasbourg CNCF 2003			
60261	PONCELET	Pascal	08/04/2005	CF-INT	IPSEN	Whats up AHA 2003			
60261	PONCELET	Pascal	08/04/2005	CF-INT	SERVIER	Kit diapositives ESH, Symposium pression pulsée - CNCF - Strasbourg 2003			
60261	PONCELET	Pascal	08/04/2005	CF-INT	NEGMA	Conférence NIBEVALOL - Endothelium, Congrès CNCF Marseille 2004, Conférence de presse Lancement N			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	IPSEN	Whats up ESC 2004 Whats up AHA 2004, Symposium du laboratoire au Louvre 2004			
60261	PONCELET	Pascal	08/04/2005	CF-INT	SANKYO	Symposium Congrès CNCF - Marseille 2004, Conférence de presse Lancement Olmesartan 2004			
60261	PONCELET	Pascal	08/04/2005	CF-INT	BAYER	Symposium Facteurs de risques Med. Int - Bruges, Symposium Sport et HTA - LILLE 2004			
60261	PONCELET	Pascal	08/04/2005	CF-INT	MENARINI	Symposium Coeur et Sport - Lille 2004			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	MSD	AHA (2001)			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	LIPHA	Journées HTA et ESC (2001)			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	MSD	ESC (2002)			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	LIPHA	Journées HTA (2002)			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	IPSEN	AHA (2003)			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	SERVIER	ESH 2003, ESC 2003			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	PFIZER	Congrès journées HTA Paris 2003			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	BAYER	ESC 2004			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	SERVIER	ESH 2004, AHA 2004			
60261	PONCELET	Pascal	08/04/2005	CF-AUD	MERCK LIPHA	Congrès HTA Paris 2004			
60261	PONCELET	Pascal	08/04/2005	IP-AUT	SOCIETE FRANCAISE DE CARDIOLOGIE				
60261	PONCELET	Pascal	08/04/2005	IP-AUT	SOCIETE FRANCAISE D'HYPERTENSION ARTERIELLE				
60261	PONCELET	Pascal	08/04/2005	IP-AUT	COLLEGE NATIONAL DES CARDIOLOGUES FRANCAIS				
60261	PONCELET	Pascal	08/04/2005	IP-AUT	PFIZER	Club des (ex) Jeunes Hypertensiologues			
60261	PONCELET	Pascal	08/04/2005	IP-AUT	BAYER	Club des Cardiologues du Sport			
60261	PONCELET	Pascal	08/04/2005	IP-AUT	3M SANTE	ACFA Paroxystique - FLECAINE LP			
60261	PONCELET	Pascal	13/01/2005	EC-CO	3M SANTE	ACFA Paroxystique - FLECAINE LP			
60261	PONCELET	Pascal	13/01/2004	IP-AC	PFIZER	Fin CV@goal			
60261	PONCELET	Pascal	13/01/2004	IP-AC	IPSEN	Consultant Valsartan			
60261	PONCELET	Pascal	13/01/2004	IP-AC	SANKYO	Conseil scientifique Olmesartan			
60261	PONCELET	Pascal	13/01/2004	IP-AC	SANOFI - AVENTIS	Consultant étude ORCHESTRE : pas de traitement, consultant étude HTA Cardiologie libérale : pas de traitement, consultant étude Echographie et Cardiologie libérale : pas de			
60261	PONCELET	Pascal	13/01/2004	IP-AC	RECORDATI	Consultation étude AGATE - publication			
60261	PONCELET	Pascal	13/01/2004	IP-CF	NEGMA	Conférence NIBEVALOL - Endothelium, Congrès CNCF Marseille 2004, conférence de presse lancement NEBILOX			
60261	PONCELET	Pascal	13/01/2004	IP-CF	IPSEN	Whats up ESC 2004, whats up AHA 2004, EPU - les grands essais thérapeutiques - Lille			
60261	PONCELET	Pascal	13/01/2004	IP-CF	SANKYO	Symposium congrès CNCF - Marseille 2004, conférence de presse lancement Olmesartan			
60261	PONCELET	Pascal	13/01/2004	IP-CF	BAYER	Symposium facteurs de risques Med. Int-Bruges, symposium sport et HTA - Lille, formation place des calciques, invitation ESC Munich			
60261	PONCELET	Pascal	13/01/2004	IP-CF	MENARINI	Symposium coeur et sport - Lille			
60261	PONCELET	Pascal	13/01/2004	IP-CF	SERVIER	Paris 2004 - ESH, AHA 2004			
60261	PONCELET	Pascal	13/01/2004	IP-CF	MERCK LIPHA	Congrès HTA Paris			
60261	PONCELET	Pascal	13/01/2003	IP-EC	3M SANTE	ACFA Paroxystique - FLECAINE LP			
60261	PONCELET	Pascal	13/01/2003	IP-AC	PFIZER	Consultant étude CV@goal - prévention cardiovasculaire, consultant essais Intima média (immédiat) pas de traitement, congrès journée HTA Paris, scénario film : les 10 ans d'A			
60261	PONCELET	Pascal	13/01/2003	IP-AC	RECORDATI	Consultation étude AGATE - publication			
60261	PONCELET	Pascal	13/01/2003	IP-CF	MENARINI	Symposium HTA et sport - Strasbourg CNCF 2003			
60261	PONCELET	Pascal	13/01/2003	IP-CF	IPSEN	AHA 2003, whats up AHA 2003			
60261	PONCELET	Pascal	13/01/2003	IP-CF	SERVIER	Kit diapositives ESH, Milan 2003, symposium pression pulsée - CNCF - Strasbourg 2003			
60261	PONCELET	Pascal	13/01/2003	IP-CF	PFIZER	Brochure HTA et sport			
60261	PONCELET	Pascal	26/01/2002	IP-EC	Toutes les firmes	HTA, IVG			
60261	PONCELET	Pascal	26/01/2002	IP-AC	Toutes les firmes	HTA			
60261	PONCELET	Pascal	26/01/2002	IP-CF	Toutes les firmes	HTA			
60261	PONCELET	Pascal	19/07/2000	IP-EC	Tous les laboratoires et leurs concurents				
60261	PONCELET	Pascal	19/07/2000	IP-AC	Tous				
60261	PONCELET	Pascal	19/07/2000	IP-CF	Tous				
60261	PONCELET	Pascal	27/01/2000	IP-EC	AVENTIS	Valsartan			
60261	PONCELET	Pascal	27/01/2000	IP-EC	BIOPROJET	Vosapeptidose et développement			
60261	PONCELET	Pascal	27/01/2000	IP-EC	MONSANTO	Etude Spirevolaciine			
60261	PONCELET	Pascal	27/01/2000	IP-EC	NOVARTIS	Etude réadaptation			
60261	PONCELET	Pascal	27/01/2000	IP-AC	SERVIER	Produit étude (1999)			
60261	PONCELET	Pascal	27/01/2000	IP-AC	ZENECA	Produit (1999)			
60261	PONCELET	Pascal	27/01/2000	IP-AC	MERCK/ WYETH LEDERLE	Produit étude (1999)			
60261	PONCELET	Pascal	27/01/2000	IP-AC	MONSANTO	Club (1999)			
60261	PONCELET	Pascal	27/01/2000	IP-AC	PARKE DAVIS	Produit étude (1999)			
60261	PONCELET	Pascal	27/01/2000	IP-AC	BMS	Produit (1999)			
60261	PONCELET	Pascal	27/01/2000	IP-CF	ROCHE	1999			
10345	POURCELOT	Yvette	19/08/2006	Néant					
10345	POURCELOT	Yvette	04/05/2005	VB	AVENTIS - GLAXO - MERCK - PIERRE FABRE - PFIZER	Taxes d'apprentissage			
10345	POURCELOT	Yvette	04/05/2005	VB	SANOFI - FOURNIER - SERVIER - ICTA	Taxes d'apprentissage			
10345	POURCELOT	Yvette	04/05/2005	VB	LABORATOIRE FACULTE DE PHARMACIE	Pharmacigalénique			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10345	POURCELOT	Yvette	25/02/2005	VB	AVENTIS	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	GLAXO	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	MERCK	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	PIERRE FABRE	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	PFIZER	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	SANOFI WINTHROP	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	FOURNIER	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	SERVIER	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	VB	ICTA	Taxes d'apprentissage au laboratoire de pharmacie galénique (dont je suis responsable)			
10345	POURCELOT	Yvette	25/02/2005	IP-AUT	ROCHE	Contrat cellule de valorisation industrielle			
10345	POURCELOT	Yvette	25/02/2005	IP-AUT	MERCK LIPHA	Contrat cellule de valorisation industrielle			
10345	POURCELOT	Yvette	25/02/2005	IP-AUT	ROCHE	Contrat (cellule de valorisation industrielle de l'université) (partenariat de service)			
10345	POURCELOT	Yvette	25/02/2005	IP-AUT	LIPHA MERCK	Contrat (cellule de valorisation industrielle de l'université) (partenariat de service)			
10345	POURCELOT	Yvette	17/12/2004	VB	ROCHE NICOLAS - MERCK LIPHA - ICTA - SERVIER - AVENTIS	Laboratoire (UFR de Pharmacie)			
10345	POURCELOT	Yvette	17/12/2004	VB	PIERRE FABRE - SANOFI AVENTIS - GSK - FOURNIER - PFIZER	Laboratoire (UFR de Pharmacie)			
10345	POURCELOT	Yvette	15/09/2003	VB	SANOFI SYNTHELABO, FOURNIER, PIERRE FABRE, SERVIER, PFIZER, MERCK, GLAXO SMITHKLINE, AVENTIS	Taxes apprentissages - UFR Pharmacie (Université de Bourgogne)			
10345	POURCELOT	Yvette	15/09/2003	VB	SANOFI SYNTHELABO	Taxes d'apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	FOURNIER PHARMA	Taxes d'apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	PIERRE FABRE	Taxes d'apprentissage (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	LABORATOIRE SERVIER	Taxes d'apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	PFIZER	Taxes d'apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	MERCK	Taxes d'apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	GSK	Taxes d'apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	15/09/2003	VB	AVENTIS	Taxes apprentissages (UFR phcie)			
10345	POURCELOT	Yvette	19/09/2002	{Autre}	PIERRE FABRE ; SANOFI ; SERVIER ; GLAXO SMITHKLINE ; LIPHA ; PARKE DAVIS ; FOURNIER	Taxes d'apprentissage			
10345	POURCELOT	Yvette	10/06/2001	IP-EC	MERCK LIPHA				
10345	POURCELOT	Yvette	10/06/2001	IP-CF	MERCK-LIPHA, IFID, IDD, ARC				
10345	POURCELOT	Yvette	10/06/2001	VB	ALCON, ICTA, CHAUVIN, FOURNIER, LIPHA, BAYER, PIERRE FABRE, SANOFI SYNTHELABO, PARKEDAVIS, SERVIER				
10345	POURCELOT	Yvette	13/07/2000	VB	BOIRON, AVENTIS, CHAUVIN, CHIESI, GLAXO WELLCOME, FOURNIER, ICTA, LIPHA, MERCK, MONOT, PIERRE FABRE SANTE, SANOFI SYNTHELABO	Taxe d'apprentissage au laboratoire			
10345	POURCELOT	Yvette	01/01/1999	IP-EC	MERCK				
10345	POURCELOT	Yvette	01/01/1999	IP-EC	LIPHA				
10345	POURCELOT	Yvette	01/01/1999	IP-CF	LIPHA				
10345	POURCELOT	Yvette	01/01/1999	IP-CF	IFIP				
10345	POURCELOT	Yvette	01/01/1999	IP-CF	IDD				
10345	POURCELOT	Yvette	01/01/1999	IP-CF	ARC				
10345	POURCELOT	Yvette	01/01/1999	VB	ALCON				
10345	POURCELOT	Yvette	01/01/1999	VB	CHAUVIN				
10345	POURCELOT	Yvette	01/01/1999	VB	FOURNIER				
10345	POURCELOT	Yvette	01/01/1999	VB	ICTA				
10345	POURCELOT	Yvette	01/01/1999	VB	LIPHA				
10345	POURCELOT	Yvette	01/01/1999	VB	BAYER				
10345	POURCELOT	Yvette	01/01/1999	VB	PIERRE FABRE SANTE				
10345	POURCELOT	Yvette	01/01/1999	VB	SANOFI WINTHROP				
10345	POURCELOT	Yvette	01/01/1999	VB	SYNTHELABO				
10345	POURCELOT	Yvette	01/01/1999	VB	GLAXO	Rémunération de travaux de recherche dans le cadre d'une thèse de doctorat d'université			
10345	POURCELOT	Yvette	01/01/1998	IP-AUT	Lipha				
10345	POURCELOT	Yvette	01/01/1998	IP-AUT	IFIP				
10345	POURCELOT	Yvette	01/01/1998	IP-AUT	ARC				
10345	POURCELOT	Yvette	01/01/1998	IP-AUT	IDD				
10345	POURCELOT	Yvette	01/01/1998	IP-AUT	DHT				
10345	POURCELOT	Yvette	01/01/1998	VB	Chauvin				
10345	POURCELOT	Yvette	01/01/1998	VB	Fournier				
10345	POURCELOT	Yvette	01/01/1998	VB	Icta				
10345	POURCELOT	Yvette	01/01/1998	VB	Lipha				
10345	POURCELOT	Yvette	01/01/1998	VB	Pierre-Fabre Santé				
10345	POURCELOT	Yvette	01/01/1998	VB	Synthélabo				
10345	POURCELOT	Yvette	01/01/1998	VB	Alcon				
10345	POURCELOT	Yvette	01/01/1998	VB	Eayer				
10345	POURCELOT	Yvette	01/01/1998	VB	Prographarm				
60515	PRADEAU	Dominique	06/11/2009	CF-INT	SERVIER	Conférences H. MOISSAN : préparation au concours de Praticien Hospitalier Pharmacien	Aucune rémunération		
60515	PRADEAU	Dominique	04/09/2009	Néant					
60515	PRADEAU	Dominique	11/05/2006	IP-CF	SERVIER	Formation au concours de pharmaciens des hopitaux - conférence MOISSAN			
60515	PRADEAU	Dominique	11/05/2006	IP-CF	FRESENIUS-KABI	La perfusion			
60515	PRADEAU	Dominique	11/05/2006	IP-RE	SAGA MEDICAL	Rapport expert O2 liquide gaz à usage médical	<5000 € ou <5% du capital		
60515	PRADEAU	Dominique	11/05/2006	IF	SANOFI AVENTIS	Actions	<5000 € ou <5% du capital		
60515	PRADEAU	Dominique	02/05/2005	IF	SANOFI AVENTIS	Actions			
60515	PRADEAU	Dominique	02/05/2005	IP-RE	SAGA MEDICAL	Rapport expert O2 liquide gaz à usage médical			
60515	PRADEAU	Dominique	02/05/2005	IP-CF	FRESENIUS-KABI	La perfusion			
60515	PRADEAU	Dominique	02/05/2005	IP-CF	SERVIER	Formation au concours de pharmaciens des hopitaux - conférence MOISSAN			
60515	PRADEAU	Dominique	12/03/2004	IP-CF	SERVIER	Conférence MOISSAN - Conférencier			
60515	PRADEAU	Dominique	26/10/1999	IP-RE	ROCHE	Lexomil (1998)			
60515	PRADEAU	Dominique	26/10/1999	VB	SERVIER	Conférence Henri Moissan (concours Praticiens Hospitaliers)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60515	PRADEAU	Dominique	26/10/1999	VB	SERVIER	ADEBIOPHARM ER 69			
65608	PREISS	Jean-Philippe	09/06/2010	CF-INT	TEMPO MEDICAL	SPONSOR ASTRA ZENECA	Rémunération personnelle	05/2010	05/2010
65608	PREISS	Jean-Philippe	21/04/2010	CF-INT	CONGRES COLLOQUE CONVENTION	PALAIS DES CONGRES STRASBOURG□□CRESTOR	Rémunération personnelle	04/2010	04/2010
65608	PREISS	Jean-Philippe	21/04/2010	CF-AUD	SERVIER	CONGRES CNCF□□PARIS		10/2009	10/2009
65608	PREISS	Jean-Philippe	21/04/2010	CF-AUD	BOEHRINGER INGELHEIM	GERARDMER□□CONGRES PATIENT A HAUT RISQUE		04/2010	04/2010
65608	PREISS	Jean-Philippe	21/04/2010	CF-AUD	PFIZER	CONGRES CARDIOLOGIE PRATIQUE□□PARIS		04/2010	04/2010
65608	PREISS	Jean-Philippe	21/04/2010	CF-INT	MERCK DOHME CHIBRET	PRISE EN CHARGE DYSLIPEMIES□□STRASBOURG□□INEGY/ EZETROL	Rémunération personnelle	03/2010	03/2010
65608	PREISS	Jean-Philippe	21/04/2010	CF-INT	ARMP PREUVES ET PRATIQUES	CONGRES PREUVES ET PRATIQUES STRASBOURG□□PRODUIT CRESTOR	Rémunération personnelle	03/2009	03/2009
65608	PREISS	Jean-Philippe	21/04/2010	CF-INT	MERCK DOHME CHIBRET	ZOOM SUR LE CHANGEMENT□□LA WANTTZENAU□□INEGY/EZETROL	Rémunération personnelle	06/2009	06/2009
65608	PREISS	Jean-Philippe	10/03/2009	CF-INT	ASTRA ZENECA	Prise en charge maladie coronaire	rémunération personnelle	05/2008	05/2008
61068	PRIOLLET	Pascal	06/02/2004	IP-EC	SANOFI SYNTHELABO - BRISTOL MYERS SQUIBB	Essai clinique			
61068	PRIOLLET	Pascal	06/02/2004	IP-CF	BEAUFOUR	Publication FMC			
61068	PRIOLLET	Pascal	06/02/2004	IP-CF	SANOFI SYNTHELABO - BMS	Prix athérothrombose opale			
61068	PRIOLLET	Pascal	06/02/2004	IP-CF	AVENTIS	Prix Hoptria			
61068	PRIOLLET	Pascal	27/10/2003	IP-AC	SANOFI, BRISTOL MYERS SQUIBB	Etude clinique			
61068	PRIOLLET	Pascal	27/10/2003	IP-AC	SANOFI	Prix Opale			
61068	PRIOLLET	Pascal	27/10/2003	IP-AC	AVENTIS	Prix Hoptria			
61068	PRIOLLET	Pascal	05/03/2000	IP-EC	SANOFI	Essai clinique			
61068	PRIOLLET	Pascal	05/03/2000	IP-EC	SERVIER	Essai clinique			
61068	PRIOLLET	Pascal	05/03/2000	IP-EC	BEAUFOUR	Rédaction de documents			
61068	PRIOLLET	Pascal	05/03/2000	IP-AC	KNOLL	Conseil pour essai clinique			
61068	PRIOLLET	Pascal	05/03/2000	IP-AC	INNOTHERA	Conseil pour essai clinique			
65315	PROBST	Vincent	08/01/2009	EC-INV	CHU DE NANTES	HYDROQUINIDINE	investigateur principal	12/2008	12/2013
65315	PROBST	Vincent	08/01/2009	CF-INT	SERVIER	place de l'ivabradine dans l'angor	rémunération personnelle	11/2008	11/2008
10347	PRUGNAUD	Jean-Louis	10/03/2010	IP-AC	LABORATOIRE SERB	Conseil dossier qualité/□□immunosérum	Rémunération personnelle	12/2009	
10347	PRUGNAUD	Jean-Louis	10/03/2010	IP-AC	LABORATOIRE CHAUVIN	conseil analytique/ indocollyre	Rémunération personnelle	12/2009	02/2010
10347	PRUGNAUD	Jean-Louis	20/03/2009	Néant					
10347	PRUGNAUD	Jean-Louis	18/12/2008	CF-INT	JANSSEN CILAG	Paris / Biosimilaires	Aucune rémunération	10/2008	10/2008
10347	PRUGNAUD	Jean-Louis	18/12/2008	CF-INT	CHUGAI	Mandelieu /Biosimilaires	Rémunération personnelle	08/2008	08/2008
10347	PRUGNAUD	Jean-Louis	18/12/2008	CF-INT	JANSSEN CILAG	Paris / Biosimilaires	Rémunération personnelle	10/2008	10/2008
10347	PRUGNAUD	Jean-Louis	18/12/2008	CF-INT	AMGEN	Roscoff /Biosimilaires	Rémunération personnelle	06/2008	06/2008
10347	PRUGNAUD	Jean-Louis	18/12/2008	IP-AC	MERCK GéNéRIQUES	Evaluation Dossier sufentanyl	Rémunération personnelle	01/2008	01/2008
10347	PRUGNAUD	Jean-Louis	18/12/2008	IP-AC	PANPHARMA	Evaluation DMF protaglandines	Rémunération personnelle	01/2008	01/2008
10347	PRUGNAUD	Jean-Louis	17/09/2008	CF-INT	AMGEN	MARSEILLE : BIOSIMILAIRES	Rémunération personnelle	09/2007	09/2007
10347	PRUGNAUD	Jean-Louis	17/03/2008	CF-INT	ARC	PARIS :biosimilaires	Rémunération personnelle	07/2007	07/2007
10347	PRUGNAUD	Jean-Louis	17/03/2008	IP-AC	MERCK GENERIQUES	Epirubicine/Oxaliplatine	Rémunération personnelle	03/2007	07/2007
10347	PRUGNAUD	Jean-Louis	17/03/2008	IP-AC	DIATOS	conseil sur IMPD	Rémunération personnelle	02/2007	02/2007
10347	PRUGNAUD	Jean-Louis	17/03/2008	IP-AC	CHAIX ET DU MARAIS	gluconate de calcium analytique	Rémunération personnelle/institution	01/2007	01/2007
10347	PRUGNAUD	Jean-Louis	13/09/2007	CF-INT	ARC	Paris/Dossier pharmaceutiques et affaires réglementaires/Biosimilaires/	Rémunération personnelle	07/2007	07/2007
10347	PRUGNAUD	Jean-Louis	13/09/2007	IP-AC	MERCK GéNéRIQUES	Consultation sur enregistrement génériques	Rémunération personnelle	09/2007	09/2007
10347	PRUGNAUD	Jean-Louis	13/09/2007	RE-DE	MERCK GéNéRIQUES	QOS/Epirubicine	Rémunération personnelle	03/2007	04/2007
10347	PRUGNAUD	Jean-Louis	26/10/2006	CF-INT	PHARMING BV	Acaddémie de Pharmacie/Les bioréacteurs animaux : une nouvelle plateforme biotechnologique/RHUCIN	Aucune rémunération		11/2006
10347	PRUGNAUD	Jean-Louis	31/07/2006	IP-AC	CHAIX DU MARAIS	Conseils analytiques/Gluconate de calcium 10%	Rémunération institution	06/2006	08/2006
10347	PRUGNAUD	Jean-Louis	22/02/2006	CF-AUD	GILEAD	Etats Unis/ASHP 2005		12/2005	12/2005
10347	PRUGNAUD	Jean-Louis	22/02/2006	RE-DE	PANPHARMA	Audit analytique/Amoxicilline	Rémunération personnelle	04/2004	01/2006
10347	PRUGNAUD	Jean-Louis	22/02/2006	RE-DE	MERCK GENERIQUES	Audit analytique/Oxaliplatine	Rémunération personnelle	09/2005	10/2005
10347	PRUGNAUD	Jean-Louis	22/02/2006	RE-DE	SANKYO PHARMA	Audit analytique/Panos	Rémunération personnelle	03/2004	07/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	RE-DE	GGAM	QOS Q / Leuproreline	rémunération personnelle	01/2005	04/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	CF-AUD	MERCK GENERIQUES	LYON / Séminaire Biosimilaire /		09/2005	09/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	CF-INT	LFB	PARIS / Séminaire DAR / CTD	rémunération personnelle	06/2005	06/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	IP-AC	FAULDING	Audit DMF/Teicoplanine	rémunération personnelle	07/2004	04/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	RE-DE	GGAM	QOS Q/Générique/Leuproréline	rémunération personnelle	12/2004	04/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	IP-AC	BT PHARMA	Audit Techniques analytiques/Adenyl cyclase	rémunération personnelle	05/2004	
10347	PRUGNAUD	Jean-Louis	21/10/2005	IP-AC	NEOVACS	Audit Techniques /Kinoides	rémunération personnelle	04/2004	
10347	PRUGNAUD	Jean-Louis	21/10/2005	IP-AC	POLIVE	Audit technique analytique CORIPEL	rémunération personnelle	07/2004	01/2005
10347	PRUGNAUD	Jean-Louis	21/10/2005	IP-AC	NOVARTIS	Audit technique analytique Miochol	rémunération personnelle	12/2004	12/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	RE-DE	IVAX	Cefadroxil Ivax		01/2004	04/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	RE-DE	NOVARTIS	Tareg		06/2004	09/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	IP-AC	NOVARTIS	Conseil fabrication et analytique	rémunération personnelle	12/2003	01/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	IP-AC	MERCK GENERIQUES	Audit DMF	rémunération personnelle	03/2004	12/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	IP-AC	SANGSTAT	Audit techniques analytiques	rémunération personnelle	10/2003	12/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	IP-AC	GENFIT	Audit techniques analytiques	rémunération personnelle	02/2003	
10347	PRUGNAUD	Jean-Louis	04/01/2005	CF-INT	A.R.C	Conférence sur dossier CTD		06/2004	06/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	CF-INT	PANPHARMA	Formation sur dossier CTD		09/2004	09/2004
10347	PRUGNAUD	Jean-Louis	04/01/2005	CF-AUD	LFB	Conférence rencontres clinique pharmaciens		11/2003	11/2003
10347	PRUGNAUD	Jean-Louis	04/01/2005	PAR	GLAXO SMITHKLINE	Conjoint	Responsable régional équipe monitoring	10/1989	
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-RE	NOVARTIS	Rapport complémentaire stabilité Voltarène			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-RE	G GAM	CTD Module 2 Gabapentine			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-RE	CdM	Rapport complémentaire Procaine chte			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-AC	LFB	Mise en place du CTD - Fabrication			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-AC	POLIVE	Stabilité pansement médicamenteux			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-AC	NOVARTIS	Reprise du dossier Fluoresceine sodique			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-AC	GENFIT	CTD sur nouveau produit			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-AC	MERCK GENERIQUE	Rapport lactulose			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-CF	LFB	3e rencontres cliniques Pharmaciens			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-CF	CHUGAI	Formation visite médicale			
10347	PRUGNAUD	Jean-Louis	20/01/2004	IP-AUT	TGI (BAXTER - AVENTIS - PASTEUR)	Expertise judiciaire Grèce			
10347	PRUGNAUD	Jean-Louis	20/01/2004	PAR	GLAXO SMITHKLINE	Conjoint			
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-RE	PANPHARMA	Ceftriaxone, Pridazolam			
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-RE	NOVARTIS	SYNTOCINON, DHE-Methergin			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-RE	AEROCID	Lactulose			
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-AC	BAXTER	Conseil scientifique sur dossier enregistrement			
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-CF	ARC	Compatibility of biotech products			
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-CF	CHIRON	Vaccins			
10347	PRUGNAUD	Jean-Louis	20/01/2003	IP-CF	Conférences MOISSAN	Préparation au pharmacopat			
10347	PRUGNAUD	Jean-Louis	20/01/2003	PAR	GLAXO SMITHKLINE	Epouse			
10347	PRUGNAUD	Jean-Louis	03/10/2001	IP-RE	MACOPHARMA	Rapport d'expertise pharmaceutique			
10347	PRUGNAUD	Jean-Louis	03/10/2001	IP-AC	BAXTER	Conseil scientifique			
10347	PRUGNAUD	Jean-Louis	03/10/2001	IP-CF	L.F.B.	Colloque "LFB-Pharmaciens"			
10347	PRUGNAUD	Jean-Louis	03/10/2001	IP-CF	A.R.C.	Conférence "Actualité Pharmaceutique"			
10347	PRUGNAUD	Jean-Louis	03/10/2001	IP-CF	ICH	Formation "Pharmaciens Hospitaliers"			
10347	PRUGNAUD	Jean-Louis	03/10/2001	PAR	GSK	Conjoint			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-RE	AEROCID	Nifuroxaride, Carbocistéine, Lactulose			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-RE	PANPHARMA	Molsidomine, Amiodarone, Ceftriaxone			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-RE	GGAM	Enalapril			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-RE	NOVARTIS	Aredia			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-RE	MACOPHARMA	Poches (NaCl, Glucose)			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-CF	APRA	Conférence Moissan - formation PH Pharmaciens			
10347	PRUGNAUD	Jean-Louis	05/06/2001	IP-CF	CHUGAI	Conférence Granocyte			
10347	PRUGNAUD	Jean-Louis	05/06/2001	PAR	GSK	conjoint			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-RE	AEROCID (M3 SANTE)	Rapport pharmaceutique			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-RE	G GAM	Rapport pharmaceutique			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-RE	PANPHARMA	Rapport pharmaceutique			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-RE	NOVARTIS	Rapport pharmaceutique			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-RE	SMITHKLINE BEECHAM	Rapport pharmaceutique			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-AC	CHUGAI	Rédaction information professionnelle			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-CF	SERVIER	Formation diabétologie			
10347	PRUGNAUD	Jean-Louis	03/10/2000	IP-CF	APRA	Formation Pharmaciens Hospitaliers			
10347	PRUGNAUD	Jean-Louis	03/10/2000	PAR	GLAXO WELLCOME	Conjoint			
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	PANPHARMA				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	CHAIX ET DU MARAIS				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	DAKOTA PHARM				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	NOVARTIS				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	SMITHKLINE BEECHAM				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	BAYER PHARMA				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	ALTHIN MEDICAL				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	GIFRER BARBEZAT				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	AEROCID				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-RE	MSD				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-CF	Association pour la Recherche avancée (APRC)				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-CF	ARC				
10347	PRUGNAUD	Jean-Louis	01/01/1999	IP-CF	DHT PHARMA				
10347	PRUGNAUD	Jean-Louis	01/01/1999	PAR	GLAXO WELLCOME	Conjoint			
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Ciba Geigy				
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Macopharma				
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Soludia				
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Leo				
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Hoechst				
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Bayer				
10347	PRUGNAUD	Jean-Louis	01/01/1998	IP-AUT	Dakota Pharm				
10347	PRUGNAUD	Jean-Louis	01/01/1998	PAR	Conjoint salarié industrie pharmaceutique				
10348	PUECH	Alain	01/01/1999	IP-AC	IRIS				
10348	PUECH	Alain	01/01/1999	IP-AC	LAFON				
10348	PUECH	Alain	01/01/1999	IP-AC	SANOFI				
10348	PUECH	Alain	01/01/1999	IP-AC	SYNTHELABO				
10348	PUECH	Alain	01/01/1999	IP-AC	WYETH				
10348	PUECH	Alain	01/01/1999	IP-AUT	LILLY				
10348	PUECH	Alain	01/01/1999	VB	BAYER PHARMA	Association Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	BEAUFOUR	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	Institut LILLY	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	LAFON	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	LOGEAIS JACQUES	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	PARKE DAVIS	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	PFIZER	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	PIERRE FABRE	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	ROCHE	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	SANOFI WINTHROP	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	SERVIER-ADIR	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	SKB	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	SYNTHELABO	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	RHONE POULENC RORE SPECIA	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	THERAPLIX	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	THERAPHARM Recherches	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1999	VB	WYETH-LEDERLE	Claude Bernard, Association Naturalia & Biologia			
10348	PUECH	Alain	01/01/1998	IP-AUT	IRIS				
10348	PUECH	Alain	01/01/1998	IP-AUT	Lafon				
10348	PUECH	Alain	01/01/1998	IP-AUT	Sanofi				
10348	PUECH	Alain	01/01/1998	IP-AUT	Synthélabo				
10348	PUECH	Alain	01/01/1998	IP-AUT	Wyeth				
10348	PUECH	Alain	01/01/1998	IP-AUT	Lilly				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10348 PUECH		Alain	01/01/1998	VB	Bayer-Pharma		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Institut Lilly		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Lafon		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Logeais		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Parke-Davis		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Pfizer		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Pierre-Fabre		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Roche		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Sanofi-Winthrop		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Sanofi Recherche		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Servier-Adir		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	SKB		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Synthélabo		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	RPR-Spécia		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Théraplix		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Wyeth-Lederlé		Association Claude Bernard, Association Naturalia et Biologia		
10348 PUECH		Alain	01/01/1998	VB	Thérapharm Recherches		Rémunération personnelle	01/2008	
60764 PUEL		Jacques	15/11/2007	CF-INT	ARDIX THERVAL	JE de la SFC Modérateur	Rémunération personnelle	01/2008	
60764 PUEL		Jacques	15/11/2007	CF-INT	PFIZER	JE de la SFC. Recommandations. TAHOR	rémunération personnelle	01/2005	
60764 PUEL		Jacques	09/01/2007	LD-AR	SANOFI-AVENTIS	Board Scientifique Acomplia	investigateur principal		
60764 PUEL		Jacques	09/01/2007	EC-INV	BOEHRINGER	registre OPTIMAL	coordonnateur	01/2005	12/2009
60764 PUEL		Jacques	09/01/2007	CF-INT	PFIZER	JE de la SFC	rémunération personnelle	01/2005	12/2005
60764 PUEL		Jacques	09/01/2007	CF-INT	AIDEX-THERVAL	JE de la SFC	rémunération personnelle	01/2006	12/2006
60764 PUEL		Jacques	09/01/2007	CF-INT	SANOFI-AVENTIS	JE de la SFC	rémunération personnelle	01/2006	12/2006
60764 PUEL		Jacques	07/02/2006	LD-AR	SOCIETE FRANCAISE DE CARDIOLOGIE	Membre du bureau	aucune rémunération		
60764 PUEL		Jacques	07/02/2006	EC-INV	ASTRA ZENECA	Crestor	investigateur principal	01/2004	12/2005
60764 PUEL		Jacques	07/02/2006	IP-AC	SANOFI	Board Rimonabant	rémunération personnelle	01/2004	12/2005
60764 PUEL		Jacques	07/02/2006	IP-AC	ASTRA ZENECA	board Crestor	rémunération personnelle	01/2004	12/2005
60764 PUEL		Jacques	07/02/2006	CF-INT	PFIZER, SERVIER, NOVARTIS	Symposia aux JE de la SFC	rémunération personnelle	01/2005	12/2005
60764 PUEL		Jacques	07/02/2006	CF-AUD	SANOFI	Rimonabant et Plavix - Paris		01/2005	
60764 PUEL		Jacques	07/02/2006	VB	ASTRA ZENECA, SANOFI, SERVIER	recherche clinique et protocole d'étude	Association pour le développement en pathologie cardiovasculaire	01/2003	12/2005
60764 PUEL		Jacques	12/08/2004	IP-EC	NOVARTIS	CIPS			
60764 PUEL		Jacques	12/08/2004	IP-EC	NOVARTIS	TYPHON			
60764 PUEL		Jacques	12/08/2004	IP-EC	NOVARTIS	ARTS II			
60764 PUEL		Jacques	12/08/2004	IP-EC	NOVARTIS	OASIS 5			
60764 PUEL		Jacques	12/08/2004	IP-AC	PFIZER	Board			
60764 PUEL		Jacques	12/08/2004	IP-AC	ASTRA ZENECA	Board			
60764 PUEL		Jacques	12/08/2004	IP-AC	NOVARTIS	Board			
60764 PUEL		Jacques	12/08/2004	IP-AC	SANOFI	Plavix			
60764 PUEL		Jacques	12/08/2004	IP-RE	BAYER	Cerivastatine			
60764 PUEL		Jacques	12/08/2004	IP-CF		Très nombreuses avec firmes impliquées dans le développement des statines et des thrombolitiques			
60764 PUEL		Jacques	28/01/2004	IP-EC	Société Française de Cardiologie	Registre angioplastie			
60764 PUEL		Jacques	28/01/2004	IP-EC	BOEHRINGER	Infarctus du myocarde aigue			
60764 PUEL		Jacques	28/01/2004	IP-EC	PFIZER	Etude EFECTS			
60764 PUEL		Jacques	28/01/2004	IP-EC	AVENTIS	Etude Diabetics			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60764	PUEL	Jacques	28/01/2004	IP-RE	BAYER	Cerivastatine			
60764	PUEL	Jacques	28/01/2004	IP-AC	PFIZER	Board			
60764	PUEL	Jacques	28/01/2004	IP-AC	ASTRA ZENECA	Board			
60764	PUEL	Jacques	28/01/2004	IP-AC	BOEHRINGER	Registre IDM			
60764	PUEL	Jacques	28/01/2004	IP-CF	BOEHRINGER	Infarctus du myocarde			
60764	PUEL	Jacques	28/01/2004	IP-CF	PFIZER	Athérosclérose			
60764	PUEL	Jacques	28/01/2004	IP-CF	Société Française de Cardiologie	Dislipidémie, angioplastie coronaire			
60764	PUEL	Jacques	28/01/2004	VB	PFIZER, AVENTIS,ASTRA ZENECA, BMS, CORDIER	Association loi 1907 de recherche clinique du service de cardiologie B du CHU de Toulouse			
60764	PUEL	Jacques	31/05/2001	IP-AC	PFIZER	Plan d'information Cardio			
60764	PUEL	Jacques	31/05/2001	IP-AC	SANOFI-SYNTHELABO	Observation des prescriptions et enquêtes épidémiologiques			
60764	PUEL	Jacques	31/05/2001	IP-CF	PFIZER, BAYER, MSD, ASTRA ZENECA	"Chimiothérapie anti-athéromateuse"			
60764	PUEL	Jacques	31/05/2001	IP-CF	BOEHRINGER-INGELHEIM	IDM aigu			
60764	PUEL	Jacques	31/05/2001	VB	Nombreuses firmes dans le cadre d'études soit multicentriques, soit (moins souvent) monocentriques	Association pour le développement de la recherche en pathologie cardiovasculaire (siège : CHU - Cardiologie B)			
60764	PUEL	Jacques	21/12/2000	VB	NOVOSTE (Promoteur)	Etude BRIE - Registre multicentrique européen sur l'étude de la prévention de la Resténose intra Stent : Association pour le développement en biophysique médicale - CHU Ra			
65415	PUISIEUX	François	01/12/2008	LD	Editeur EDIMEDICA	Redacteur en chef de la Revue de gériatrie	rémunération personnelle	01/2004	
65415	PUISIEUX	François	01/12/2008	IP-EC	LEO PHARMA	Thromboses veineuses profondes : Tinzaparine sodique (Innohep)	rémunération institution		
65415	PUISIEUX	François	01/12/2008	IP-EC	OPTIMER PHARACEUTICALS	Infection à C difficile	rémunération institution	12/2007	
65415	PUISIEUX	François	01/12/2008	IP-AC	JANSSEN CILAG	Comité scientifique des rencontres de gériatrie	rémunération personnelle	01/2003	
65415	PUISIEUX	François	01/12/2008	IP-AC	GLAXO SMITHKLINE	Groupe de reflexion Epilepsie du sujet âgé / deux fois par an depuis 2006	rémunération personnelle	01/2006	
65415	PUISIEUX	François	01/12/2008	IP-AC	EISAI	Groupe de rédaction des fiche s"Maladie d'Alzheimer et pathologies associées"	rémunération institution	01/2006	
65415	PUISIEUX	François	01/12/2008	IP-AC	ROCHE	Groupe d'expert Grippe / 2 fois par an depuis 2005	rémunération personnelle	01/2005	
65415	PUISIEUX	François	01/12/2008	CF-INT	SERVIER	Congrès Interrégional de Gériatrie à Rouen: Ostéoporose	rémunération personnelle	11/2008	11/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	JANSSEN CILAG	Oncogériatrie à Chantilly	rémunération personnelle	06/2008	06/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	EUTHERAPIE	HTA du plus de 80 ans à Lille	rémunération personnelle	05/2008	05/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Diabète du sujet âgé à Lille	rémunération personnelle	03/2008	03/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Diabète du sujet âgé à Lille	rémunération personnelle	03/2008	03/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Diabète du sujet âgé à Lille	rémunération personnelle	03/2008	03/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	UCB	Epilepsie du sujet à Cannes	rémunération personnelle	06/2008	06/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI PASTEUR MSD	Vaccination du sujet âgé à Lille	rémunération institution	03/2007	03/2007
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	01/2006	01/2006
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	01/2006	01/2006
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	02/2007	02/2007
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	02/2007	02/2007
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	01/2008	01/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	01/2008	01/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	01/2009	01/2009
65415	PUISIEUX	François	01/12/2008	CF-INT	NOVARTIS	Nouvelles Dimensions en Gériatrie à Paris	rémunération personnelle	01/2009	01/2009
65415	PUISIEUX	François	01/12/2008	CF-INT	ARDIX	Rééducation du patient âgé démenl à Roubaix	rémunération personnelle	06/2007	06/2007
65415	PUISIEUX	François	01/12/2008	CF-INT	LUNDBECK	Alzheimer: déclin clinique rapide	rémunération personnelle	03/2008	03/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	LUNDBECK	Alzheimer: déclin clinique rapide	rémunération personnelle	03/2008	03/2008
65415	PUISIEUX	François	01/12/2008	CF-INT	THERVAL MEDICAL	HTA et diabète du sujet âgé à Vendin en Veil	rémunération personnelle	09/2006	09/2006
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Journées de Gériatrie du Nord Pas-de-Calais à Bruxelles et à Lille	rémunération personnelle	12/2005	12/2005
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Journées de Gériatrie du Nord Pas-de-Calais à Bruxelles et à Lille	rémunération personnelle	12/2005	12/2005
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Journées de Gériatrie du Nord Pas-de-Calais à Bruxelles et à Lille	rémunération personnelle	05/2006	05/2006
65415	PUISIEUX	François	01/12/2008	CF-INT	SANOFI AVENTIS	Journées de Gériatrie du Nord Pas-de-Calais à Bruxelles et à Lille	rémunération personnelle	05/2006	05/2006
65415	PUISIEUX	François	01/12/2008	CF-INT	LEO PHARMA	Maladies thrombo-emboliques du sujet âgé à Lille	rémunération personnelle	05/2005	05/2005
65415	PUISIEUX	François	01/12/2008	CF-AUD	SANOFI PASTEUR MSD	Congrès Européen "Influenzz Conférence" à Vilamoura (Portugal)		09/2008	09/2008
65415	PUISIEUX	François	01/12/2008	CF-AUD	EUTHERAPIE	5th Global Cardiovascular Clinical Trialists Forum à Cannes			
65415	PUISIEUX	François	01/12/2008	CF-AUD	NOVARTIS	International Springfield à Hong-Kong		02/2008	03/2008
65415	PUISIEUX	François	01/12/2008	CF-AUD	SERVIER	Journées européennes de la Société Française de Cardiologie Paris		01/2006	01/2006
65415	PUISIEUX	François	01/12/2008	CF-AUD	EISAI	Congrès de l'American Geriatrics Society. Chaque année 1ere semaine de mai.			
65415	PUISIEUX	François	01/12/2008	IP-AUT	EDITEUR ACALIS	Parcours du Praticien: risque de fracture du sujet âgé: rédaction d'un chapitre	rémunération personnelle	01/2007	
65415	PUISIEUX	François	01/12/2008	IP-AUT	EDITEUR ELSEVIER	Traité de médecine ARKOS: écriture d'un chapitre	rémunération personnelle	01/2006	
65415	PUISIEUX	François	01/12/2008	IP-AUT	EDITEUR FLAMMARION	Le livre de l'interne en Gériatrie, auteur	rémunération personnelle	01/2008	
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-RE	INNOVUS	Rapport expertise pour une société de conseil			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-AC	GSK	International Health Economic Advisory Board			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-AC	GSK	Comité Marly pour la santé publique et économie de la santé			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-AC	SANOFI SYNTHELABO Groupe	European Global Health Outcome Board			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-AC	PHARMACIA	Conseil scientifique, enquête Glaucome			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-AC	SANOFI SYNTHELABO France	Conseil en économie de la santé			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-CF	MSD	Les auditions de la santé (non rémunérée)			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-CF	GSK	Les journées Economie de la santé (non rémunérée)			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	IP-CF	SNIP	Conférence information sur irritation (non rémunérée)			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	VB	SERVIER	Analyse économique de la prévention secondaire dans AVC			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	VB	MSD	Le coût de la prise en charge angine instable			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	VB	MSD (à venir)	Analyse économique du contrôle hypercholestérolimie			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	VB	BMS	La prise en charge de l HTA en médecine générale			
60692	PUYOU DE POUVOURVILLE	Gérard	26/09/2002	VB	SANOFI SYNTHELABO	Présence des évènements thrombo-emboliques en chirurgie orthopédique			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	LD		A partie d octobre 2000 : chef de service de l Institut Gustave Roussy - Aide à la décision et information médicale - en cumul de fonction			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	VB	MSD	Le coût indirect des AVC (99)			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	VB	MSD	Le coût de la prise en charge de l Alzheimer en Europe (2000-en cours)			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	VB	PROCTER & GAMBLE	(2000-en cours) Le coût de la défibrillation auriculaire en France			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	VB	BMS	(à venir) coût-efficacité du contrôle de l HTA			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	VB	SERVIER	(à venir) Coût-efficacité de la prévention de la récidive dans AVC			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	VB		Bourse CIFRE-ANRT/ALIANCE MEDICA (Thèse en santé Publique)			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	IP-RE	MONSANTO-SEARLE-CELEBREX	Rapport sur le dossier économique			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	IP-AC	MSD	Activités ponctuelles (avis sur dossiers)			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	IP-AC	MONSANTO-SEARLE	Membre Global Health Outcome Board (Chicago)			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	IP-CF	Institut Gustave Roussy	Cours Economie de la Santé			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	IP-CF	PFIZER	Accoss II. Formation continue en économie de la santé			
60692	PUYOU DE POUVOURVILLE	Gérard	14/06/2000	IP-CF	CNAMTS	Formation continue			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60692	PUYOU DE PDUVOURVILLE	Gérard	14/08/2000	IP-CF	FNMF	Formation continue			
65485	QUARTIER	Pierre	09/03/2009	EC-INV	NOVARTIS	ACZ 885 Etude phase II Forme systémique (FS-) d'Arthrite Juvénile Idiopathique (AJI)□□(Etude CACZ 885/	investigateur coordonnateur	06/2007	
65485	QUARTIER	Pierre	09/03/2009	EC-INV	INSERM	Etude ANAJIS« phase II b Anakino FS-AJI	investigateur coordonnateur	06/2006	04/2008
65485	QUARTIER	Pierre	09/03/2009	EC-INV	ABBOTT	ADALIMUMAB Etude phase III AJI polyarticulaire (Etude DEO)	investigateur coordonnateur	09/2007	
65485	QUARTIER	Pierre	09/03/2009	EC-INV	BMS	ABATACEPT Etude phase III AJI poly articulaire (Etude IM101-033)	investigateur coordonnateur	09/2006	
65485	QUARTIER	Pierre	09/03/2009	EC-CO	NOVARTIS	ACZ 885 et MuchleWells. Etudes CACZ885/D2304/ CACZ885/D2306	co-investigateur	09/2007	
65485	QUARTIER	Pierre	09/03/2009	EC-CO	INSERM	Registre Corpus pour AJI	Co-investigateur	01/2005	12/2005
65485	QUARTIER	Pierre	09/03/2009	EC-CO	PRINTO (www.printo.it)	Etude Health-e-child	co-investigateur	09/2006	
65485	QUARTIER	Pierre	09/03/2009	EC-CO	PRINTO	Etude dermatomyosite juvenile	co-investigateur	09/2007	
65485	QUARTIER	Pierre	09/03/2009	RE-DE	ABBOTT	Expertise pour le laboratoire du dossier de transparence en préparation pour l'Adalimumab (Humira) dans l'A	rémunération personnelle	01/2009	
65485	QUARTIER	Pierre	09/03/2009	RE-AUT	PFIZER	Londes, réunion d'experts dossier pour AMM européenne Hormone de croissance dans l'AJI	rémunération personnelle	01/2008	01/2008
65485	QUARTIER	Pierre	09/03/2009	RE-DE	SERVIER	Expertise dossier du d' AMM enropéen en cours de préparation pour le le ranelate de strontium dans l'osteo	rémunération personnelle	01/2009	
65485	QUARTIER	Pierre	09/03/2009	RE-DE	ROCHE	Groupe d'expert , une rénion sur le Toclizumab	rémunération personnelle	12/2007	
65485	QUARTIER	Pierre	09/03/2009	CF-INT	NOVARTIS	Bâle chez Novartis Campus; présentation d'un exposé sur forme systémique d'AJI et le rôle de l'IL-1	rémunération personnelle	02/2009	02/2009
65485	QUARTIER	Pierre	09/03/2009	CF-INT	PFIZER	Paris, Réunion KIGS KM4 de formation (=animation d'atelier) pour médecins sur hormone de croissance et /	rémunération personnelle	11/2008	11/2008
65485	QUARTIER	Pierre	09/03/2009	CF-AUD	ROCHE	Rome, Réunion investigateurs future étude tocilizumab FS-AJI		02/2008	12/2008
65485	QUARTIER	Pierre	09/03/2009	(Autre)	BMS	Payement d'un infirmier de recherche clinique pour étude de phase III dans l'AJI avec Alzatocept, à temps partiel		01/2006	12/2009
65485	QUARTIER	Pierre	09/03/2009	(Autre)	NOVARTIS	Payement d'un ARC mi-temps via contrat avec l'URC Paris-centre (Nuke-Cockin) pour les études ACZ885 forme systémique d'AJI et Herkle-		06/2007	06/2007
10349	QUENEAU	Patrice	06/12/2010	PAR	GROUPE SERVIER	cadre	fils	05/1995	
10349	QUENEAU	Patrice	06/12/2010	PAR	THUASNE SAS	Président	soeur	12/2004	
10349	QUENEAU	Patrice	06/12/2010	PAR	THUASNE PARTICIPATION SAS	Président	soeur	12/2005	
10349	QUENEAU	Patrice	06/12/2010	IF	THUASNE SAS	ACTIONS - CAPITAUX PROPRES,	<5000 € ou <5% du capital	01/1993	
10349	QUENEAU	Patrice	06/12/2010	IF	THUASNE PARTICIPATIONS	ACTIONS - CAPITAUX PROPRES	<5000 € ou <5% du capital	04/2006	
10349	QUENEAU	Patrice	26/07/2010	EC-INV	APNET	étude scientifique sur LATROGENIE MEDICAMENTEUSE : évaluation de la part de l'automédication - état d	investigateur-coordinateur	02/2010	
10349	QUENEAU	Patrice	01/10/2008	IF	THUASNE PARTICIPATION SAS	Actions - capitaux propres - détention en cours à ce jour	2 sur 2 777 481 titres	04/2006	
10349	QUENEAU	Patrice	01/10/2008	IF	THUASNE SAS	Actions - capitaux propres - détention en cours à ce jour - Avant 1994	2 sur 55 000 titres		
10349	QUENEAU	Patrice	01/10/2008	LD	THUASNE PARTICIPATIONS SAS	Administrateur - Mandat en cours - Fin AG 2009	Nomination AG	08/2006	12/2009
10349	QUENEAU	Patrice	01/10/2008	LD	THUASNE SAS	Administrateur - Mandat en cours - Fin AG 2010	Nomination AG	12/2004	12/2010
10349	QUENEAU	Patrice	01/10/2008	LD-AR	THUASNE SAS	Conseil, évaluation thérapeutique sur les effets de la contention lombaire - produits THUASNE	rémunération personnelle	01/2003	01/2008
10349	QUENEAU	Patrice	01/10/2008	IP-AC	THUASNE SAS	Participation au Congrès P2T 2008 - Clermont Ferrand : présentation d'un poster sur les effets de la contenti	rémunération personnelle	04/2008	04/2008
10349	QUENEAU	Patrice	01/10/2008	PAR	THUASNE PARTICIPATION SAS	Président (mandataire non salariée / contrat de travail suspendu)	sœur	12/2005	12/2009
10349	QUENEAU	Patrice	01/10/2008	PAR	THUASNE SAS	Président (mandataire non salariée / contrat de travail suspendu)	sœur	12/2004	12/2010
10349	QUENEAU	Patrice	01/10/2008	PAR	SERVIER	Cadre	fils	05/1995	
10349	QUENEAU	Patrice	01/01/2000	IF	Groupe THUASNE	Actionnaire			
10349	QUENEAU	Patrice	01/01/2000	PAR	Groupe de recherche SERVIER	Un fils employé			
10349	QUENEAU	Patrice	01/01/1999	IF	THERMOGENE 6, rue des Marroniers 92300 Levallois-Perret	1 action			
10349	QUENEAU	Patrice	01/01/1999	IF	Société THUASNE	Participation financière au capital			
10349	QUENEAU	Patrice	01/01/1999	IP-EC	SERVIER	CD-ROM en partenariat			
10349	QUENEAU	Patrice	01/01/1998	IF	Thermogène				
10349	QUENEAU	Patrice	01/01/1998	IF	Thuasne				
10349	QUENEAU	Patrice	01/01/1998	IP-AUT	Servior			06/2009	
62314	QUERA SALVA	Maria Antonia	25/01/2010	CF-AUD	LUNDBECK	Congres APSS	enfant étiduant en médecine	03/2007	
62314	QUERA SALVA	Maria Antonia	17/03/2009	PAR	ALIX CONSULTING	Assitant de recherche	Fondation de Garches, Hopital Poincaré	07/2007	07/2008
62314	QUERA SALVA	Maria Antonia	17/03/2009	VB	COFIROUTE	protocole de recherche sur la lumiere et la cafeine		06/2008	
62314	QUERA SALVA	Maria Antonia	17/03/2009	CF-AUD	ADEP ASSISTANCE	congrès APSS		11/2008	11/2008
62314	QUERA SALVA	Maria Antonia	17/03/2009	CF-AUD	RESPIRONICS	congrès SFRMS			
62314	QUERA SALVA	Maria Antonia	17/03/2009	IP-AC	LUNDBECK	conseils circadin	Rémunération institution	03/2008	
62314	QUERA SALVA	Maria Antonia	17/03/2009	EC-INV	SERVIER	agomelatine	investigateur coordonnateur	05/2007	
62314	QUERA SALVA	Maria Antonia	17/03/2009	LD-ODE	ALIX CONSULTING	Directeur scientifique benevole	conseil dans les metiers de la santé	01/1999	
62314	QUERA SALVA	Maria Antonia	17/03/2009	EC-CO	ACTELION	etude phase III	investigateur	12/2008	
62314	QUERA SALVA	Maria Antonia	19/12/2008	IP-AC	LUNDBECK	Conseil/circadin	Rémunération institution	04/2008	07/2008
62314	QUERA SALVA	Maria Antonia	19/12/2008	EC-CO	ACTELION	etude phase III	investigateur	12/2008	
62314	QUERA SALVA	Maria Antonia	17/09/2007	IF	ALIX CONSULTING (CONSEILS DANS LES MéTIERS DE LA SANTé)	capital < 5000 € ou < 5% du capital	<5000 € ou <5% du capital	01/1992	
62314	QUERA SALVA	Maria Antonia	17/09/2007	LD-AR	SERVIER (RIS)	Membre d'un groupe d'experts	rémunération personnelle	01/2005	12/2007
62314	QUERA SALVA	Maria Antonia	17/09/2007	EC-INV	ALIX CONSULTING	Agomelatine (Valdoxan)	coordinateur	05/2007	
62314	QUERA SALVA	Maria Antonia	17/09/2007	EC-CO	TAKEDA	Ramelteon	expérimentateur non principal	09/2004	09/2006
62314	QUERA SALVA	Maria Antonia	17/09/2007	EC-CO	SANOFI AVENTIS	Eprivaserine	expérimentateur non principal	01/2007	12/2007
62314	QUERA SALVA	Maria Antonia	17/09/2007	CF-AUD	SERVIER	Congrès du ECNP - Vienne		10/2007	10/2007
62314	QUERA SALVA	Maria Antonia	17/09/2007	CF-AUD	SERVIER	APSS Congrès annuel de la société Américaine de sommeil - Utah		06/2006	06/2006
62314	QUERA SALVA	Maria Antonia	17/09/2007	PAR	ALIX CONSULTING	Assistante partie du temps	enfant étudiant en médecine	08/2006	
62314	QUERA SALVA	Maria Antonia	13/10/2005	LD-AR	SERVIER	Expert	Rémunération personnelle		
62314	QUERA SALVA	Maria Antonia	13/10/2005	LD-AR	IRIS	Conseil		01/1992	
62314	QUERA SALVA	Maria Antonia	13/10/2005	EC-INV	IRIS	Agomelatine	Investigateur	01/2002	12/2004
62314	QUERA SALVA	Maria Antonia	13/10/2005	EC-INV	LUNDBECK	Glosoxadol	Investigateur	01/2003	
62314	QUERA SALVA	Maria Antonia	13/10/2005	IP-RE	ENST	Projet mise à disposition personnes handicapées d'un interface permettant de communier avec l'extérieur	Rémunération versée à une Institution	01/2005	12/2005
62314	QUERA SALVA	Maria Antonia	13/10/2005	IP-AC	TAKEDA	Consultant ponctuel	Rémunération personnelle	02/2005	02/2005
62314	QUERA SALVA	Maria Antonia	13/10/2005	CF-INT	SERVIER	AIPS	Aucune rémunération	10/2005	
62314	QUERA SALVA	Maria Antonia	13/10/2005	CF-AUD	GSK	Réunion European Sleep Research Society / Prague	Aucune rémunération	09/2004	09/2004
62314	QUERA SALVA	Maria Antonia	13/10/2005	CF-AUD	GSK	World sleep meeting / Berlin	Aucune rémunération	10/2005	
62217	RAPIN	Jean-Robert	05/03/2004	IP-EC	MERCK-SANTE	Travaux expérimentaux			
62217	RAPIN	Jean-Robert	05/03/2004	IP-CF	ASTRA-ZENECA	Chiralité - Inexium			
62217	RAPIN	Jean-Robert	05/03/2004	IP-CF	SCHWARZ-PHARMA	Nausées, vomissments, Vogalib			
62217	RAPIN	Jean-Robert	12/09/2002	IP-EC	MERCK	Travaux scientifiques : antidiabétiques			
62217	RAPIN	Jean-Robert	12/09/2002	IP-EC	CHIESI	Travaux scientifiques : Alzheimer			
62217	RAPIN	Jean-Robert	12/09/2002	IP-EC	SERVIER	Travaux scientifiques : antidiabétiques			
62217	RAPIN	Jean-Robert	12/09/2002	IP-EC	AIR LIQUIDE	Travaux scientifiques : sestenos			
62217	RAPIN	Jean-Robert	12/09/2002	IP-AUT	AIM (publication mensuelle)	Directeur scientifique			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62217	RAPIN	Jean-Robert	12/09/2002	IP-AUT	NAFAS (publication trimestrielle)	Directeur scientifique			
62217	RAPIN	Jean-Robert	27/06/2001	IP-EC	MERCK-LIPHA	Préclinique - Expérience animale			
62217	RAPIN	Jean-Robert	27/06/2001	IP-EC	IPSEN	Préclinique - Expérience animale			
62217	RAPIN	Jean-Robert	27/06/2001	IP-EC	CHIESI	Préclinique - Expérience animale			
62217	RAPIN	Jean-Robert	27/06/2001	IP-EC	AIR LIQUIDE	Préclinique - Expérience animale			
62217	RAPIN	Jean-Robert	27/06/2001	IP-RE	CHIESI	Rapport VASOBRAL			
62217	RAPIN	Jean-Robert	27/06/2001	IP-CF	ASTRA ZENECA	Conférences sur la Chiralite			
62217	RAPIN	Jean-Robert	27/06/2001	IP-CF	KNOLL	Conférences sur obésité			
61072	RASCOL	Olivier	20/09/2004	LD	SCHERING PLOUGH - LUNDBECK - KYOWA	Consultations, plan du développement anti-parkinsoniens			
61072	RASCOL	Olivier	20/09/2004	IP-EC	GSK - SERVIER - PFEIZER - SCHARZ - MERCK - NOVARTIS - TEVA	Consultant et investigation, essais cliniques			
61072	RASCOL	Olivier	20/09/2004	IP-EC	LUNDBEK - NEUROBIOTEC - SANOFI - BOEHRINGER - TAKEDA - SERONO	Consultant et investigation, essais cliniques			
61072	RASCOL	Olivier	20/09/2004	IP-AC	GSK - SERVIER - PFEIZER - SCHWARZ - MECK - NOVARTIS - TEVA	Conseil développement anti-parkinsoniens			
61072	RASCOL	Olivier	20/09/2004	IP-AC	LUNDBECK - NEUROBIOTEC - SANOFI - BOEHRINGER - TAKEDA - SERONO	Conseil développement anti-parkinsoniens			
61072	RASCOL	Olivier	20/09/2004	IP-CF	GSK - TEVA - NOVARTIS - SERVIER - HAMMERSHAM	Conférences, enseignement anti-parkinsoniens			
61072	RASCOL	Olivier	23/02/2000	IP-EC	SMITHKLINE BEECHAM	Etude "125" Ropinirole			
61072	RASCOL	Olivier	23/02/2000	IP-EC	AVENTIS	Etude "320","321" riluzol			
61072	RASCOL	Olivier	23/02/2000	IP-EC	ROCHE	Etude modopar DR			
61072	RASCOL	Olivier	23/02/2000	IP-AC	SMITHKLINE BEECHAM	Ropinirole développement			
61072	RASCOL	Olivier	23/02/2000	IP-AC	AVENTIS	Riluzole développement			
61072	RASCOL	Olivier	23/02/2000	IP-AC	NOVARTIS	Entacopone développement			
61072	RASCOL	Olivier	23/02/2000	IP-AC	SERVIER	Piribedil développement			
61072	RASCOL	Olivier	23/02/2000	IP-AC	PHARMACIA UPJOHN	Pramipexole développement			
61072	RASCOL	Olivier	23/02/2000	IP-CF	SMITHKLINE BEECHAM	Agonistes chez le parkinsonien			
61072	RASCOL	Olivier	23/02/2000	IP-CF	SERVIER	Agonistes chez le parkinsonien			
61074	RAVAUD	Philippe	06/10/2003	IP-EC	MERCK SHARP & DOHME				
61074	RAVAUD	Philippe	06/10/2003	IP-EC	SERVIER				
61074	RAVAUD	Philippe	06/10/2003	IP-EC	GRUNENTHAL				
61074	RAVAUD	Philippe	06/10/2003	IP-RE	LILLY				
61074	RAVAUD	Philippe	06/10/2003	IP-AC	SANOFI				
61074	RAVAUD	Philippe	06/10/2003	IP-AC	BRISTOL MYERS SQUIBB				
61074	RAVAUD	Philippe	06/10/2003	IP-AC	PFIZER				
61074	RAVAUD	Philippe	06/10/2003	IP-AC	MERCK SHARP & DOHME				
61074	RAVAUD	Philippe	06/10/2003	IP-CF	SANOFI, BRISTOL MYERS SQUIBB, PFIZER, MERCK SHARP & DOHME, GRUNENTHAL				
61074	RAVAUD	Philippe	06/10/2003	IP-AC	GRUNENTHAL				
61074	RAVAUD	Philippe	06/10/2003	VB	SCHERING				
60335	RENACCO	Elisabeth	28/11/2010	RE-DE	EG LABO EUROGENERIC	Variation de type II: mise à jour de la documentation chimique et pharmaceutique pour 3 spécialités:Thiocolc	Rémunération personnelle	11/2010	
60335	RENACCO	Elisabeth	24/09/2009	PAR	SERVIER	Cadre supérieur à l'international	enfant	08/2005	
60335	RENACCO	Elisabeth	30/09/2008	PAR	SERVIER	Cadre supérieur à l'international	enfant	08/2005	
60335	RENACCO	Elisabeth	16/05/2006	RE-DE	MERCK GENERIQUES	EDMF : PAMIDRONATE		12/2003	12/2003
60335	RENACCO	Elisabeth	16/05/2006	RE-DE	MERCK GENERIQUES	EDMF : DIACEREINE		03/2004	03/2004
60335	RENACCO	Elisabeth	16/05/2006	RE-DE	MERCK SANTE	QOS : DIACEREINE capsules		07/2003	07/2003
60335	RENACCO	Elisabeth	16/05/2006	RE-DE	MERCK SANTE	QOS : PIPERACILLINE 10 gr, 20 gr, 4 gr		11/2003	11/2003
60335	RENACCO	Elisabeth	16/05/2006	RE-DE	MERCK SANTE	GONNON - Propofol 1%, 2%		07/2003	07/2004
60335	RENACCO	Elisabeth	16/05/2006	RE-DE		Variations type II : TOSRAMYCINE		05/2004	05/2004
60335	RENACCO	Elisabeth	16/05/2006	RE-DE		Variations type II : SIMVASTATINE		07/2004	07/2004
60335	RENACCO	Elisabeth	16/05/2006	RE-DE		Variations type II : FORIDETIC		12/2004	12/2004
60335	RENACCO	Elisabeth	16/05/2006	RE-DE		Variations type II : SERTRALINE GONNON		05/2005	05/2005
60335	RENACCO	Elisabeth	16/05/2006	PAR	SERVIER INTERNATIONAL	Adjoint du directeur de zone en europe orientale	enfant	08/2005	
60335	RENACCO	Elisabeth	15/02/2005	PAR	BOEHRINGER INGELHEIM	Fils, chef de projet			
60335	RENACCO	Elisabeth	22/08/2000	Néant					
10357	REYNIER	Jean-Pierre	21/09/2010	CF-INT	STRAGEN	ARBIDOL - Paris	Aucune rémunération		
10357	REYNIER	Jean-Pierre	21/09/2010	VB		Taxes d'apprentissage < 15% d'une même source			
10357	REYNIER	Jean-Pierre	21/09/2010	PAR	THERAMEX (MONACO)	Chef de gamme médicament	Enfant	01/2003	
10357	REYNIER	Jean-Pierre	08/10/2008	CF-INT	STRAGEN	Paris - ARBIDOL	aucune rémunération		
10357	REYNIER	Jean-Pierre	08/10/2008	VB		Taxes d'apprentissage < 15% d'une même source			
10357	REYNIER	Jean-Pierre	08/10/2008	PAR	THERAMEX (MONACO)	Chef de gamme médicament	enfant	01/2003	
10357	REYNIER	Jean-Pierre	29/08/2007	CF-INT	STRAGEN	Arbidol - Paris	aucune rémunération		
10357	REYNIER	Jean-Pierre	29/08/2007	VB		Taxe d'apprentissage < 15 % d'une même source			
10357	REYNIER	Jean-Pierre	29/08/2007	PAR	THERAMEX	Chef de gamme médicament - Monaco	Enfant	01/2003	
10357	REYNIER	Jean-Pierre	06/09/2006	CF-INT	STRAGEN	Paris - ARBIDOL	aucune rémunération		
10357	REYNIER	Jean-Pierre	06/09/2006	PAR	THERAMEX (MONACO)	Chef de gamme médicament	Enfant	01/2003	
10357	REYNIER	Jean-Pierre	06/09/2006	VB		Taxes d'apprentissage < 15 % d'une même source			
10357	REYNIER	Jean-Pierre	06/09/2006	CF-AUD	AMGEN, ASTRA ZENECA, BAXTER, BAYER, BEAUFOUR, BOEHRINGER, BMS, EISAI, ELILILLY, ETHYPHARM, FRESENIUS FUJISAWA, GILEAD, GSK, JANSSEN CILAG, LFB, LEO, LUNDBECK, MERCK, MSD, NOVARTIS, NOVONORDISK, OCTAPHARMA, PFIZER, PIERRE FABRE, ROCHE, SANOFI-AVENTIS, SCHE	Invité en qualité d'auditeur (prise en charge des frais de déplacement et d'hébergement, financement de la formation médicale continue)			
10357	REYNIER	Jean-Pierre	23/03/2006	CF-AUD	AMGEN - ASTRA ZENECA - BAXTER - BAYER - BEAUFOUR - BOEHRINGER - BMS - EISAI - ELILILLY - ETHYPHARM - FRESENIUS - FUJISAWA - GILEAD - GSK - JANSSEN CILAG - LFB - LEO - LUNDBECK - MERCK - MSD - NOVARTIS - NOVONORDISK - OCTAPHARMA - PFIZER - PIERRE FABRE -	Prise en charge des frais de déplacement et d'hébergement, financement de la formation médicale continue			
10357	REYNIER	Jean-Pierre	23/03/2006	PAR	THERAMEX	Chef de Produit Expert	Fille		
10357	REYNIER	Jean-Pierre	21/02/2005	PAR	THERAMEX	Fille, Chef de Produit Expert			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10357	REYNIER	Jean-Pierre	21/02/2005	IP-CF	IPSEN PHARMA - BOEHRINGER - BMS - EISAI - ELI LILLY - FRESENIUS - FUJISAWA				
10357	REYNIER	Jean-Pierre	21/02/2005	IP-CF	GILEAD - GSK - JANSSEN CILAG - LFB - LEO - LUNDBECK - MERCK - MSD				
10357	REYNIER	Jean-Pierre	21/02/2005	IP-CF	NOVARTIS - NOVONORDISK - OCTAPHARMA - PFIZER - PIERRE FABRE - ROCHE				
10357	REYNIER	Jean-Pierre	21/02/2005	IP-CF	SANOFI - SCHERING PLOUGH - SERVIER - SOLVAY - 3 M SANTE - WYETH LEDERLE				
10357	REYNIER	Jean-Pierre	07/02/2005	PAR	THERAMEX (Monaco)	Enfant			
10357	REYNIER	Jean-Pierre	11/05/2004	IP-CF	API	Conférence sur les Génériques			
10357	REYNIER	Jean-Pierre	11/05/2004	(Autre)	THERAMEX (MONACO)	Enfant			
10357	REYNIER	Jean-Pierre	16/04/2003	PAR	THERAMEX (Monaco)	Enfant			
10357	REYNIER	Jean-Pierre	30/01/2002	PAR	THERAMEX	Fille			
10357	REYNIER	Jean-Pierre	11/09/2000	(Autre)	THERAMEX	Enfant stagiaire (thèse)			
10357	REYNIER	Jean-Pierre	02/05/2000	PAR	THERAMEX (Monaco)	Fille stagiaire du 01/2000 au 30/06/2000 (sixième année de Pharmacie)			
10357	REYNIER	Jean-Pierre	25/10/1999	(Autre)	PFIZER	Enfant			
10357	REYNIER	Jean-Pierre	01/01/1999	VB	ANADERM (New York - USA) Produits Cosmétiques	Conseils, Versements à l'Université de la Méditerranée			
10357	REYNIER	Jean-Pierre	01/01/1999	PAR	PFIZER	Fils médecin en pharmacovigilance depuis fin novembre 1997			
10357	REYNIER	Jean-Pierre	01/01/1998	IP-AUT	Nestle				
10357	REYNIER	Jean-Pierre	01/01/1998	VB	ANADERM				
64631	RIBRAG	Vincent	26/03/2010	EC-INV	MPI	Préclinique Bortezomib	investigateur principal	01/2004	12/2006
64631	RIBRAG	Vincent	26/03/2010	EC-INV	CELGENE	Préclinique	investigateur principal	01/2008	12/2009
64631	RIBRAG	Vincent	26/03/2010	EC-INV	LFB	Préclinique	investigateur principal	01/2009	12/2009
64631	RIBRAG	Vincent	26/03/2010	EC-INV	SERVIER	Préclinique	investigateur principal	01/2009	12/2009
64631	RIBRAG	Vincent	26/03/2010	IP-AC	JOHNSON & JOHNSON	DSMC (en cours)	rémunération personnelle	01/2009	
64631	RIBRAG	Vincent	26/03/2010	IP-AC	PFIZER	Board	rémunération personnelle	01/2009	12/2009
64631	RIBRAG	Vincent	26/03/2010	IP-AC	NOVARTIS	Board	rémunération personnelle	01/2010	12/2010
64631	RIBRAG	Vincent	26/03/2010	IP-AC	CELGENE	DSMC	rémunération personnelle	01/2009	
64631	RIBRAG	Vincent	26/03/2010	IP-AC	LFB	Board	rémunération personnelle	01/2009	12/2009
64631	RIBRAG	Vincent	26/03/2010	IP-AC	WYETH	Board	rémunération personnelle	01/2009	12/2009
64631	RIBRAG	Vincent	26/03/2010	CF-INT	JANSSEN		rémunération personnelle		
64631	RIBRAG	Vincent	26/03/2010	CF-AUD	JANSSEN	ASH (american société of hematology)		12/2009	
64631	RIBRAG	Vincent	17/11/2007	IP-AC	NOVARTIS	Board RAD 001	Rémunération personnelle/institution	01/2007	04/2007
64631	RIBRAG	Vincent	17/11/2007	IP-AC	ASTRA ZENECA	Board inhibiteur JAK2	Rémunération personnelle/institution	01/2007	04/2007
64631	RIBRAG	Vincent	02/05/2007	LD-AR	SANOFI-AVENTIS	Groupe experts : syndrome de Lyse	Rémunération personnelle	01/2002	12/2006
64631	RIBRAG	Vincent	02/05/2007	EC-INV	MILLENIUM	Evaluation activité : VELCADE sur modèle animal lymphome du manteau	expérimentateur	06/2005	10/2006
64631	RIBRAG	Vincent	02/05/2007	RE-AUT	IGR	Evaluation CSET - en cours	Aucune rémunération	01/2002	
61197	RIBSTEIN	Jean	16/10/2006	LD-AR	NEGMA-LERADS	consultation / groupe expert	rémunération personnelle	01/2004	
61197	RIBSTEIN	Jean	16/10/2006	LD-AR	MENARINI	consultation / groupe expert	rémunération personnelle	01/2005	
61197	RIBSTEIN	Jean	16/10/2006	LD-AR	RECORDATI	consultation / groupe expert	rémunération personnelle	01/2000	12/2003
61197	RIBSTEIN	Jean	16/10/2006	EC-INV	RECORDATI- SANKYO	Lercanidipine - Olmesartan	investigateur principal	01/2005	
61197	RIBSTEIN	Jean	16/10/2006	RE-DE	RECORDATI	Lercanidipine	rémunération personnelle	01/2002	12/2004
61197	RIBSTEIN	Jean	16/10/2006	CF-INT	SANOFI AVENTIS-BMS-ASTRA ZENECA-SERVIER	Région (EPU)	rémunération personnelle / institution		
61197	RIBSTEIN	Jean	16/10/2006	CF-INT	RECORDATI	Prague / ESH	rémunération personnelle		
60694	RINGA	Virginie	17/03/2010	IP-RE	BESINS	Traitement jormonal de la ménopause	Rémunération personnelle	09/2006	12/2006
60694	RINGA	Virginie	17/03/2010	CF-AUD	BESINS	Congrès de gynécologie : Londres		11/2008	
60694	RINGA	Virginie	13/03/2010	IP-RE	BESINS	Traitement hormonal de la ménaupose	Rémunération personnelle	09/2006	12/2006
60694	RINGA	Virginie	13/03/2010	CF-AUD	BESINS	Congrès de Gynécologie : Londres 2008		11/2008	
60694	RINGA	Virginie	21/11/2008	RE-DE	BESINS INTERNATIONAL	Rapport sur risque thromboembolique et traitement hormonal de la ménopause	rémunération personnelle	07/2007	09/2007
60694	RINGA	Virginie	21/11/2008	IP-AC	BESINS INTERNATIONAL	Présentation des études épidémiologiques sur THM à des médecins	rémunération peraonnelle	01/2005	12/2007
60694	RINGA	Virginie	07/04/2006	IP-AUT	BESINS INTERNATIONAL	Présentation d'études épidémiologiques, "cours" sur les études épidémiologiques		01/2005	02/2006
60694	RINGA	Virginie	12/01/2005	IP-AUT		Paris XI, enseignement			
60694	RINGA	Virginie	12/01/2005	VB	SERVIER				
60694	RINGA	Virginie	12/01/2005	VB	ENVOL				
60694	RINGA	Virginie	12/01/2005	VB	INSERM	Unité 149			
60694	RINGA	Virginie	13/07/2000	Néant					
64181	RITZ	Patrick	26/09/2008	LD-AR	CHIESI SA	consultance		01/2001	
64181	RITZ	Patrick	26/09/2008	LD-AR	ROCHE SA	consultance		01/2008	
64181	RITZ	Patrick	26/09/2008	EC-CO	SERVIER	PERINDOPRIL	co-investigateur	01/2004	12/2008
64181	RITZ	Patrick	26/09/2008	LD-AR	ABBOTT	SIBUTRAMINE	co-investigateur	01/2004	12/2008
64181	RITZ	Patrick	26/09/2008	IP-CF	PIERRE FABRE	entretiens du CARLA 2008 (2 fois)	rémunération personnelle	01/2008	12/2008
64181	RITZ	Patrick	26/09/2008	CF-AUD	SERVIER	EASD Rome 2008		09/2008	09/2008
64181	RITZ	Patrick	29/08/2007	EC-CO	ABBOTT	Sibutramine	Co-investigateur	01/2003	
64181	RITZ	Patrick	29/08/2007	RE-DE	CHIESI SA	Analyse de résultats étude Escarre / nutrition	rémunération personnelle	01/2005	12/2006
64181	RITZ	Patrick	29/08/2007	CF-INT	MERCK	Plusieurs congrès / diabétologie (avant 2000)	aucune rémunération		
64181	RITZ	Patrick	29/08/2007	CF-INT	ROCHE	Plusieurs congrès / nutrition	aucune rémunération		
64181	RITZ	Patrick	29/08/2007	CF-INT	LILLY	Plusieurs congrès / diabétologie	aucune rémunération		
64181	RITZ	Patrick	29/08/2007	CF-INT	NOVO	Plusieurs congrès / diabétologie	aucune rémunération		
64181	RITZ	Patrick	29/08/2007	IP-AUT	ASTRA ZENECA	EPU sur dyslipidémies		01/2005	12/2005
64181	RITZ	Patrick	29/08/2007	IP-AUT	GSK, TAKEDA	EPU sur diabète		01/2005	12/2007
64181	RITZ	Patrick	18/04/2006	LD-AR	CHIESI SA	Board développement Cetoman	rémunération personnelle	01/2006	
64181	RITZ	Patrick	18/04/2006	EC-INV	NOVO NORDISK	Insulines	investigateur principal	01/2000	
64181	RITZ	Patrick	18/04/2006	EC-INV	ROCHE	Xenical (Orlistat)	investigateur principal	01/2000	
64181	RITZ	Patrick	18/04/2006	EC-INV	TAKEDA	Pioglitazone	investigateur principal	01/2000	
64181	RITZ	Patrick	18/04/2006	EC-CO	SANOFI	Rimonabant	investigateur principal	01/2000	
64181	RITZ	Patrick	18/04/2006	CF-INT	MERCK	formations multiples avec ou sans relation avec Metformine	rémunération personnelle	01/2000	
64181	RITZ	Patrick	18/04/2006	CF-AUD	ROCHE	prise en charge obésité - sans relation avec médicament (Xénical)		01/2000	
63995	ROBERT-GNANSIA	Elisabeth	14/06/2006	RE-AUT	GALDERMA	Evaluation des données 'grossesse " sur " Différine"	rémunération versée à une institution		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63995	ROBERT-GNANSIA	Elisabeth	14/06/2006	RE-AUT	WYETH	évaluation des données grossesse sur "Enbrel"	rémunération versée à une institution		
63995	ROBERT-GNANSIA	Elisabeth	14/06/2006	IP-AC	SERVIER	Dossier de passage en OTC pour "Pneumorel"	rémunération institution		
63995	ROBERT-GNANSIA	Elisabeth	14/06/2006	CF-AUD	SERVIER	Teratology Society - Tucson (Az)□□Invitation en échange de l'écriture d'un rapport détaillé sur le congrès		06/2006	06/2006
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	IP-RE	SERVIER	Fenspiride	Rémunération versée à l'institution	06/2003	06/2003
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	IP-AC	WYETH	Etanercept/sirolimus	Rémunération versée à l'institution	07/2004	07/2004
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	RE-AUT	GALDERMA	Différine	Rémunération versée à l'institution	01/2005	01/2005
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	CF-AUD	SERVIER	Société Américaine de Tératologie Philadelphie		06/2003	06/2003
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	CF-AUD	SERVIER	Société Américaine de Tératologie Vancouver		06/2004	06/2004
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	VB	AVENTIS	Contrat de surveillance des Médicaments	IEG	01/1999	12/1999
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	VB	SANOFI PASTEUR	Contrat de surveillance des Médicaments	IEG	01/1995	12/1995
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	VB	GALDERMA	Contrat de surveillance des Médicaments	IEG	01/1995	12/1995
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	VB	LILLY	Contrat de surveillance des Médicaments	IEG	01/1994	12/1994
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	VB	SERVIER	Contrat de surveillance des Médicaments	IEG	01/1992	12/1992
63995	ROBERT-GNANSIA	Elisabeth	14/11/2005	VB	WYETH	Contrat de surveillance des Médicaments	IEG	01/1993	12/1993
63179	ROBINET-COMBES	Anne	22/12/2003	IP-EC	SERVIER - IRIS				
60438	ROQUES	Bernard	25/06/1999	IP-CF		1 à 2 fois par an dans des colloques organisés par des firmes pharmaceutiques. Divers : Depuis la toxicomanie jusqu'au inhibiteurs de peptides en passant par la biologie struct			
60438	ROQUES	Bernard	25/06/1999	VB	SYNTHELABO	Contrat : Développement nouveaux analgésiques			
60438	ROQUES	Bernard	25/06/1999	VB	SANOFI	Contrat : Propriétés substitution de l'antagoniste des récepteurs CB1			
60438	ROQUES	Bernard	25/06/1999	VB	SERVIER	Contrat : Inhibiteurs double et triple de la NEP/ACE/ECE			
10365	ROUJEAU	Jean-Claude	23/04/2008	LD-AR	PFIZER	Groupe d'expertise des effets cutanés graves	rémunération personnelle / institution	01/2000	12/2006
10365	ROUJEAU	Jean-Claude	23/04/2008	LD-AR	VERTEX (Cambridge USA) - SERVIER	Expertise d'effets secondaires graves cutanés VX 07-950-108 PROTELOS	rémunération institution	01/2008	
10365	ROUJEAU	Jean-Claude	23/04/2008	EC-CO	ETUDES UNIVERSITAIRES	DERMOCATICORDER	co-investigateur	01/2002	12/2005
10365	ROUJEAU	Jean-Claude	23/04/2008	EC-CO	ETUDES UNIVERSITAIRES	METHOTREXATE	co-investigateur		12/2008
10365	ROUJEAU	Jean-Claude	23/04/2008	EC-CO	ETUDES UNIVERSITAIRES	rituximab	co-investigateur	01/2001	12/2005
10365	ROUJEAU	Jean-Claude	23/04/2008	EC-CO	ETUDES UNIVERSITAIRES	REGRICAR (multi médicaments)	co-investigateur	01/2003	
10365	ROUJEAU	Jean-Claude	23/04/2008	RE-DE	LFB	TEGELINES dans le traitement de la dermatomyosite	rémunération institution	01/2004	12/2005
10365	ROUJEAU	Jean-Claude	23/04/2008	RE-AUT	OM PHARMA	Cas de XXX - Immocur		01/2006	12/2006
10365	ROUJEAU	Jean-Claude	23/04/2008	RE-AUT	MED XXX	XXX effets cutanés		01/2005	12/2008
10365	ROUJEAU	Jean-Claude	23/04/2008	RE-AUT	CEPHALON	Cas de SJS	rémunération institution	01/2006	12/2006
10365	ROUJEAU	Jean-Claude	23/04/2008	RE-AUT	SANOFI AVENTIS	Cas de SCAR	rémunération personnelle / institution	01/2007	12/2008
10365	ROUJEAU	Jean-Claude	23/04/2008	CF-INT	SCHERING PLOUGH	Cannes : universités Dermato et allergo - syndrome de XXX (XXX specific XXX)	rémunération personnelle	12/2007	12/2007
10365	ROUJEAU	Jean-Claude	23/04/2008	CF-INT	VERTEX	Cambridge (USA) : severe cutaneous adresse reacteurs to XXX (XXX specific XXX)	rémunération personnelle	12/2007	12/2007
10365	ROUJEAU	Jean-Claude	23/04/2008	(Autre)		Activité occasionnelle de conseil d'avocats dans des procés sur des réactions indicateurs graves (1/2 ans)			
10365	ROUJEAU	Jean-Claude	12/06/2006	LD-AR	PFIZER	Dermatology expert panel - Cox2 Inhibitors	rémunération partagée personnelle / institution	01/2002	
10365	ROUJEAU	Jean-Claude	12/06/2006	LD-AR	MEDIMMUNE	Expert Dermatology Panel - Amifostine	rémunération personnelle	01/2005	
10365	ROUJEAU	Jean-Claude	12/06/2006	EC-INV	SANOFI, AVENTIS NOVARTIS, GSK, PFIZER, PIERRE FABRE, IRIS-SERVIER	Etude épidémiologique EuroSCAR		01/1997	12/2002
10365	ROUJEAU	Jean-Claude	12/06/2006	EC-INV	NOVARTIS	étude cas-témoins des dermatophyties dans l'Erysipèle		01/2001	12/2003
10365	ROUJEAU	Jean-Claude	12/06/2006	EC-CO	SANOFI AVENTIS, NOVARTIS, GSK, PFIZER, PIERRE FABRE, IRIS-SERVIER, BOEHRINGER INGELHEIM	Etude épidémiologique RegiSCAR		01/2003	
10365	ROUJEAU	Jean-Claude	12/06/2006	EC-CO	LFB	Tégéline et dermatomyosite		01/2003	12/2005
10365	ROUJEAU	Jean-Claude	12/06/2006	RE-AUT	OM PHARMA	Evaluation of one case of TEN attributed to Immocur	rémunération versée à une institution		
10365	ROUJEAU	Jean-Claude	12/06/2006	RE-AUT	PIERRE FABRE	Expertises de fiches CIOMS milnacipran	rémunération versée à une institution		
10365	ROUJEAU	Jean-Claude	12/06/2006	RE-AUT	BOEHRINGER	Adverse reactions observed in phase I	rémunération versée à une institution		
10365	ROUJEAU	Jean-Claude	12/06/2006	IP-AC	SERONO	Evaluation of a cutaneous reaction in a phase I	rémunération versée à une institution	01/2006	01/2006
10365	ROUJEAU	Jean-Claude	12/06/2006	CF-INT	NOVARTIS	Journées dermatologiques de Paris , prélèvements mycologiques - Lamisil	rémunération versée à une institution	12/2005	12/2005
10365	ROUJEAU	Jean-Claude	12/06/2006	CF-INT	GSK	Severe cutaneous drug reactions - symposium on management of ADR to ARV - Paris - Abacavir	rémunération versée à une institution	05/2006	05/2006
10365	ROUJEAU	Jean-Claude	09/03/2004	IP-EC	AVENTIS ; BAYER ; BOEHRINGER-INGELHEIM ; GLAXO SMITHKLINE ; NOVARTIS ; PFIZER ; SERVIER	Etude REGISCAR cofinancée par ces sociétés (versement au budget d'une institution)			
10365	ROUJEAU	Jean-Claude	09/03/2004	IP-EC	LFB	IgIV et Dermatory advise - (versement au budget d'une institution)			
10365	ROUJEAU	Jean-Claude	09/03/2004	IP-RE	PHARMACIA (PFIZER)	Réactions cutanées graves des COX-2			
10365	ROUJEAU	Jean-Claude	09/03/2004	IP-RE	ALIZYRNE UK ; PIERRE FABRE ; AVENTIS	Expertises ponctuelles de dossiers de réactions cutanées graves			
10365	ROUJEAU	Jean-Claude	09/03/2004	IP-CF	NOVARTIS	Symposium			
10365	ROUJEAU	Jean-Claude	09/03/2004	VB		cf étude REGISCAR			
10365	ROUJEAU	Jean-Claude	20/10/2001	IP-EC	NOVARTIS				
10365	ROUJEAU	Jean-Claude	20/10/2001	IP-RE	PHARMACIA	Effets secondaires du Celebrex			
10365	ROUJEAU	Jean-Claude	20/10/2001	IP-AC	LFB	Evaluation des IGIV			
10365	ROUJEAU	Jean-Claude	20/10/2001	IP-CF	DIA	1/an colloque de formation (non rémunéré)			
10365	ROUJEAU	Jean-Claude	20/10/2001	VB	Contrat INSERM Industrie avec initialement 13 compagnies	Etude Euroscar (épidémiologie des accidents graves des médicaments)			
10365	ROUJEAU	Jean-Claude	20/10/2001	VB	BOEHRINGER + INSERM	Physiopathologie des accidents à la naissance			
10365	ROUJEAU	Jean-Claude	08/04/2000	IP-EC	Divers industriels	Environ de 1 à 3 en 2000, Sujet : expertise de cas de réaction cutanée grave			
10365	ROUJEAU	Jean-Claude	08/04/2000	IP-CF	SYNTHELABO	Colloque de Pharmacovigilance			
10365	ROUJEAU	Jean-Claude	08/04/2000	VB	GLAXO WELLCOME, AVENTIS, NOVARTIS, SERVIER, PFIZER, BAYER, LILLY, LEO, PARKE DAVIS	Subvention par contrat (projet épidémiologique) : Inserm			
10365	ROUJEAU	Jean-Claude	01/01/1999	IP-RE	GLAXO WELLCOME	Lamotrigine			
10365	ROUJEAU	Jean-Claude	01/01/1999	IP-RE	RHONE POULENC RORER				
10365	ROUJEAU	Jean-Claude	01/01/1999	IP-RE	NOVARTIS-SANDOZ				
10365	ROUJEAU	Jean-Claude	01/01/1999	IP-CF	SYNTHELABO				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10365	ROUJEAU	Jean-Claude	01/01/1999	IP-AUT	BOEHRINGER INGELHEIM	Plaquette d'information sur les réactions cutanées aux médicaments			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	SERVIER-ADIM	Financement d'une étude épidémiologique Euroscar par contrat Inserm-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	BAYER	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	LILLY	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	JOUVEINAL	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	RPR	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	LEO	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	SANOFI	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	GLAXO	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	CASSENNE	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	ROUSSEL	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	HOECHST	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	NOVARTIS	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1999	VB	PFIZER	INSERM-Industrie			
10365	ROUJEAU	Jean-Claude	01/01/1998	IP-AUT	Laphal				
10365	ROUJEAU	Jean-Claude	01/01/1998	IP-AUT	Sandoz				
10365	ROUJEAU	Jean-Claude	01/01/1998	IP-AUT	RPR				
10365	ROUJEAU	Jean-Claude	01/01/1998	IP-AUT	Glaxo-Welcome				
10365	ROUJEAU	Jean-Claude	01/01/1998	IP-AUT	Synthélabo				
10365	ROUJEAU	Jean-Claude	01/01/1998	VB	Glaxo Welcome		contrats en cours INSERM		
10365	ROUJEAU	Jean-Claude	01/01/1998	VB	Sandoz		contrats en cours INSERM		
55665	ROULLET	Etienne	29/05/2007	CF-AUD	BIOGEN IDEC FRANCE	AAN, Boston, Mai 2007			
55665	ROULLET	Etienne	29/05/2007	CF-INT	SANOFI AVENTIS	JNLF Avril 2007, Paris, Symposium sur la réponse au traitement ds la SEP	Rémunération personnelle		
55665	ROULLET	Etienne	12/04/2006	EC-CO	SANOFI AVENTIS	Tériflunomide - essai thérapeutique	co-investigateur	01/2005	12/2008
55665	ROULLET	Etienne	12/04/2006	IP-AC	SANOFI AVENTIS	Groupe de réflexion PEPS	rémunération personnelle	09/2005	10/2005
55665	ROULLET	Etienne	12/04/2006	CF-INT	BIOGEN - IDEC	Paris - suivi IRM SEP	rémunération personnelle	01/2006	01/2006
55665	ROULLET	Etienne	12/04/2006	CF-AUD	SANOFI AVENTIS	AAN		01/2006	12/2006
55665	ROULLET	Etienne	12/04/2006	CF-AUD	BIOGEN IDEC	AAN		01/2005	12/2005
55665	ROULLET	Etienne	12/04/2006	CF-AUD	SERONO	AAN		01/2004	12/2004
55665	ROULLET	Etienne	10/02/2005	LD	SCHERING SA	Consultant pour le programme ACT (2001-2004)			
55665	ROULLET	Etienne	10/02/2005	IP-AC	BIOGEN	Avonex (2003)			
55665	ROULLET	Etienne	10/02/2005	IP-AC	SERONO	Rebif (2004)			
55665	ROULLET	Etienne	10/02/2005	IP-CF	BIOGEN, SCHERING, SERONO				
55665	ROULLET	Etienne	10/02/2005	IP-CF		Deux fois par an depuis 5 ans alternativement			
55665	ROULLET	Etienne	10/02/2005	IP-EC		Tous les produits dans la SEP (Sclérose en plaques)			
55665	ROULLET	Etienne	30/06/2004	IP-EC	SCHERING, TEVA, SERONO, BIOGEN...(nombreuses firmes)	Essais thérapeutiques dans le domaine de la sclérose en plaques (SEP)			
55665	ROULLET	Etienne	30/06/2004	IP-AC	SCHERING, BIOGEN, SERONO ...	Firmes pharmaceutiques impliquées dans la SEP			
55665	ROULLET	Etienne	30/06/2004	IP-CF	SCHERING, BIOGEN, SERONO	Firmes pharmaceutiques impliquées dans la SEP			
55665	ROULLET	Etienne	30/06/2004	VB	Firmes impliquées dans la SEP (BIOGEN, SERONO)	Soutien à la recherche clinique - Association NATURALIA et BIOLOGIA (structure bénéficiaire)	37 boulevard des Invalides - 75007 Paris		
55665	ROULLET	Etienne	26/08/2003	IP-EC	La plupart des firmes dans le domaine de la sclérose en plaques (ex. SCHERING, BIOGEN, TEVA, etc.)	Essais thérapeutiques phases II, III et IV.			
55665	ROULLET	Etienne	26/08/2003	IP-RE	La plupart des firmes dans le domaine de la sclérose en plaques (ex. SCHERING, BIOGEN, TEVA, etc.)	Occasionnellement			
55665	ROULLET	Etienne	26/08/2003	IP-AC	La plupart des firmes dans le domaine de la sclérose en plaques (ex. SCHERING, BIOGEN, TEVA, etc.)				
55665	ROULLET	Etienne	26/08/2003	IP-CF	La plupart des firmes dans le domaine de la sclérose en plaques (Schering, Biogen, Teva...)				
55665	ROULLET	Etienne	26/08/2003	IP-AUT	La plupart des firmes dans le domaine de la sclérose en plaques (ex. SCHERING, BIOGEN, TEVA, etc.)	Congrès subventions de recherche, aide financière pour FMC			
55665	ROULLET	Etienne	30/06/2000	IP-AC	SCHERING PLOUGH	Comité scientifique			
55665	ROULLET	Etienne	30/06/2000	VB	BIOGEN, SCHERING, TEVA, SERONO, BMS, PFIZER	Essais thérapeutiques : associations ADNEI, Claude Bernard			
55665	ROULLET	Etienne	10/05/1999	IP-EC	SCHERING, BIOGEN, SERONO, TEVA, SMITHKLINE BEECHAM, PARKE DAVIS, PFIZER	Essais cliniques dans les domaines de la sclérose en plaques, de la migraine, des accidents vasculaires cérébraux.			
55665	ROULLET	Etienne	10/05/1999	VB	SERONO	Association			
55665	ROULLET	Etienne	10/05/1999	IP-CF	SCHERING, BIOGEN	EPU			
55665	ROULLET	Etienne	01/01/1999	IP-EC	SCHERING AG	Essais dans le domaine de la neurologie : sclérose en plaque			
55665	ROULLET	Etienne	01/01/1999	IP-EC	BIOGEN	Essais dans le domaine de la neurologie : sclérose en plaque			
55665	ROULLET	Etienne	01/01/1999	IP-EC	SERONO	Essais dans le domaine de la neurologie : sclérose en plaque			
55665	ROULLET	Etienne	01/01/1999	IP-EC	TEVA	Essais dans le domaine de la neurologie : sclérose en plaque			
55665	ROULLET	Etienne	01/01/1999	IP-EC	PFIZER	Essais dans le domaine de la neurologie			
55665	ROULLET	Etienne	01/01/1999	IP-EC	AL MIRATL	Essais dans le domaine de la neurologie			
55665	ROULLET	Etienne	01/01/1999	IP-EC	BRISTOL MYERS SQUIBB	Essais dans le domaine de la neurologie			
55665	ROULLET	Etienne	01/01/1999	IP-RE	ROCHE				
55665	ROULLET	Etienne	01/01/1999	IP-AC	SERVIER				
55665	ROULLET	Etienne	01/01/1999	IP-CF	BIOGEN				
55665	ROULLET	Etienne	01/01/1999	IP-CF	SCHERING				
55665	ROULLET	Etienne	01/01/1999	IP-CF	SERONO				
55665	ROULLET	Etienne	01/01/1999	VB	SCHERING				
55665	ROULLET	Etienne	01/01/1999	VB	BIOGEN				
55665	ROULLET	Etienne	01/01/1999	VB	SERENO				
55665	ROULLET	Etienne	01/01/1999	VB	TEVA				
55665	ROULLET	Etienne	01/01/1999	VB	PFIZER				
55665	ROULLET	Etienne	01/01/1999	VB	AL MIRALT				
55665	ROULLET	Etienne	01/01/1999	VB	BRISTOL MYERS SQUIBB				
55665	ROULLET	Etienne	01/01/1999	VB	ROCHE				
55665	ROULLET	Etienne	01/01/1999	VB	SERVIER		investigateur principal	09/2009	
63932	ROUSIERE	Mickaël	01/02/2010	EC-INV	AMGEN	Denosumab	co-investigateur	03/2008	12/2009
63932	ROUSIERE	Mickaël	01/02/2010	EC-CO	ROCHE	Ibandronate	rémunération personnelle	04/2008	
63932	ROUSIERE	Mickaël	01/02/2010	RE-AUT	SERVIER	Ranelate de Stontium - réalisation de diaporama sur les traitements de l'ostéoporose	aucune rémunération		
63932	ROUSIERE	Mickaël	01/02/2010	RE-AUT	AFSSAPS	Rapport d'expertise sur le dossier de demande d'AMM du dénosumab d'AMGEN			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63932	ROUSIERE	Mickaël	01/02/2010	IP-AC	PROCTER AND GAMBLE	Groupe de réflexion sur l'ostéoporose (2 à 3 réunions / an)	aucune rémunération	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	MSD, PROCTER AND GAMBLE, ROCHE, LILLY, SERVIER, AMGEN	Fosavance, Actonel, Bonviva, Forsteo, Protelos, Prolia	Conférences, EPU et actions de formation - sujet : Ostéoporose et ses traitements - rémunération personnelle	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	GILEAD, GSK	Conférences, actions de formation - sujet : ostéoporose chez le patient VIH	rémunération personnelle	01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	CF-AUD	PROCTER AND GAMBLE, SERVIER	Fosavance, Protelos	Conférences et actions de formation - sujet : ostéoporose et ses traitements	01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	VB	AMGEN	Projet de recherche clinique sur une filière ostéoporose	AERER (Association d'Enseignement et de Recherche En Rhumatologie) - Je suis le trésorier de cette association	09/2009	09/2010
63932	ROUSIERE	Mickaël	01/02/2010	EC-INV	AMGEN	DENOSUMAB (en cours)	investigateur principal	09/2009	
63932	ROUSIERE	Mickaël	01/02/2010	EC-CO	ROCHE	IBANDRONATE	co-investigateur	03/2008	12/2009
63932	ROUSIERE	Mickaël	01/02/2010	RE-AUT	SERVIER	RANELATE DE STRONTIUM. Réalisation de diaporama sur les traitements de l'ostéoporose (en cours)	rémunération personnelle	04/2008	
63932	ROUSIERE	Mickaël	01/02/2010	RE-AUT	AFSSAPS	Rapport d'expertise sur le dossier de demande d'AMM du dénosumab d'AMGEN	aucune rémunération		
63932	ROUSIERE	Mickaël	01/02/2010	IP-AC	PROCTER ET GAMBLE	Groupe de réflexion sur l'osteoporose (2 à 3 réunions / an)	aucune rémunération	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	MSD	FOSAVANCE : conférence, EPU et actions de formation . Sujet = ostéoporose et ses traitements	rémunération personnelle	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	PROCTER ET GAMBLE	ACTONEL : conférence, EPU et actions de formation . Sujet = ostéoporose et ses traitements (en cours)	rémunération personnelle	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	ROCHE	BONVIVA : conférence, EPU et actions de formation . Sujet = ostéoporose et ses traitements (en cours)	rémunération personnelle	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	LILLY	FORSTEO : conférence, EPU et actions de formation . Sujet = ostéoporose et ses traitements (en cours)	rémunération personnelle	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	SERVIER	PROTELOS : conférence, EPU et actions de formation . Sujet = ostéoporose et ses traitements (en cours)	rémunération personnelle	01/2007	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	AMGEN	PROLIA : conférence, EPU et actions de formation . Sujet = ostéoporose et ses traitements (en cours)	rémunération personnelle	01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	GILEAD	PROLIA : conférence actions de formation. Sujet = osteoporose chez le patient VIH	rémunération personnelle	01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	CF-INT	GDK	PROLIA : conférence actions de formation. Sujet = ostéoporose chez le patient VIH (en cours)	rémunération personnelle	01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	CF-AUD	PROTEC ET GAMBLE	PROLIA : conférence actions de formation. Sujet = ostéoporose chez le patient VIH (en cours)		01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	CF-AUD	SERVIER	PROTELOS : conférence actions de formation. Sujet = ostéoporose chez le patient VIH (en cours)		01/2009	
63932	ROUSIERE	Mickaël	01/02/2010	VB	AMGEN	Projet de recherche clinique sur une filière ostéoporose	AERER (association d'enseignement et de recherche en rhumatologie)	09/2009	09/2010
63932	ROUSIERE	Mickaël	28/11/2005	IP-EC	ROCHE	Ibandronate - étude BALTO II	investigateur principal	02/2005	09/2005
63932	ROUSIERE	Mickaël	28/11/2005	EC-CO	Société Française de Rhumatologie (SFR)	Suivi de polyarthrite COHORTE ESPOIR (pas de produit) étude en cours	co-investigateur	11/2003	
63932	ROUSIERE	Mickaël	28/11/2005	EC-CO	SFR	Etude GUEPARD Adalimumab (HUMIRA) étude en cours	co-investigateur	11/2004	
63932	ROUSIERE	Mickaël	28/11/2005	IP-AC	ZAMBON France	Consultant ponctuel pour ZAMBON France sur le développement de la calcitonine	aucune rémunération	02/2004	02/2004
63932	ROUSIERE	Mickaël	28/11/2005	IP-CF	MSD	Alendronate - "fracture vertébrale : la mesure du risque" Paris	rémunération personnelle	10/2005	
63932	ROUSIERE	Mickaël	28/11/2005	CF-AUD	MSD	Congrès ECTS - Genève		06/2005	
63932	ROUSIERE	Mickaël	28/11/2005	CF-AUD	SANOFI	Congrès SFR - Paris		11/2004	
10367	ROUX	Christian	10/07/2009	CF-INT	AMGEN	DENOSUMAB□□SFR 2009	Aucune rémunération		
10367	ROUX	Christian	10/07/2009	CF-INT	SERVIER	STRONTIUM□EULAR 2008	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	CF-INT	MSD	FRACTURES VERTEBRALES□□REUNION ANNUELLE	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	CF-INT	PROCTER	DUREE DES TRAITEMENTS□□ECCEO 2009	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	IP-AC	SERVIER	RANELATE DE STRONTIUM	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	IP-AC	ROCHE	OSTEOPOROSE	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	IP-AC	AMGEN	DENOSUMAB	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	IP-AC	MSD	OSTEOPOROSE	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	IP-AC	NOVARTIS	ZOLEDRONATE	Rémunération personnelle		
10367	ROUX	Christian	10/07/2009	EC-CO	MSD	ODANACATIB	Co-investigateur	01/2009	
10367	ROUX	Christian	20/04/2006	EC-CO	LILLY	TERIPARATIDE	Co-investigateur	01/2002	03/2009
10367	ROUX	Christian	20/04/2006	EC-CO	AMGEN	AMG 162	Co-investigateur	01/2004	
10367	ROUX	Christian	20/04/2006	EC-CO	PROCTER	RISEDRONATE	Co-investigateur	01/2005	12/2008
10367	ROUX	Christian	20/04/2006	EC-CO	NOVARTIS	ZOLEDRONATE	Co-investigateur	01/2005	12/2008
10367	ROUX	Christian	20/04/2006	EC-CO	SERVIER	RANELATE DE STRONTIUM	Co-investigateur	01/1999	
10367	ROUX	Christian	20/04/2006	IP-AC	NOVARTIS	Groupe de reflexion ZOLEDRONATE	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	IP-AC	MSD	Groupe de reflexion ALENDRONATE	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	IP-AC	MSD	Groupe de reflexion ANTI CATHEPSINE	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	IP-AC	AMGEN	Groupe de reflexion DENOSUMAB	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	IP-AC	ASTRA	Groupe de reflexion ANASTROZOLE	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	IP-AC	NYCOMED	Groupe de reflexion PARATHORMONE	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	IP-AC	LILLY	Groupe de reflexion TERIPARATIDE	Rémunération personnelle	01/2005	
10367	ROUX	Christian	20/04/2006	CF-INT	PROCTER, MSD, SERVIER, ASTRA	Symposia sur l'ostéoporose et ses traitements (chaque année)	Rémunération personnelle		
10367	ROUX	Christian	19/08/2003	IP-RE	LILLY	Reriparatide (Forteo®)			
10367	ROUX	Christian	19/08/2003	IP-AC	PROCTER & GAMBLE	Ostéoporose			
10367	ROUX	Christian	19/08/2003	IP-CF	NOVARTIS, SERVIER, LILLY	Ostéopathies			
10367	ROUX	Christian	19/08/2003	VB	PFIZER, LILLY, MSD	Essais thérapeutiques et épidémiologiques - Association de Recherche Clinique en Rhumatologie (Hôpital Cochin)			
10367	ROUX	Christian	15/10/2002	IP-EC	MSD	Essais thérapeutiques			
10367	ROUX	Christian	15/10/2002	IP-EC	PROCTER	Essais thérapeutiques			
10367	ROUX	Christian	15/10/2002	IP-EC	PHARMACIA	Essais thérapeutiques			
10367	ROUX	Christian	15/10/2002	IP-CF	MSD, PROCTER, ORGANON	EPU, Symposiums			
10367	ROUX	Christian	02/03/2000	IP-RE	PROCTER & GAMBLE	Rapport etidronate ostéoporose cortisonique (1998)			
10367	ROUX	Christian	02/03/2000	IP-AC	ROCHE	Ostéoporose cortisonique			
10367	ROUX	Christian	02/03/2000	IP-AC	PROCTER & GAMBLE	Risedronate et ostéoporose			
10367	ROUX	Christian	02/03/2000	IP-AC	LILLY	Raloxifène et ménopause			
10367	ROUX	Christian	02/03/2000	IP-CF	LILLY	Raloxifène et ostéoporose (février 2000)			
10367	ROUX	Christian	02/03/2000	IP-CF	PROCTER & GAMBLE	Risedronate et ostéoporose (1999 et 2000)			
10367	ROUX	Christian	02/03/2000	VB	GLAXO WELLCOME, TAKADA, MSD, PROCTER & GAMBLE, ORGANON	Essais thérapeutiques : Association de Recherche			
10367	ROUX	Christian	21/06/1999	IP-EC	PROCTER & GAMBLE, MSD, ORGANON, GLAXO	Essais thérapeutiques (Association Recherche loi 1901)			
10367	ROUX	Christian	21/06/1999	IP-CF	PROCTER & GAMBLE, MSD	Nombreuses			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10367	ROUX	Christian	01/01/1999	IP-EC		Investigateur de plusieurs essais thérapeutiques. Coordinateur de procédures de contrôle de qualité de plusieurs essais cliniques.			
10367	ROUX	Christian	01/01/1999	IP-RE	PROCTER & GAMBLE	Pour l'industrie ostéoporose cortisonique			
10367	ROUX	Christian	01/01/1999	IP-RE		Pour l'Agence : nombreux rapports AMM et Transparence			
10367	ROUX	Christian	01/01/1999	IP-AC	PROCTER & GAMBLE	Ponctuellement			
10367	ROUX	Christian	01/01/1999	IP-AC	LILLY				
10367	ROUX	Christian	01/01/1999	IP-CF		Très nombreux EPU, participations à des congrès internationaux et réunions médicales.			
10367	ROUX	Christian	01/01/1999	IP-AUT		Prise en charge des frais de déplacement et d'hôtels par diverses compagnies industrielles.			
10367	ROUX	Christian	01/01/1999	VB		La totalité des honoraires des essais cliniques et thérapeutiques est versée sur une association loi 1901 (AF ARCR			
10367	ROUX	Christian	01/01/1998	IP-AUT	Sanofi				
10367	ROUX	Christian	01/01/1998	IP-AUT	Servier				
10367	ROUX	Christian	01/01/1998	IP-AUT	Procter et Gamble				
10367	ROUX	Christian	01/01/1998	IP-AUT	Lilly				
10367	ROUX	Christian	01/01/1998	VB	Sanofi		Association de recherche clinique en rhumatologie, loi 1901		
10367	ROUX	Christian	01/01/1998	VB	Procter et Gamble		Association de recherche clinique en rhumatologie, loi 1901		
10367	ROUX	Christian	01/01/1998	VB	Servier		Association de recherche clinique en rhumatologie, loi 1901		
10367	ROUX	Christian	01/01/1998	VB	Organon		Association de recherche clinique en rhumatologie, loi 1901		
10367	ROUX	Christian	01/01/1998	VB	Lilly		Association de recherche clinique en rhumatologie, loi 1901		
10367	ROUX	Christian	01/01/1998	VB	Glaxo		Association de recherche clinique en rhumatologie, loi 1901		
10367	ROUX	Christian	01/01/1998	VB	Chiesi		Association de recherche clinique en rhumatologie, loi 1901		
10368	ROYER	René-Jean	01/01/1999	LD	IRIS, Institut de Recherche International Servier				
10368	ROYER	René-Jean	01/01/1999	IP-RE	Laboratori BALDACI, Pise (Italie)				
10368	ROYER	René-Jean	01/01/1998	IF	RPR				
10368	ROYER	René-Jean	01/01/1998	LD	Guerbet				
10368	ROYER	René-Jean	01/01/1998	VB	ADIS		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Boehringer Ingelheim		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Cassenne		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Negma		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Pharmascience		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Pierre Fabre		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Promédica		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	RPR		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Roche		Université ou CHU		
10368	ROYER	René-Jean	01/01/1998	VB	Sanofi Winthrop		Université ou CHU		
64125	ROZENBAUM	Henri	26/10/2005	LD-AR	ORION	Occasionnelle, sur produits utilisés en THS	Rémunération personnelle	01/2001	12/2004
64125	ROZENBAUM	Henri	26/10/2005	LD-AR	SOLVAY	Occasionnelle, sur produits utilisés en THS	Rémunération personnelle	01/1995	
64125	ROZENBAUM	Henri	26/10/2005	LD-AR	LILLY	Occasionnelle, sur produits utilisés en THS	Rémunération personnelle	01/1998	
64125	ROZENBAUM	Henri	26/10/2005	EC-INV	SERVIER	Etude multicentrique sur Aérodiol	coordonnateur	01/2001	12/2003
64125	ROZENBAUM	Henri	26/10/2005	LD-AR	NOVO	Occasionnelle sur produits utilisés en THS	Rémunération personnelle	01/2001	12/2004
64125	ROZENBAUM	Henri	26/10/2005	LD-AR	WYETH	Occasionnelle sur produits utilisés en THS	émunération personnelle	01/1995	
60398	ROZENBERG	Sylvie	12/11/2008	CF-INT	LABORATOIRES GILEAD	HIV et os	Rémunération personnelle	01/2008	
60398	ROZENBERG	Sylvie	12/11/2008	CF-INT	LABORATOIRE GSK	HIV et os	Rémunération personnelle	01/2008	
60398	ROZENBERG	Sylvie	12/11/2008	CF-INT	LABORATOIRE SANOFI AVENTIS	Congres mexicain orthopedie/ Thiocolchicoside	Rémunération personnelle	01/2008	
60398	ROZENBERG	Sylvie	12/11/2008	IP-AC	LABORATOIRE GRUNENTHAL	conseil	Rémunération personnelle	01/2008	
60398	ROZENBERG	Sylvie	20/08/2007	LD-AR	PHARMASCIENCE	Groupe d'experts arthrose	rémunération personnelle		06/2007
60398	ROZENBERG	Sylvie	20/08/2007	EC-INV	SANOFI AVENTIS	Coltramyl	Investigateur principal	03/2007	
60398	ROZENBERG	Sylvie	20/08/2007	EC-INV	MENARINI	Essai clinique Ketum gel	investigateur principal	01/2007	
60398	ROZENBERG	Sylvie	20/08/2007	EC-CO	WYETH	Essai clinique ENBREL	Co-investigateur	01/2006	
60398	ROZENBERG	Sylvie	20/08/2007	EC-CO	ROCHE	Essai clinique MRA	co-investigateur	01/2006	
60398	ROZENBERG	Sylvie	20/08/2007	EC-CO	ROCHE	Essai clinique Rituximab	co-investigateur	01/2006	
60398	ROZENBERG	Sylvie	20/08/2007	EC-CO	ROCHE	Essai clinique Ibondronate	co-investigateur	01/2007	
60398	ROZENBERG	Sylvie	20/08/2007	EC-CO	ABBOTT	Essai clinique Humira	co-investigateur	01/2004	12/2007
60398	ROZENBERG	Sylvie	20/08/2007	EC-CO	SERVIER	Essai clinique Protelos	co-investigateur	01/2000	12/2005
60398	ROZENBERG	Sylvie	20/08/2007	IP-AC	GRUNENTHAL	Conseils antalgique et lombalgie	aucune rémunération	01/2000	12/2006
60398	ROZENBERG	Sylvie	20/08/2007	CF-INT	PFIZER	Congrès Français de Rhumatologie - Lyrica - douleur neuropathique	rémunération personnelle	01/2006	12/2006
60398	ROZENBERG	Sylvie	18/01/2006	EC-INV	PFIZER	Essai Celebrex - qualité de vie	investigateur principal	01/2002	12/2005
60398	ROZENBERG	Sylvie	18/01/2006	EC-CO	MAYOLY	Etudes cliniques Atepadène	co-investigateur	01/2004	12/2005
60398	ROZENBERG	Sylvie	18/01/2006	EC-CO	ROCHE	Etudes cliniques IRA (Insuffisance Rénale Aguë) en cours	co-investigateur	01/2005	
60398	ROZENBERG	Sylvie	18/01/2006	RE-DE	GENEVRIER	Transparence Chondrosulf	rémunération personnelle	09/2005	12/2005
60398	ROZENBERG	Sylvie	18/01/2006	IP-AC	GRUNENTHAL	Lombalgie et antalgiques (en cours)	rémunération personnelle	01/2004	
60398	ROZENBERG	Sylvie	18/01/2006	IP-CF	GRUNENTHAL	Société Française de Rhumatologie	rémunération personnelle	11/2003	
63050	ROZENBERG	Patrick	07/04/2005	Néant					
60398	ROZENBERG	Sylvie	27/03/2001	IP-EC	WYETH	Polyarthrite rhumatoïde - ENDREL			
60398	ROZENBERG	Sylvie	27/03/2001	IP-EC	SCHERING PLOUGH	Plyartrite rhumatoïde - REMICADE			
60398	ROZENBERG	Sylvie	27/03/2001	IP-AC	GRUNENTHAL				
60398	ROZENBERG	Sylvie	27/03/2001	IP-AC	MAYOLY				
60398	ROZENBERG	Sylvie	27/03/2001	IP-AC	UCB				
60398	ROZENBERG	Sylvie	27/03/2001	IP-AC	AVENTIS	Propofan			
60398	ROZENBERG	Sylvie	27/03/2001	IP-CF	GENEVRIER				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60398	ROZENBERG	Sylvie	06/07/2000	IP-EC	MERCK	Essai clinique Vioxx Polyarthrite			
60398	ROZENBERG	Sylvie	06/07/2000	IP-RE	AVENTIS	Risadronate Ostéoporose			
60398	ROZENBERG	Sylvie	06/07/2000	IP-EC	PROCTER GAMBLE	Risadronate Gonarthrose			
60398	ROZENBERG	Sylvie	06/07/2000	IP-RE	SERVIER	Ostéoporose			
60398	ROZENBERG	Sylvie	06/07/2000	IP-CF	UCB	Aceclofenac			
60398	ROZENBERG	Sylvie	06/07/2000	IP-AC	PHARMASCIENCE	Piascledine			
60398	ROZENBERG	Sylvie	06/07/2000	IP-CF	MAYOLY	Nabumetose Colloque			
60398	ROZENBERG	Sylvie	06/07/2000	IP-CF	SEARLE PFIZER	Celecoxib			
60398	ROZENBERG	Sylvie	06/07/2000	EC-CO	ROCHE	Etudes cliniques IRA (2005-en cours)	co-investigateur	01/2005	
60398	ROZENBERG	Sylvie	06/07/2000	EC-CO	ROCHE	Etudes cliniques IRA	co-investigateur		
61085	RUMBACH	Lucien	10/03/2008	EC-INV	BIOGEN - ELAN	COPAXONE	expérimentateur principal	01/2004	
61085	RUMBACH	Lucien	10/03/2008	EC-INV	BIOGEN - ELAN	NATALIZUMAB	expérimentateur principal	01/2004	
61085	RUMBACH	Lucien	10/03/2008	EC-INV	NEUROCHEM	ALZHEMED	expérimentateur principal	01/2006	
61085	RUMBACH	Lucien	10/03/2008	EC-INV	SANOFI AVENTIS	TERIFLUNOMIDE	expérimentateur principal	01/2006	
61085	RUMBACH	Lucien	10/03/2008	RE-DE	AFSSAPS	Rapport MEMANTINE	aucune rémunération		
61085	RUMBACH	Lucien	10/03/2008	RE-DE	AFSSAPS	Rapport GALANTAMINE	aucune rémunération		
61085	RUMBACH	Lucien	10/03/2008	CF-INT	BIOGEN - SERONO - TEVA - SCHERING - SANOFI	Plusieurs séances de formation médicales continues et d'enseignement	aucune rémunération		
61085	RUMBACH	Lucien	10/03/2008	CF-AUD	Plusieurs laboratoires pharmaceutiques avec produits à visée neurologique	France - Etranger (années 2006 - 2007 - en cours)		01/2006	
61085	RUMBACH	Lucien	10/03/2008	EC-INV	TEVA	COPAXONE	expérimentateur principal	01/2004	
61085	RUMBACH	Lucien	15/05/2006	EC-INV	TEVA	Copaxone	expérimentateur principal	01/2004	
61085	RUMBACH	Lucien	15/05/2006	EC-INV	BIOGEN - ELAN	Natalizumab	expérimentateur principal	01/2004	
61085	RUMBACH	Lucien	15/05/2006	EC-INV	NEUROCHEM	Alzhemed	expérimentateur principal	01/2006	
61085	RUMBACH	Lucien	15/05/2006	RE-DE	AFSSAPS	Rapports Memantine	aucune rémunération		
61085	RUMBACH	Lucien	15/05/2006	RE-DE	AFSSAPS	rapport Galantamine	aucune rémunération		
61085	RUMBACH	Lucien	15/05/2006	IP-CF	BIOGEN, SERONO, TEVA, SCHERING, SANOFI	Plusieurs séances de formations médicales continues et d'enseignement	aucune rémunération		
61085	RUMBACH	Lucien	15/05/2006	CF-AUD	Plusieurs laboratoires avec produits à visée neurologique	France- étranger			
61085	RUMBACH	Lucien	18/08/2003	IP-EC	SERONO	Rebif (interféron B)			
61085	RUMBACH	Lucien	18/08/2003	IP-EC	BIOGEN-ELAN	Antegren			
61085	RUMBACH	Lucien	18/08/2003	IP-EC	SANOFI	Plavix - Aspirine			
61085	RUMBACH	Lucien	18/08/2003	IP-CF	Diverses firmes	E.P.U. formation de délégués			
61085	RUMBACH	Lucien	18/08/2003	IP-AUT	Divers laboratoires	Participations à des congrès, réunions diverses			
61085	RUMBACH	Lucien	22/05/2002	IP-EC		Essais cliniques			
61085	RUMBACH	Lucien	22/05/2002	IP-CF		Conférences, EPU, Formations délégués			
61085	RUMBACH	Lucien	25/02/2000	IP-EC	BIOGEN INNOVEX	Sclérose en plaques			
61085	RUMBACH	Lucien	25/02/2000	IP-RE	SERONO France	Sclérose en plaques			
61085	RUMBACH	Lucien	25/02/2000	IP-EC	TEVA	Sclérose en plaques			
61085	RUMBACH	Lucien	25/02/2000	IP-EC	SERVIER	Parkinson			
63856	SCHERRMANN	Jean-Michel	04/01/2010	LD-AR	NEORPHYS	consultant (en cours)	rémunération personnelle	05/2007	
63856	SCHERRMANN	Jean-Michel	04/01/2010	LD-AR	HOFFMANN LA ROCHE	consultant (en cours)	rémunération personnelle	12/2005	
63856	SCHERRMANN	Jean-Michel	04/01/2010	LD-AR	PIERRE FABRE	consultant (en cours)	rémunération personnelle	07/2004	
63856	SCHERRMANN	Jean-Michel	04/01/2010	EC-INV	VECT-HORUS	contrat de recherche ANR	expérimentateur pré-clinique	01/2010	01/2013
63856	SCHERRMANN	Jean-Michel	04/01/2010	VB		Contrats de recherche versés à l'unité avec les laboratoires SERVIER - FABRE - SCHERING - AIR LIQUIDE mais d'un montant individuel <		01/2007	12/2009
63856	SCHERRMANN	Jean-Michel	11/05/2006	Néant					
10376	SECHTER	Daniel	01/01/1999	IP-EC	PIERRE FABRE				
10376	SECHTER	Daniel	01/01/1999	IP-EC	SANOFI				
10376	SECHTER	Daniel	01/01/1999	IP-EC	SYNTHELABO				
10376	SECHTER	Daniel	01/01/1999	IP-EC	WYETH-LEDERLE				
10376	SECHTER	Daniel	01/01/1999	IP-AC	PIERRE FABRE				
10376	SECHTER	Daniel	01/01/1999	IP-AC	PFIZER				
10376	SECHTER	Daniel	01/01/1999	IP-CF	JANSSEN				
10376	SECHTER	Daniel	01/01/1999	IP-CF	LILLY				
10376	SECHTER	Daniel	01/01/1999	IP-CF	LUNDBECK				
10376	SECHTER	Daniel	01/01/1999	IP-CF	SMITHKLINE BEECHAM				
10376	SECHTER	Daniel	01/01/1999	VB	ORGANON	Association universitaire Franc-comtoise pour la recherche en phychiatrie			
10376	SECHTER	Daniel	01/01/1999	VB	PIERRE FABRE	Association universitaire Franc-comtoise pour la recherche en phychiatrie			
10376	SECHTER	Daniel	01/01/1999	VB	SERVIER	Association universitaire Franc-comtoise pour la recherche en phychiatrie			
10376	SECHTER	Daniel	01/01/1999	VB	SYNTHELABO	Association universitaire Franc-comtoise pour la recherche en phychiatrie			
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Pfizer				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Sanofi				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Smithkline Beecham				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Synthélabo				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Wyeth Lederlé				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Pierre Fabre				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Janssen Cilag				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Lilly France				
10376	SECHTER	Daniel	01/01/1998	IP-AUT	Lundbeck				
10376	SECHTER	Daniel	01/01/1998	VB	Jouveinal		pour l'association universitaire Franc-Contoise pour la recherche en psychiatrie		
10376	SECHTER	Daniel	01/01/1998	VB	organon		pour l'association universitaire Franc-Contoise pour la recherche en psychiatrie		
10376	SECHTER	Daniel	01/01/1998	VB	Servier		pour l'association universitaire Franc-Contoise pour la recherche en psychiatrie		
61450	SENARD	Jean-Michel	12/07/2006	VB	ASTRA-ZENECA	Subvention recherche	Ademip	01/2003	12/2006
61450	SENARD	Jean-Michel	12/07/2006	CF-INT	LILLY	Congres francophone sur la maladie de Parkinson, Bruxelles. Pas de produits cités	Rémunération institution	01/2005	
61450	SENARD	Jean-Michel	12/07/2006	VB	SERVIER	Contrat CIFRE	Inserm	01/2003	12/2006
61450	SENARD	Jean-Michel	12/07/2006	IP-AC	BOEHRINGER	consulting développement clinique produits X	Rémunération institution	01/2005	
61450	SENARD	Jean-Michel	12/07/2006	IP-AC	PIERRE FABRE	consulting Ikaran LP	Rémunération institution	01/2006	
61450	SENARD	Jean-Michel	12/07/2006	RE-AUT	NYCOMED	Commisssion de transparence, Gutron°	Rémunération institution	01/2005	12/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61450	SENARD	Jean-Michel	12/07/2006	EC-INV	EREMPHARMA	Ampecycal®, essai de phase II	Investigateur principal	01/2004	07/2005
61450	SENARD	Jean-Michel	12/07/2006	EC-INV	PIERRE FABRE	phase I F 15845	Expert indépendant	01/2006	
61450	SENARD	Jean-Michel	12/07/2006	EC-INV	EREMPHARMA	Ampecycal®: efficacité dans le traitement de l'hypotension orthostatique au cours de la maladie de Parkinson	Investigateur principal	01/2004	12/2005
61450	SENARD	Jean-Michel	12/07/2006	IF	VIRBAC	Actions	<5000 € ou <5% du capital		
61450	SENARD	Jean-Michel	12/07/2006	IF	SANOFI-AVENTIS	Actions	<5000 € ou <5% du capital		
63077	SETA	Nathalie	17/03/2006	PAR	SERVIER	Conjoint		10/1984	
63077	SETA	Nathalie	21/02/2005	PAR	SERVIER	Conjoint		10/1984	
63077	SETA	Nathalie	08/04/2004	(Autre)	SERVIER	Conjoint			
60247	SIE	Pierre	21/04/2010	IP-AC	BAYER SANTE	Board National XARELTO	Rémunération personnelle	01/2007	
60247	SIE	Pierre	21/04/2010	EC-CO	CSL BEHRING	FEIBA	Experimentateur non principal	04/2009	
60247	SIE	Pierre	21/04/2010	IP-AC	LFB	Conseil scientifque PASS Cloiafact	Rémunération personnelle	07/2009	
60247	SIE	Pierre	21/04/2010	EC-CO	LFB	PMS BETAFACT, HEMOLEVEN	Experimentateur non principal	04/2009	
60247	SIE	Pierre	21/04/2010	EC-CO	SANOFI-AVENTIS	essai clinique AVE 5026	Laboratoire central Biologie des TIH	04/2009	
60247	SIE	Pierre	21/04/2010	EC-CO	MITSUBICHI	essai clinique ARGATROBAN	EXPERIMENTATEUR NON PRINCIPAL	08/2009	
60247	SIE	Pierre	30/03/2009	RE-DE	LFB	Avis sur dossier de transparence COFACT	rémunération personnelle	01/2008	12/2008
60247	SIE	Pierre	30/03/2009	RE-DE	BAYER	Avis sur dossier de transparence Xarelto	rémunération personnelle	01/2008	12/2008
60247	SIE	Pierre	30/03/2009	IP-AC	BAYER	Board national Xarello	rémunération personnelle		
60247	SIE	Pierre	30/03/2009	CF-INT	LFB, OCTAPHARMA, NOVONORDISK, SANOFI AVENTIS, GSK	Symposium divers : Novoseven, Cofact, Lovenox, Octaplex, etc	rémunération personnelle	09/2009	
60247	SIE	Pierre	21/11/2007	VB	SANOFI	essai antithrombotique pré-clinique	Groupe Etudes sur l'Hemostase	01/2007	12/2007
60247	SIE	Pierre	21/11/2007	CF-INT	OCTAPHARMA	Octaplex	Rémunération personnelle	01/2007	12/2007
60247	SIE	Pierre	21/11/2007	IP-AUT	EVOLVA (SUISSE)	anti-thrombotique pré-clinique	rémunération personnelle	01/2007	12/2007
60247	SIE	Pierre	21/11/2007	IP-AC	BAYER	RIVAROXABAN (ponctuel)	Rémunération personnelle	06/2007	07/2008
60247	SIE	Pierre	27/07/2006	IP-AC	MITSUBISHI	conseil ARGATROBAN	Rémunération personnelle	05/2006	12/2006
60247	SIE	Pierre	27/07/2006	IP-AC	GSK	conseil ARIXTRA	Rémunération personnelle	05/2006	12/2006
60247	SIE	Pierre	01/06/2006	EC-INV	LFB	TEGELINE	investigateur coordonnateur	05/2006	05/2007
60247	SIE	Pierre	01/06/2006	EC-CO	LFB	PMS produits biologique hémophilie	expérimentateur	01/2005	12/2007
60247	SIE	Pierre	01/06/2006	IP-AC	MITSUBISHI	ARGATROBAN (ponctuel)	rémunération personnelle	01/2006	12/2006
60247	SIE	Pierre	01/06/2006	IP-AC	GSK	ARIXTRA (ponctuel)	rémunération personnelle	01/2006	12/2006
60247	SIE	Pierre	01/06/2006	CF-INT	NOVO NORDISK	Anti-hémorragique - NOVOSEVEN régulières 2-4 fois / an	aucune rémunération	01/2006	12/2006
60247	SIE	Pierre	01/06/2006	CF-INT	LFB	Anti-hémorragique - facteurs coagulants régulières 2-4 fois / an	aucune rémunération	01/2006	12/2006
60247	SIE	Pierre	01/06/2006	CF-INT	GSK	Antithrombotiques ARIXTRA régulières 2-4 fois / an	aucune rémunération	01/2006	12/2006
60247	SIE	Pierre	01/06/2006	CF-INT	SANOFI-SYNTHELABO	E.G de la Thrombose - LEVEMIR	rémunération personnelle	01/2005	01/2005
60247	SIE	Pierre	01/06/2006	CF-INT	SANOFI-SYNTHELABO	E.G de la Thrombose - LEVEMIR	rémunération personnelle	01/2007	01/2007
60247	SIE	Pierre	01/06/2006	IP-AUT	SANOFI-SYNTHELABO	groupe de réflexion Thrombose		01/2005	12/2005
60247	SIE	Pierre	01/06/2006	VB	LILLY	essai	groupe de recherche sur la Thrombose (Toulouse)		12/2006
60247	SIE	Pierre	01/06/2006	VB	SANOFI-SYNTHELABO	évaluation de nouveaux antithrombotiques	groupe de recherche sur la Thrombose	01/2005	12/2006
60247	SIE	Pierre	09/03/2006	EC-CO	LFB	PMS	expérimentateur	01/2005	12/2007
60247	SIE	Pierre	09/03/2006	CF-INT	NOVORDISK	régulièrement (2/4 fois par an)	aucune rémunération	01/2006	12/2006
60247	SIE	Pierre	09/03/2006	CF-INT	LFB	régulièrement (2/4 fois par an)	aucune rémunération	01/2006	12/2006
60247	SIE	Pierre	09/03/2006	CF-INT	GSK	régulièrement (2/4 fois par an)	aucune rémunération	01/2006	12/2006
60247	SIE	Pierre	09/03/2006	CF-INT	SANOFI SYNTHELABO	Lovenox	rémunération personnelle	01/2005	12/2008
60247	SIE	Pierre	09/03/2006	IP-AUT	SANOFI SYNTHELABO	Groupe de reflexion Thrombose		01/2005	12/2005
60247	SIE	Pierre	09/03/2006	VB	LILLY				12/2006
60247	SIE	Pierre	09/03/2006	VB	SANOFI SYNTHELABO	évaluation de nouveaux antibiotiques	groupe de recherche sur la Thrombose	01/2005	12/2006
60247	SIE	Pierre	10/12/2002	IP-AC	ASTRA-ZENECA	Hémostase			
60247	SIE	Pierre	10/12/2002	IP-CF	LFB	Hémostase			
60247	SIE	Pierre	10/12/2002	IP-CF	BAYER	Hémostase			
60247	SIE	Pierre	10/12/2002	VB	NOVO NORDISK	Association Midi Pyrénées Santé			
60247	SIE	Pierre	02/10/2000	IP-EC	SERVIER	Essais cliniques			
60247	SIE	Pierre	02/10/2000	IP-EC	GENETIC INSTITUT	Essais cliniques			
60247	SIE	Pierre	02/10/2000	IP-CF	WINTHROP SANOFI	Conseil ligne Hémobiologie			
60247	SIE	Pierre	02/10/2000	IP-AC	RPR	Cercle de réflexion thrombose			
60247	SIE	Pierre	02/10/2000	IP-CF	LFB	Conférences			
60247	SIE	Pierre	02/10/2000	IP-CF	BAYER PHARMA	Séminaires			
60247	SIE	Pierre	02/10/2000	VB	NOVO NORDISK	Centre de recherche : "Groupe de recherche sur l'hémostase " Association loi 1901			
60247	SIE	Pierre	08/07/2000	IP-EC	SERVIER	Essais cliniques			
60247	SIE	Pierre	08/07/2000	IP-EC	GENETIC INSTITUT	Essais cliniques			
60247	SIE	Pierre	08/07/2000	IP-AC	WINTHROP SANOFI	Conseil Ligne Hémobiologie			
60247	SIE	Pierre	08/07/2000	IP-AC	RPR	Cercle de Réflexion Thrombose			
60247	SIE	Pierre	08/07/2000	IP-CF	LFB	Conférences			
60247	SIE	Pierre	08/07/2000	IP-AUT	BAYER PHARMA	Séminaires... Hémostase, Produit sanguins, MDS			
60247	SIE	Pierre	08/07/2000	VB	NOVO NORDISK	Centre de recherche - association loi 1901 - Groupe de recherche sur l'hémostase			
60247	SIE	Pierre	17/01/2000	IP-AC	RPR (AVENTIS)	Cercle de réflexion Thrombose			
60247	SIE	Pierre	17/01/2000	IP-CF	LFB	Conférence symposium SRLF (réanimateur d'hémostase) 19/01/00			
60247	SIE	Pierre	17/01/2000	IP-CF	LFB	Symposium Produits sanguins - juin 1999			
60247	SIE	Pierre	17/01/2000	VB	Centre de recherche de SANOFI	Conseil scientifique Ligne Hémiobiologie / Association			
61278	SIMON	Dominique	26/06/2003	IP-RE	ANAES	Dépistage du diabète			
61278	SIMON	Dominique	26/06/2003	IP-AC	Société de communication new yorkaise	Interprétation d'essais du GLP1			
61278	SIMON	Dominique	26/06/2003	IP-AC	Recherche en Médecine générale (MG France)	Etudes épidémies en Médecine générale			
61278	SIMON	Dominique	26/06/2003	IP-CF	MSD	Néphropathie diabétique			
61278	SIMON	Dominique	26/06/2003	IP-CF	BMS	tout de l'HTA chez le DT2			
61278	SIMON	Dominique	26/06/2003	IP-CF	GLAXO SMITHKLINE	Prévention du DT2			
61278	SIMON	Dominique	26/06/2003	IP-CF	SERVIER	Prise en charge du DT2 en France			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61278	SIMON	Dominique	26/06/2003	VB	LILLI France, NOVO NORDISK, AVENTIS, JOHNSON & JOHNSON, MERCK LIPHA, SERVIER, BERTON DICKINSON, MSD, MINIMED MEDTRONIC, BMS, IPSEN BIOTECH, GLAXO SMITHKLINE? MENARINI	Association Claude Bernard qui gère les fonds pour l'organisation de la réunion de l'International Diabeter Epidemiology Group dont je suis en charge et qui se tiendra à Tours en			
61278	SIMON	Dominique	26/06/2003	PAR	SERVIER	Cousine germaine de mon épouse			
61278	SIMON	Dominique	11/10/2002	IP-EC	BESSINS-INVESCO	En 1995 : Androgènes			
61278	SIMON	Dominique	11/10/2002	IP-RE	ASTRA ZENECA	Atenolol vs captopril dans l'UKPDS (1998)			
61278	SIMON	Dominique	11/10/2002	IP-AC	BAYER PHARMA	Risque cardio-cardiovasculaire et diabète (1996 à 2000)			
61278	SIMON	Dominique	11/10/2002	IP-AC	SANOFI	Utilisation des alpha glucosidoses dans le diabète (1997 à 1999)			
61278	SIMON	Dominique	11/10/2002	IP-CF	BMS	HTA, diabète de type 2 de néphropathie (2001-2002)			
61278	SIMON	Dominique	11/10/2002	IP-CF	MSD	HTA, diabète de type 2 et risque vasculaire (2002)			
61278	SIMON	Dominique	11/10/2002	IP-CF	SERVIER	Epidémiologie du diabète - Congrès MGSD (1996, 1998, 2000 et 2002)			
61278	SIMON	Dominique	11/10/2002	VB	NOVO NORDISK	Association Claude Bernard			
61278	SIMON	Dominique	11/10/2002	VB	BESSINS-INVESCO	Association Claude Bernard (1995)			
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai phase I de la thioxanthone, cytotoxique du sillon mineur de l'ADN, ARD5530	investigateur principal	01/2003	12/2005
63615	SORIA	Jean-Charles	07/10/2008	LD-AR	METAGENES	en cours	rémunération personnelle		
63615	SORIA	Jean-Charles	07/10/2008	LD-AR	ABBOTT	en cours	rémunération personnelle		
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de chimioprévention sur les lésions précancéreuses des VADS traitées par l'inhibiteur oral de HER1 (	investigateur principal	01/2003	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I associant le cisplatine avec l'anti-vasculaire AVE8062 en association avec le cisplatine, A	investigateur principal	01/2005	12/2008
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSITUT GUSTAVE ROUSSY	l'essai de phase I avec l'inhibiteur oral du cycle cellulaire, CYC202, essai CYC202-C-01-03	co-investigateur	01/2003	12/2004
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I/II associant le temozolomide avec l'inhibiteur oral de HER1 (gefitibi)	co-investigateur	01/2003	12/2004
63615	SORIA	Jean-Charles	07/10/2008	IP-AC	METAGENES	en cours	rémunération personnelle		
63615	SORIA	Jean-Charles	07/10/2008	IP-AC	ABBOTT	en cours	rémunération personnelle		
63615	SORIA	Jean-Charles	07/10/2008	CF-INT	GSK - PFIZER - MERCK SERONO - ROCHE - SANOFI	multiples interventions dont le détail est oublié pour plusieurs laboratoires :□□SA, LILLY, PFIZER, GSK, RIC	rémunération personnelle	01/2004	12/2008
63615	SORIA	Jean-Charles	07/10/2008	LD-AR	AVENTIS - WYETH	en cours	rémunération personnelle		
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'étude de phase II testant l'inhibiteur du protéasome (bortézomib), essai PEAK étude multicentrique ouverte	investigateur principal	01/2005	12/2007
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'étude de phase II avec l'inhibiteur oral pan-HER (HER1, HER2 et HER4) HKI-272, étude HKI 3144A1-200W	investigateur principal	01/2005	12/2008
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'étude de phase II testant en 2ème ligne du cancer bronchique non à petites cellules l'anti-angiogénique ora	investigateur principal	01/2005	12/2008
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole MO17426 essai randomisé de phase III comparant l'effet préopératoire de	investigateur principal	01/2006	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	essai de phase I, protocole A6181060 étude de phase I sur le SU-011248 associé à l'irinotecan chez des pa	investigateur principal	01/2006	12/2007
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec l'inhibiteur du cycle cellulaire PHA-793887, protocole CDKC-887-001 une étude de pi	investigateur principal	01/2006	12/2007
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'anti-vasculaire AVE8062 en monothérapie, TED6297 étude d'escalade de dose, n	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'inhibiteur du signal de tranduction BMS690514 en monothérapie, protocole CA 18	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I, protocole ES-A-285-001-002 étude de phase I(perfusion de 3 heures toutes les 3 semaine	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I, protocole PM104-A-004-05 étude clinique et pharmacocinétique de phase I, multicentrique	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'inhibiteur des kinases mitotiques EMD534085, protocole EMR 200024-001 étude	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I de l'inhibiteur de mTOR (RAD001) avec la chimiothérapie, protocole CRAD001C22116 étu	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'anti-angiogénique (VEGF-TRAP) avec une triple chimiothérapie, protocole TCD61	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'inducteur d'apoptose AMG951, protocole 20050190 essai multicentrique, randomi	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie testant l'anti-angiogénique (VEGF-TRAP), ARD6123 étude multicentrique, en ouvert,	investigateur principal	01/2007	12/2008
63615	SORIA	Jean-Charles	07/10/2008	IP-EC	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole 308901 étude de phase II, en ouvert, portant sur l'efficacité et la sécurité d	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole 3144A1-200-WW étude de phase 2, de l'HKI-272 chez des patients attein	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole 26866138 LUC 2001 étude randomisée, multicentrique, en ouvert, compar	investigateur principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole A6181057 essai randomisé de phase III comparant l'effet préopératoire de	investigetru principal	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	essai de phase I testant l'anticorps anti-IGF 1R, TED6421 étude multicentrique, de recherche de dose, porte	investigateur principal	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de phase I, BAY 43-9006-11879 étude de phase I, non contrôlée, en ouvert, monocentrique, évaluant	investigateur principal	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	étude de phase I de l'AFP464 (prodrogue de l'Aminoflavone) chez des patients avec des tumeurs solides de	investigateur principal	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, CRAD001C2235 étude ouverte de phase II, non randomisée, évaluant l'effet de RAI	investigateur principal	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-INV	INSTITUT GUSTAVE ROUSSY	essai de phase I avec escalade de dose du PHA-848125AC administré par voie orale en association avec la	investigateur principal	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase III comparant l'association cisplatine-irinotecan à l'association cisplatine-etoposide, essai X	co-investigateur	01/2002	12/2005
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II testant l'association oxaliplatine-gemcitabine versus cisplatine-gemcitabine, CLEO 05-02	investigateur principal	01/2003	12/2005
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec l'inhibiteur oral du cycle cellulaire, CYC202, essai CYC202-C-01-03 étude clinique de	co-investigateur	01/2003	12/2004
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I-II associant le temozolomide avec l'inhibiteur oral de HER1 (gefitinib) 1839IL-0109 étude c	co-investigateur	01/2003	12/2004
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec l'inhibiteur oral panHER (HER1, HER2 et HER4) BMS-599626, CA181-003 étude de	co-investigateur	01/2003	12/2005
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec l'inhibiteur oral de c-KIT, AB1010, PISTO3002 essai de phase I d'administrationorale	co-investigateur	01/2003	12/2005
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I associant l'irinotecan avec l'epothilone B (agent tubulo-affin) BMS-247550, CA 163-025 étu	co-investigateur	01/2003	12/2005
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec l'ES285, cytotoxique marin, ES-A-285-001-002 étude de phase I (perfusion de 3 lieu	co-investigateur	01/2003	12/2006
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I-II associant le temozolomide avec l'inhibiteur oral de HER1 (erlotinib), EORTC 26034 étu	co-investigateur	01/2003	12/2004
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II testant l'inhibiteur de topo-isomérase I (diflomotecan), IPSEN 2-91-52990-708 étude de pl	co-investigateur	01/2003	12/2004
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II avec l'inhibiteur oral de HER1 (gefitinib) IFCT-04-01 étude de phase II du Gefitinib admini	co-investigateur	01/2004	12/2005
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II testant en 1ère ligne l'inhibiteur oral HER1 (erlotinib), essai MO17426étude de phase II d	co-investigateur	01/2004	12/2005
63615	SORIA	Jean-Charles	07/10/2008	IP-AC	GSK - LILLY - PFIZER - MERCK SERONO - ROCHE - SANOFI AVENTIS - WYETH	en cours	rémunération personnelle		
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II avec l'inhibiteur oral de mTOR (RAD001), essai CRAD001C2235 "étude ouverte de phase	co-investigateur	01/2005	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I associant l(interféron avec l'anti-angiogénique oral BAY 43-9006, essai MAXIMA étude de	co-investigateur	01/2005	12/2006
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai dde phase I associant le DTIC avec l'anti-angiogénique oral BAY 43-9006, BAY 43-9006/11879 Etude	co-investigateur	01/2005	12/2007
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec le PM104, cytotoxique marin, PM104-A-004-05, à des patients porteurs de tumeurs s	co-investigateur	01/2005	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I, protocole NN1875-1783 Etude d'extension de phase I en ouvert, évaluant la sécurité et la	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'inhibiteur du signal de transduction BMS699514 en association avec FOLFOX OL	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I avec l'inhibiteur de mTOR (RAD001) en association avec la radiothérapie, RAD-RT étude	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I l'inhibiteur de mTOR (RAD001) avec la chimiothérapie dans le cancer du sein, protocole C	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I testant l'anti-angiogénique (sorafenib) avec le temozolomide, étude monocentrique, ouvert	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I : étude de phase I d'une association imatinib-interleukine-2 dans le cadre de traitement de	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II en 1ère ligne de l'inhibiteur d'EGFR (erlotinib), protocole MO 18660 essai clinique de pha	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	phase III testant en adjuvant une HBPM, étude TILT effet d'une héparine de bas poids moléculaire sur la mo	co-investigateur	01/2007	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phaseI, AURA-6202-006 Etude de phase II du PHA-739358 administré en perfusion IV de 24h tou	co-investigateur	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase I-II multicentrique, en ouvert, évaluant TKI 258 administré par voie orale selon un schéma	co-investigateur	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	Essai de phase I-II du PHA-848125AC administré par voie orale quotidiennement pendant 14 jours consécut	co-investigateur	01/2008	
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de phase II, AURA-6202-006 Etude de phase II du PHA-739358 administré en perfusion IV de 24h to	co-investigateur		
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole CLEO 05/0210 Etude de phase II multicentrique sur l'association gemcitat	co-investigateur		
63615	SORIA	Jean-Charles	07/10/2008	EC-CO	INSTITUT GUSTAVE ROUSSY	l'essai de pneumologie, protocole MO 18660 essai clinique de phase II avec groupes,parallèles, chez des pa	co-investigateur		

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Chicago - Etats-unis : 43ème congrès de l'ASCO		06/2007	06/2007
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Séoul - Corée : 12ème world conference on lung cancer RAD001 Everdimus		08/2007	09/2007
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Houston - Etats-unis : anual symposium on cancer research tailoring adjuvant chemotherapy in lung cancer		10/2007	10/2007
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		San francisco - Etats unis : AACR-NCI-EORTC Conference molecular targets and cancer therapeutics		10/2007	10/2007
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Bruxelles -Belgique : EORTC-NCI-ASCO Meeting molecular markers in cancer		11/2007	11/2007
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Paris - France : 19ème international congress on anti cancer treatment molecular targeted agents in non-small cell lung cancer targeted ther		02/2007	02/2008
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		San diego - Etats unis : AACR annual meeting		04/2008	04/2008
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Bethesda - Etats unis : 6th international symposium on targeted anticancer therapies RAD001 everolimus		03/2008	03/2008
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Genève - Suisse : ASLC-ESMO First european lung cancer conference should we adapt therapies according to histology, biology, prognostic and predictive markers in NSCLC			
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Chicago - Etats unis : 44th ASCO annual meeting application and limitation of biomarker analysis		05/2008	06/2008
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Stockholm - Suède : 33ed ESMO congress developmental therapeutics		09/2008	09/2008
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Dresden - Allemagne : international NSCLC advisory board meeting therapyguided by immunohistochemistry		10/2008	10/2008
63615	SORIA	Jean-Charles	07/10/2008	CF-INT		Genève - Suisse : AACR-EORTC-NCI : the plenary session 2 - profferd paper session		10/2008	10/2008
63615	SORIA	Jean-Charles	18/04/2006	IP-AC	SANOFI-AVENTIS	Consultant Scientifique	Rémunération personnelle	01/2004	
63615	SORIA	Jean-Charles	18/04/2006	IP-AC	LILLY	Advisory Board	Rémunération personnelle	01/2006	12/2006
63615	SORIA	Jean-Charles	18/04/2006	CF-INT	ASTRA ZENECA	EPU + enseignement aux Etats-Unis	Rémunération personnelle	01/2004	12/2005
63615	SORIA	Jean-Charles	18/04/2006	CF-INT	MERCK	Journée cancerologie digestive - PACA	Rémunération personnelle	01/2005	12/2005
63615	SORIA	Jean-Charles	18/04/2006	CF-INT	ROCHE	Journée ROCHE	Rémunération personnelle	01/2005	12/2005
63615	SORIA	Jean-Charles	18/04/2006	CF-INT	LILLY	Journée d'onco-pneumologie	Rémunération personnelle	01/2006	12/2006
63615	SORIA	Jean-Charles	18/04/2006	IP-AC	SERVIER	Consultant	Rémunération personnelle	01/2006	12/2006
63615	SORIA	Jean-Charles	01/10/2004	IP-EC	SANOFI	Essai de phase 1	Investigateur principal		
63615	SORIA	Jean-Charles	01/10/2004	IP-EC	BMS+ PHARMAMAR+ AB SCIENCES	Essai de phase 1	Co - investigateur		
63615	SORIA	Jean-Charles	01/10/2004	IP-EC	ROCHE+ ASTRA ZENECA+NOVARTIS	Essai de phase 2			
63615	SORIA	Jean-Charles	01/10/2004	IP-AC	AVENTIS, ASTRA ZENECA	Activité de conseil scientifique (rémunérée)			
63615	SORIA	Jean-Charles	01/10/2004	IP-CF	KUDOS PHARMACEUTICALS	Advisory board meetings (rémunéré ponctuellement)			
10386	SOULEAU	Charles	01/01/1999	LD	Consultant pour les laboratoires Servier : Problèmes d'environnement et de sécurité des installations industrielles				
10386	SOULEAU	Charles	01/01/1999	LD	Travaux sur les argiles : Ipsen Beaufour				
10386	SOULEAU	Charles	01/01/1999	IP-RE	Beaufour Ipsen : Spécialité à base d'argiles				
10386	SOULEAU	Charles	01/01/1999	PAR	Fille chez R.P.R				
10386	SOULEAU	Charles	01/01/1998	IP-AUT	Ipsen Beaufour				
10386	SOULEAU	Charles	01/01/1998	IP-AUT	Servier				
10386	SOULEAU	Charles	01/01/1998	VB	Ipsen Beaufour pour le Ministère de la Recherche				
10386	SOULEAU	Charles	01/01/1998	PAR	Epouse ingenieur Sanofi et P.S.D				
10386	SOULEAU	Charles	01/01/1998	PAR	fille juriste RPR				
64922	STEG	Philippe Gabriel	14/01/2008	LD-AR	ASTELLAS, ASTRA ZENECA, BAYER, BOEHRINGER INGELHEIM, BMS, GSK, MEDTRONIC, MSD, MYCOMED, SANOFI AVENTIS, SERVIER, THE MEDICINES COMPANY	Consultant	rémunération personnelle	01/2007	12/2008
64922	STEG	Philippe Gabriel	14/01/2008	EC-INV	SERVIER	Etude Ivabradine dans l'infarctus	investigateur principal	01/2008	12/2008
64922	STEG	Philippe Gabriel	14/01/2008	EC-INV	SANOFI, BMS	registre REACH	Co-président	01/2004	12/2009
64922	STEG	Philippe Gabriel	14/01/2008	EC-INV	SANOFI	Registre GRACE	Co-président du comité	01/2000	12/2008
64922	STEG	Philippe Gabriel	14/01/2008	EC-INV	SANOFI BMS	OASIS 7 - Current	membre du steering committee	01/2006	12/2008
64922	STEG	Philippe Gabriel	14/01/2008	EC-INV	ASTRA ZENECA	Etude PLATO	membre du steering committee	01/2006	12/2009
64922	STEG	Philippe Gabriel	14/01/2008	CF-INT	BOEHRINGER, BMS, GSK, MEDTRONIC, NYCOMED, SANOFI AVENTIS, SERVIER, ASTRA ZENECA, MSD, ZLB BEHRING	AHA, ESC, ACC, Euro PCR	rémunération personnelle	01/2005	12/2008
64922	STEG	Philippe Gabriel	14/01/2008	IP-AUT	SANOFI AVENTIS	Brevet sur l'utilisation de l'enoxaparine en angioplastie coronaire		01/2007	
64922	STEG	Philippe Gabriel	14/01/2008	VB	SANOFI AVENTIS	Rémunération d'un Assistant de Recherche Clinique (ARC) à temps plein	Association Naturalia et Biologia	01/2000	12/2007
55609	STERKERS	Olivier	24/03/2004	Néant					
55609	STERKERS	Olivier	11/07/2002	IP-EC	COCHLEAR	Implants - tronc cérébral			
55609	STERKERS	Olivier	11/07/2002	IP-EC	MED EL	Implant cochléaire bilatéral			
55609	STERKERS	Olivier	11/07/2002	IP-CF	EUROPEAN NUCLEUS OUTCOMES	Seminar jl - Crète juin 22-24/2001 : Surgical complications with nucleus			
55609	STERKERS	Olivier	17/01/2000	IP-RE	SOLVAY	mécausim action			
55609	STERKERS	Olivier	17/01/2000	IP-CF	SOLVAY	vertiges			
55609	STERKERS	Olivier	17/01/2000	IP-CF	GLAXO	journée ORL actualité			
55609	STERKERS	Olivier	17/01/2000	VB	SERVIER	association de recherche ORL beaujon			
55609	STERKERS	Olivier	17/01/2000	VB	NEWMEDIC	association de recherche ORL beaujon			
55609	STERKERS	Olivier	17/01/2000	VB	COUMEAR	association de recherche ORL beaujon			
55609	STERKERS	Olivier	17/01/2000	VB	SOLVAY	association de recherche ORL beaujon			
55609	STERKERS	Olivier	01/01/2000	IP-EC	BIOPHARMA : Acouphènes, vertiges				
55609	STERKERS	Olivier	01/01/2000	IP-RE	SOLVAY : Action du SERC				
55609	STERKERS	Olivier	01/01/2000	IP-CF	GLAXO : journées ORL				
55609	STERKERS	Olivier	01/01/2000	VB	Association de recherche en O.R.L. de l'hôpital Beaujon		Association de recherche en O.R.L. de l'hôpital Beaujon		
64896	TABARIN	Antoine	04/12/2007	EC-INV	PFIZER	Evaluation comparative du Pegvisomant versus sandostatine dans l'acromégalie	Investigateur coordinateur	01/2005	12/2006
64896	TABARIN	Antoine	04/12/2007	EC-CO	NOVARTIS	SOM230B dans le traitement de la maladie de Cushing (en cours)	Co-investigateur	08/2007	
64896	TABARIN	Antoine	04/12/2007	EC-CO	NOVARTIS	Essai clinique HOSCAR tolérance Sandostatine LP à haute dose en association chez les acromégales non	Co-investigateur	08/2006	
64896	TABARIN	Antoine	04/12/2007	CF-INT	NOVARTIS	Paris - Stratégies thérapeutiques dans le suivi des acromégales	Rémunération personnelle	01/2007	
64896	TABARIN	Antoine	04/12/2007	VB	GENZYME, NOVO, IPSEN, GSK, NOVARTIS, MERCK, PFIZER, LILLY, ASTRA ZENECA, TAKEDA, SERVIER	Journée d'endocrinologie du Haut-Lévêque : financement de multiples partenaires industriels à l'association citée en regard pour l'oragnisation de la recherche et de l'enseignen			
63616	TAILLANDIER	Luc	24/09/2006	EC-INV	CHU Nancy	Evaluation de la fertilité potentielle avant et après traitement pour gliomes de grade II OMS par chimiothérap investigateur coordonnateur		11/2005	
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	APHP	Etude de phase III évaluant l'efficacité de la RTH dans le traitement des gliomes anaplasiques supratentorie co-investigateur		01/2001	12/2005
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	STE FRANCAISE DE GREFFE DE MOELLE	Protocole de 2° ligne pour les lymphomes malins non hodgkiniens primitifs du SNC et les lymphomes intraoc co-investigateur		01/2001	12/2005
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	LABORATOIRES SERVIER	Chimiothérapie comprenant Folémustine, Cisplatine, Etoposide suivie de radiothérapie versus radiothérapie co-investigateur		05/2001	01/2005
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	CHU Nancy	Etude de phase II testant l'efficacité d'une irradiation ultra fractionnée chez des patients ayant un GBM (RTH co-investigateur		09/2003	12/2006
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	LABORATOIRE XENOVA	a phase III multicenter study of intratumoral/interstitial therapy with transMID® compared to best standard car co-investigateur		09/2004	02/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	CHU Nancy	Etude de phase II testant l'efficalité d'une association concomitante radiothérapie/fotemustine chez des patie	co-investigateur	09/2004	
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	APHM	Chimiothérapier première par association BCNU/TZ dans les tumeurs oligodendrocytaires anaplasiques nou	co-investigateur	12/2005	
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	LABORATOIRES ARK THERAPEUTICS	A controlled, randomised, parallel Group, Multicentre study of the safety of Herpex Simplex virus thymidine l	co-investigateur	02/2006	
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	LABORATOIRES LILLY	Etude randomisée de phase III de l'enzastaurine versus la lomustine dans le traitement des rechutes de GB	co-investigateur	06/2006	
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	EORTC	Primary chemotherapy with temozolomide versus radiotherapy in patients with ow grades gliomas after strati	co-investigateur	06/2006	
63616	TAILLANDIER	Luc	24/09/2006	EC-CO	INCA	Etat des lieux des pratiques chirurgicales, radiothérapiques et chimiothérapiques, dans la prise en charge de	co-investigateur	06/2006	
63616	TAILLANDIER	Luc	24/09/2006	RE-DE	DAMIEN RICARD	essai phase I de bon cholestérol Liposomal intra tumoral dans les gliomes malins	aucune rémunération	01/2005	
63616	TAILLANDIER	Luc	13/09/2004	LD	SNCF	Consultant neurologue (1h30 par semaine)			
63616	TAILLANDIER	Luc	13/09/2004	IP-EC	ANOCEF (Association des neurooncologues d'expression française)	Essais cliniques coordonnés par l'Association			
63616	TAILLANDIER	Luc	13/09/2004	IP-EC		essais cliniques neuro oncologique en provenance de l'industrie (ponctuellement)			
63616	TAILLANDIER	Luc	13/09/2004	IP-EC		Actuellement Xenova Biomedix phase III trans Mid Im kSB 311R/c III/00D			
63616	TAILLANDIER	Luc	13/09/2004	IP-RE		Rapports d'expertise thématiques neuro oncologiques pour des structures type PHRC régionaux ou nationaux mais pas pour des firmes privées.			
63616	TAILLANDIER	Luc	13/09/2004	IP-CF		Pas pour des firmes			
61583	TCHORELOFF	Pierre-Cyril	27/11/2009	IP-AC	ETHYPHARM	Travaux sur les films d'enrobage et leur stabilité	Rémunération institution		
61583	TCHORELOFF	Pierre-Cyril	07/02/2009	(Autre)	BIOALLIANCE	Suivi de travaux Master	Travaux ne faisant pas l'objet de rémunération personnelle mais pouvant être contractuellement accompagnés de supports financiers au niveau du laboratoire de recherche auquel je suis rattaché	01/2009	07/2009
61583	TCHORELOFF	Pierre-Cyril	07/02/2009	IP-AC	NOVARTIS	Formation continue. Intervention sur site.	Rémunération personnelle/institution	01/2009	02/2009
61583	TCHORELOFF	Pierre-Cyril	07/02/2009	IP-AC	SERVIER	Formation continue. Intervention sur site.	Rémunération personnelle/institution	01/2009	01/2009
61583	TCHORELOFF	Pierre-Cyril	07/02/2009	RE-AUT	SANOFI-AVENTIS	expertise sur les procédés de compression	Rémunération institution	01/2009	
61583	TCHORELOFF	Pierre-Cyril	02/01/2008	(Autre)	EPMO	Suivi de travaux Master+ thèse d'université	Travaux ne faisant pas l'objet de rémunération personnelle mais pouvant être contractuellement accompagnés de supports financiers au niveau du laboratoire de recherche auquel je suis rattaché	01/2008	09/2008
61583	TCHORELOFF	Pierre-Cyril	02/01/2008	(Autre)	SANOFI AVENTIS	Suivi de travaux Master+ thèse d'université	Travaux ne faisant pas l'objet de rémunération personnelle mais pouvant être contractuellement accompagnés de supports financiers au niveau du laboratoire de recherche auquel je suis rattaché	01/2008	12/2008
61583	TCHORELOFF	Pierre-Cyril	02/01/2008	(Autre)	ETHYPHARM	Suivi de travaux Master+ thèse d'université	Travaux ne faisant pas l'objet de rémunération personnelle mais pouvant être contractuellement accompagnés de supports financiers au niveau du laboratoire de recherche auquel je suis rattaché	01/2008	12/2009
61583	TCHORELOFF	Pierre-Cyril	02/01/2008	LD-AR	ETHYPHARM	Convention d'exploitation de brevet	Aucune rémunération		
61583	TCHORELOFF	Pierre-Cyril	12/05/2006	IP-AUT	SERVIER	formation sur site		05/2006	05/2006
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	LD	ETHYPHARM	Convention d'exploitation de brevet			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-EC	SANOFI AVENTIS	Caractérisations physico-chimiques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-EC	GSK	Caractérisations physico-chimiques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-EC	EPMO	Propriétés mécaniques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-EC	CEGITAB	Propriétés mécaniques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-RE	EPMO	Propriétés mécaniques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-RE	CEGITAB	Propriétés mécaniques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-RE	SANOFI AVENTIS	Caractérisations physico-chimiques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-RE	ETHYPHARM	Caractérisations physico-chimiques			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-AC	ETHYPHARM	Propriétés mécaniques physico-chimiques	Aucune rémunération		
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-AC	EPMO	Propriétés mécaniques	Aucune rémunération		
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-AC	CEGITAB	Propriétés mécaniques	Aucune rémunération		
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-CF	EUROFORUM	Systèmes granulaires et transformations			05/2006
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	IP-CF	CPE (LYON FORMATION CONTINUE)	Systèmes granulaires et transformations			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	VB	SANOFI AVENTIS	Université Paris Sud			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	VB	ETHYPHARM	Université Paris Sud			
61583	TCHORELOFF	Pierre-Cyril	27/04/2005	VB	EPMO	Université Paris Sud			
61583	TCHORELOFF	Pierre-Cyril	20/12/2004	IP-EC	ETHYPHARM	Travaux de recherche en pharmacotechnie			
61583	TCHORELOFF	Pierre-Cyril	20/12/2004	IP-RE	CEGITAB	Propriétés mécaniques, systèmes compactés			
61583	TCHORELOFF	Pierre-Cyril	20/12/2004	IP-AC	CEGITAB	Propriétés mécaniques, systèmes compactés			
61583	TCHORELOFF	Pierre-Cyril	20/12/2004	IP-CF	CPE Lyon	Propriétés mécaniques, systèmes compactés, analyse systèmes granulaires, mélanges			
61583	TCHORELOFF	Pierre-Cyril	20/12/2004	IP-CF	EUROFORUM	Systèmes faiblement dosés			
61583	TCHORELOFF	Pierre-Cyril	20/12/2004	IP-AUT	SANOFI - AVENTIS - GSK - ETHYPHARM	Suivi d'étudiants stagiaires (pharmacie et Masters)			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	ETHYPHARM	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	NP PHARM	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	INNOTHERA	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	RHODIA	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	EPMO	UP Sud			

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	DIGIPHARM	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	GSK	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	AVENTIS PHARMA	UP Sud			
61583	TCHORELOFF	Pierre-Cyril	22/12/2003	VB	FMC				
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	IP-EC	AVENTIS PHARMA	Thèse d'Université (sans rémunération)			
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	IP-EC	ETHYPHARM	DEA (sans rémunération)			
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	IP-EC	DIGIPHARM	DEA (sans rémunération)			
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	IP-AC	BIORGA	Expertise scientifique/juridique			
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	IP-CF	GLAXO SMITHKLINE	Formations - Compression			
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	IP-CF	AVENTIS	Formations - Compression			
61583	TCHORELOFF	Pierre-Cyril	20/09/2002	VB	AVENTIS PHARMA, ETHYPHARM, DIGIPHARM	Université Paris Sud - UMR CNRS 8612			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-EC	ETHYPHARM	DEA + thèse université			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-EC	DIGIPHARM	DEA			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-EC	RHODIA	Thèse université			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-EC	AVENTIS	Thèse université			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-EC	NP PHARM	DEA			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-AC	GSK (site de Mayenne)	Essais de Pharmacotechnie			
61583	TCHORELOFF	Pierre-Cyril	11/06/2001	IP-CF	EUROFORUM	Conférences			
65757	THIBAUT	Florence	11/10/2010	LD-AR	SCHERING	expert : asenapine 1 réunion	rémunération institution	06/2009	06/2010
65757	THIBAUT	Florence	11/10/2010	EC-CO	JANSSEN	étude cohorte L abenhaim investigateur secondaire et comité scientifique cosponsorisée par janssen		01/2006	12/2009
65757	THIBAUT	Florence	11/10/2010	CF-INT	DIVERSES	organisation de congrès mondiaux de psychiatrie président WFBSP avec sponsors industriels□□□□AFPB c	aucune rémunération	01/2009	12/2011
65757	THIBAUT	Florence	11/10/2010	CF-INT	SERVIER	Moscou réunion conjointe des sociétés de psychiatrie biologique France-Russie	aucune rémunération	01/2010	12/2010
65757	THIBAUT	Florence	15/03/2009	RE-AUT	LUNDBECK	Etude Sartindole/ Risperdal	rémunération institution	01/2008	
65757	THIBAUT	Florence	15/03/2009	CF-INT	JANSSEN	RMC société			
65757	THIBAUT	Florence	15/03/2009	CF-INT	BMS	RMC Schizosem			
65757	THIBAUT	Florence	15/03/2009	CF-INT	LILLY	RMC Société			
65757	THIBAUT	Florence	15/03/2009	CF-AUD	SERVIER	Congrès de l' Encéphale (2 nuits d'hôtel)		01/2009	
63891	THIS	Pascale	27/01/2007	EC-CO	AKZO NOBEL	Essai LIBERATE (Livial versus placebo après cancer du sein)	investigateur	01/2003	12/2008
63891	THIS	Pascale	27/01/2007	EC-CO	AKZO NOBEL	Essai SOFT(Hormonothérapie du cancer du sein chez la femme non ménopausée)	co-investigateur	01/2007	12/2012
63891	THIS	Pascale	27/01/2007	CF-INT	ORGANON, AKZO NOBEL	Cancer du sein - ménopause - qualité de vie - Nice	rémunération personnelle	02/2004	02/2004
63891	THIS	Pascale	27/01/2007	CF-INT	IPSEN BEAUFOUR	Fonction ovarienne après traitement d'un cancer du sein / Paris	rémunération personnelle	05/2004	05/2004
63891	THIS	Pascale	27/01/2007	CF-INT	ASTRA ZENECA	Hormonothérapie soignale du cancer du sein et qualité de vie / Paris	rémunération personnelle	02/2004	02/2004
63891	THIS	Pascale	27/01/2007	CF-INT	ASTRA ZENECA	Tamoxifène chez la femme pré ménopausée / Paris	rémunération personnelle	01/2005	05/2005
63891	THIS	Pascale	27/01/2007	CF-INT	NOVARTIS	Hormonothérapie du cancer du sein et qualité de vie	rémunération personnelle	03/2006	03/2006
63891	THIS	Pascale	27/01/2007	CF-INT	PFIZER	Statut ovarien et ménopause après cancer du sein	rémunération personnelle	04/2006	04/2006
63891	THIS	Pascale	27/01/2007	PAR	SANOFI-AVENTIS	poste informatique	belle sœur		
63891	THIS	Pascale	28/10/2005	EC-CO	AKZO-NOBEL	Essai randomisé Liberate Livial vs placebo après cancer du sein	Investigateur à Curie	01/2003	12/2008
63891	THIS	Pascale	28/10/2005	IP-AC	SERVIER MEDICAL	Groupe de travail THS. 2003 =3 réunions	Rémunération personnelle	01/2003	12/2003
63891	THIS	Pascale	28/10/2005	IP-AC	LILLY	Raloxifène. Revue gynéco-obstétrique fertilité	Rémunération personnelle	01/2003	12/2003
63891	THIS	Pascale	28/10/2005	CF-INT	ASTRA ZENECA	Amiens / THS avant et après cancer du sein	Rémunération personnelle	10/2002	10/2002
63891	THIS	Pascale	28/10/2005	CF-INT	ORGANON	Quelles alternatives pour le traitement de la Ménopause /Tarbes	Rémunération personnelle	10/2003	10/2003
63891	THIS	Pascale	28/10/2005	CF-INT	ORGANON	Cancer du sein - ménopause et qualité de vie / Nice	Rémunération personnelle	02/2004	02/2004
63891	THIS	Pascale	28/10/2005	CF-INT	IPSEN	Fonction ovarienne après traitement d'un cancer du sein /Paris	Rémunération personnelle	05/2004	05/2004
63891	THIS	Pascale	28/10/2005	CF-INT	ASTRA ZENECA	Cancer du sein	Rémunération personnelle	02/2004	02/2004
63891	THIS	Pascale	28/10/2005	CF-INT	ASTRA-ZENECA	Tamoxifène chez la femme pré-ménopausée, Paris	Rémunération personnelle	01/2005	01/2005
63891	THIS	Pascale	19/09/2005	EC-CO	AKZO NOBEL	Essai Liberate (randomisé) □□Essai Livial versus placebo après cancer du sein	Investigateur à Curie	01/2003	12/2008
63891	THIS	Pascale	19/09/2005	IP-AC	SERVIER MEDICAL	Groupe de travail THS - 3 réunions	Rémunération personnelle	01/2003	12/2003
63891	THIS	Pascale	19/09/2005	IP-AC	LILLY	Raloxifene - revue gynéco obstétrique fertilité	rémunération personnelle	06/2003	
63891	THIS	Pascale	19/09/2005	CF-INT	ASTRA ZENECA	THS avant et après cancer du sein / Amiens	rémunération personnelle	10/2002	10/2002
63891	THIS	Pascale	19/09/2005	IP-CF	ORGANON	Tarbes / Demain quelle alternative pour traiter la ménopause?	rémunération personnelle	10/2003	10/2003
63891	THIS	Pascale	19/09/2005	IP-CF	ORGANON, AKZO NOBEL	Cancer du sein ménopause et qualité de vie / Nice	rémunération personnelle	02/2004	02/2004
63891	THIS	Pascale	19/09/2005	IP-CF	IPSEN BEAUFOUR	Fonction ovarienne après traitement d'un cancer du sein / Paris	rémunération personnelle	05/2004	05/2004
63891	THIS	Pascale	19/09/2005	IP-CF	ASTRA ZENECA	Cancer du sein et qualité de vie / Paris	rémunération personnelle	05/2004	05/2004
63891	THIS	Pascale	19/09/2005	IP-CF	ASTRA ZENECA	Tamoxifène chez la femme pré-ménopausée / Paris	rémunération personnelle	01/2005	01/2005
63764	THOMAS	Thierry	09/12/2010	IP-AC	NOVARTIS	Zoledronate	Rémunération personnelle	01/2010	12/2010
63764	THOMAS	Thierry	09/12/2010	IP-AC	DANONE	Conseil produits enrichis en calcium	Rémunération personnelle	01/2010	06/2010
63764	THOMAS	Thierry	09/12/2010	IP-AC	ROCHE	Ibandronate	Rémunération personnelle	01/2010	10/2010
63764	THOMAS	Thierry	09/12/2010	EC-CO	SERVIER	Strontium	Co-investigateur	01/2006	06/2010
63764	THOMAS	Thierry	09/12/2010	EC-INV	SERVIER	Enquête observationnelle Protelos	Investigateur coordonnnateur	02/2008	12/2010
63764	THOMAS	Thierry	03/12/2009	CF-AUD	ALLIANCE				
63764	THOMAS	Thierry	03/12/2009	CF-INT	LILLY		Rémunération personnelle		
63764	THOMAS	Thierry	03/12/2009	CF-INT	MSD		Aucune rémunération		
63764	THOMAS	Thierry	03/12/2009	CF-INT	SERVIER		Rémunération personnelle		
63764	THOMAS	Thierry	03/12/2009	CF-INT	IPSEN		Aucune rémunération		
63764	THOMAS	Thierry	03/12/2009	CF-INT	AMGEN		Rémunération personnelle		
63764	THOMAS	Thierry	03/12/2009	CF-INT	ROCHE		Rémunération personnelle		
63764	THOMAS	Thierry	03/12/2009	CF-INT	NOVARTIS		Rémunération personnelle		
63764	THOMAS	Thierry	03/12/2009	CF-INT	ALLIANCE		Rémunération personnelle		
63764	THOMAS	Thierry	17/07/2008	CF-INT	MSD	Conférence de Presse, Paris 01/08, Fosavance 5600	Rémunération personnelle	01/2008	01/2008
63764	THOMAS	Thierry	17/07/2008	CF-INT	NOVARTIS	Congrès SFR, Paris, 12/2008, Conférence de presse Etudes cliniques Aclasta	Rémunération personnelle	12/2007	12/2007
63764	THOMAS	Thierry	17/07/2008	CF-INT	AMGEN	ESCEO, Istanbul, 04/2008 Symposium Résultats études animales Denosumab	Rémunération personnelle	04/2008	04/2008
63764	THOMAS	Thierry	17/07/2008	EC-CO	NICOMED	Essai clinique Préotact	Co-investigateur	01/2008	12/2009
63764	THOMAS	Thierry	17/07/2008	EC-INV	SERVIER	Enquête observationnelle/Protelos	investigateur principal	02/2008	
63764	THOMAS	Thierry	17/07/2008	LD-AR	MSD	Membre groupe expert fosavance 5600, MK0822	Rémunération personnelle	11/2007	10/2008
63764	THOMAS	Thierry	17/07/2008	IP-AC	AMGEN	Groupe de réflexion - Denosumab 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2003	
63764	THOMAS	Thierry	17/07/2008	IP-AC	ROCHE-GSK	Groupe de réflexion - Ibandronate 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2005	
63764	THOMAS	Thierry	17/07/2008	IP-AC	SERVIER	Groupe de réflexion - Strontium ranelate 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2005	
63764	THOMAS	Thierry	17/07/2008	IP-AC	ALLIANCE	Groupe de travail sur les pathologies osseuses 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2003	
63764	THOMAS	Thierry	17/07/2008	IP-AC	NOVARTIS	Groupe de réflexion - Zoledronate 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2005	
63764	THOMAS	Thierry	17/07/2008	EC-CO	AMGEN	Essai clinique Denosumab - en cours	Co-investigateur	01/2006	12/2009
63764	THOMAS	Thierry	17/07/2008	EC-CO	LILLY	Essai clinique Teriparatide - en cours	Co-investigateur	01/2005	12/2009
63764	THOMAS	Thierry	17/07/2008	EC-CO	ROCHE	Essai clinique Rituximab - en cours	Co-investigateur	01/2006	12/2009

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63764	THOMAS	Thierry	17/07/2008	EC-CO	ROCHE	Essai clinique Ibandronate - en cours	Co-investigateur	01/2007	12/2009
63764	THOMAS	Thierry	17/07/2008	EC-CO	ABBOTT	Essai clinique Adalimumab - en cours	Co-investigateur	01/2009	06/2009
63764	THOMAS	Thierry	17/07/2008	EC-CO	SERVIER	Essai clinique Strontium - en cours	Co-investigateur	12/2005	
63764	THOMAS	Thierry	17/07/2008	EC-CO	PROCTER ET GAMBLE	Essai clinique Risédronate - en cours	Co-investigateur	01/2005	12/2009
63764	THOMAS	Thierry	17/07/2008	LD-AR	ROCHE,GSK,AMGEN,NOVARTIS, SERVIER	Membre groupe experts pour respectivement :Ibandronate, Denosumab, Zoledronate, Ranelate de Strontium	rémunération personnelle	01/2005	
63764	THOMAS	Thierry	19/07/2007	LD-AR	ROCHE,GSK,AMGEN,NOVARTIS, SERVIER	Membre groupe experts pour respectivement :Ibandronate, Denosumab, Zoledronate, Ranelate de Strontium	rémunération personnelle	01/2005	
63764	THOMAS	Thierry	19/07/2007	LD-AR	MSD, LILLY	Consultation individuelle pour respectivement : Alendronate, Teriparatide		01/2005	12/2005
63764	THOMAS	Thierry	19/07/2007	EC-INV	SCHERING PLOUGH	Observatoire paramètres osseux sous Remicade	Investigateur principal	01/2004	12/2006
63764	THOMAS	Thierry	19/07/2007	EC-CO	PROCTER ET GAMBLE	Essai clinique Risédronate - en cours	Co-investigateur	01/2005	
63764	THOMAS	Thierry	19/07/2007	EC-CO	SERVIER	Essai clinique Strontium - en cours	Co-investigateur	12/2005	
63764	THOMAS	Thierry	19/07/2007	EC-CO	ABBOTT	Essai clinique Adalimumab - en cours	Co-investigateur	01/2006	
63764	THOMAS	Thierry	19/07/2007	EC-CO	ROCHE	Essai clinique Ibandronate - en cours	Co-investigateur	01/2007	
63764	THOMAS	Thierry	19/07/2007	EC-CO	ROCHE	Essai clinique Rituximab - en cours	Co-investigateur	01/2006	
63764	THOMAS	Thierry	19/07/2007	EC-INV	MSD	Etude épidémiologique	Investigateur principal	01/2004	12/2006
63764	THOMAS	Thierry	19/07/2007	EC-CO	NOVARTIS	Etude médico-économique	Co-investigateur	01/2006	12/2007
63764	THOMAS	Thierry	19/07/2007	EC-CO	LILLY	Essai clinique Teriparatide - en cours	Co-investigateur	01/2005	
63764	THOMAS	Thierry	19/07/2007	EC-CO	AMGEN	Essai clinique Dénosumab - en cours	Co-investigateur	01/2006	
63764	THOMAS	Thierry	19/07/2007	IP-AC	ALLIANCE	Groupe de travail sur les pathologies osseuses 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2003	
63764	THOMAS	Thierry	19/07/2007	IP-AC	NOVARTIS	Groupe de réflexion - Zoledronate 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2005	
63764	THOMAS	Thierry	19/07/2007	IP-AC	SERVIER	Groupe de réflexion - Strontium ranelate 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2005	
63764	THOMAS	Thierry	19/07/2007	IP-AC	ROCHE-GSK	Groupe de réflexion - Ibandronate 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2005	
63764	THOMAS	Thierry	19/07/2007	IP-AC	AMGEN	Groupe de réflexion - Denosumab 2 à 3 réunions par an - en cours	Rémunération personnelle	01/2003	
63764	THOMAS	Thierry	19/07/2007	IP-AC	MSD	Groupe de réflexion	Rémunération personnelle	01/2006	12/2006
63764	THOMAS	Thierry	19/07/2007	CF-INT	SERVIER	Symposium SFR - Paris - Strontium ranelate	Rémunération personnelle	12/2005	12/2005
63764	THOMAS	Thierry	19/07/2007	CF-INT	SERVIER	Réunions formations MG et Rhumatologues Rhône-Alpes	Rémunération personnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	ALLIANCE	Symposium SFR, Paris - Risédronate	Rémunération personnelle	12/2005	12/2005
63764	THOMAS	Thierry	19/07/2007	CF-INT	ALLIANCE	Symposium SFR - Paris - Risédronate	Rémunération personnelle	12/2006	12/2006
63764	THOMAS	Thierry	19/07/2007	CF-INT	ALLIANCE	Réunions formations MG et Rhumatologues Rhône-Alpes	Rémunération personnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	ALLIANCE	Symposium satellite ECCEO - Porto - Risédronate	Rémunération personnelle	03/2007	03/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	ALLIANCE	Réunion board Suisse - Berne - Risédronate	Rémunération personnelle	04/2007	04/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	ROCHE-GSK	Symposium Réflexions Rhumatologiques - Paris - Ibandronate	Rémunération personnelle	03/2006	03/2006
63764	THOMAS	Thierry	19/07/2007	CF-INT	ROCHE-GSK	Symposium - Avignon - Ibandronate	Rémunération personnelle	09/2006	09/2006
63764	THOMAS	Thierry	19/07/2007	CF-INT	ROCHE-GSK	Réunions formations MG et Rhumatologues Rhône-Alpes	Rémunération personnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	LILLY	Symposium SFR 2005 - Paris - Raloxifène	Rémunération personnelle	12/2005	12/2005
63764	THOMAS	Thierry	19/07/2007	CF-INT	LILLY	Réunions formations MG et Rhumatologues Rhône-Alpes	Rémunération personnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	MSD	Réunions formations MG et Rhumatologues Rhône-Alpes, Alendronate	Rémunération personnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	NOVARTIS	Réunions formations Rhumatologues Rhône-Alpes - Zolédronate	Rémunération personnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-INT	WYETH	Réunions formations Rhumatologues Rhône-Alpes - Etanercept	Rémunération peronnelle	01/2005	12/2007
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ALLIANCE	Congrès SFR - Paris		12/2006	12/2006
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ALLIANCE	ECCEO - Porto		03/2007	03/2007
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ALLIANCE	Congrès ASBMR - Hawaii		09/2007	09/2007
63764	THOMAS	Thierry	19/07/2007	CF-AUD	MSD	Congrès ASBMR- Philadelphie		09/2006	09/2006
63764	THOMAS	Thierry	19/07/2007	CF-AUD	SCHERING-PLOUGH	Journée Nationale du CRI - Paris		05/2006	05/2006
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ALLIANCE	ASBMR - Nashville		09/2005	09/2005
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ALLIANCE	Congrès SFR - Paris		09/2005	09/2005
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ECCEO	Aclasta		04/2007	04/2007
63764	THOMAS	Thierry	19/07/2007	CF-AUD	ROCHE	Aclasta		06/2007	06/2007
63764	THOMAS	Thierry	19/07/2007	CF-AUD	Lettre du Rhumatologue	Aclasta		02/2007	02/2007
63764	THOMAS	Thierry	01/02/2006	LD-AR	ROCHE,GSK,AMGEN,NOVARTIS, SERVIER	Membre groupe experts pour respectivement :Ibandronate, Denosumab, Zoledronate, Ranelate de Strontium	rémunération personnelle	01/2005	
63764	THOMAS	Thierry	01/02/2006	LD-AR	MSD, LILLY	Consultation individuelle pour respectivement : Alendronate, Teriparatide		01/2005	12/2005
63764	THOMAS	Thierry	01/02/2006	EC-INV	SCHERING-PLOUGH	Investigateur principal pour observatoire paramètres osseus sous Remicade	investigateur principal	01/2004	12/2005
63764	THOMAS	Thierry	01/02/2006	EC-CO	PROCTER & GAMBLE	Essai clinique Risédronate		01/2003	12/2005
63764	THOMAS	Thierry	01/02/2006	EC-CO	SERVIER	Essai clinique Strontium	co-investigateur	01/2006	
63764	THOMAS	Thierry	01/02/2006	EC-CO	PROCTER & GAMBLE	essai clinique Risédronate	co-investigateur	01/2006	
63764	THOMAS	Thierry	01/02/2006	EC-CO	LILLY	Essai clinique Teriparatide		01/2005	
63764	THOMAS	Thierry	01/02/2006	IP-AC	ALLIANCE	Groupe de réflexion et d'information sur les pathologies osseuses - Risédronate	rémunération personnelle	01/2003	
63764	THOMAS	Thierry	01/02/2006	CF-INT	SERVIER	Symposium SFR 2005 - Paris - opinion stratégie thérapeutique dans l'ostéoporose (Strontium)	rémunération personnelle	12/2005	
63764	THOMAS	Thierry	01/02/2006	CF-INT	ALLIANCE	Symposium SFR - Paris - Observance thérapeutique Risédronate	rémunération personnelle	12/2005	
63764	THOMAS	Thierry	01/02/2006	CF-INT	LILLY, ALLIANCE, MSD	Réunions locales de formation continue auprès des médecins généralistes et rhumatologues	rémunération personnelle	01/2003	12/2005
63764	THOMAS	Thierry	01/02/2006	CF-AUD	ALLIANCE	ASBMR - Nashville		09/2005	
63764	THOMAS	Thierry	01/02/2006	CF-AUD	ALLIANCE	Congrès SFR - Paris		09/2005	
63764	THOMAS	Thierry	01/02/2006	CF-AUD	MSD	Congrès ECTS - Genève		06/2005	
10395	THUILLEZ	Christian	16/05/2010	LD-AR	NOVARTIS	Expert - Participation à des réunions scientifiques. Produits : Exforge - Aliskiren□□En cours	rémunération personnelle	01/2006	
10396	THUILLEZ	Christian	16/05/2010	LD-AR	MENARINI	Expert - Participation à des réunions scientifiques. Produit : Ranexa	rémunération personnelle	01/2008	12/2010
10395	THUILLEZ	Christian	16/05/2010	LD-AR	NEGMA	Expert - Participation des réunions scientifiques. Produit : Nebilox□□En cours	rémunération personnelle	01/2003	
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE SERVIER	Etude pré-clinique - Ivabradine	Investigateur principal	01/2005	12/2007
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE SERVIER	Etude pré-clinique - Inhibiteur DPP IV	Investigateur principal	01/2009	12/2009
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE SERVIER	Etude pré-clinique - Inhibiteur DPP IV	Investigateur principal	01/2006	12/2007
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE SERVIER	Etude pré-clinique - Inhibiteur DPP IV	Investigateur principal	01/2007	12/2008
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE SERVIER	Etude pré-clinique - Inhibiteur mixte ACE - ECE	Investigateur principal	01/2007	12/2009
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE NOVARTIS	Etude pré-clinique - Inhibiteur aldostérone synthase	Investigateur principal	01/2005	12/2006
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE MENARINI	Etude pré-clinique - Nebivolol	Investigateur principal	01/2007	12/2008
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE PFIZER	Etude clinique - Stomastatine	Investigateur principal	01/2003	12/2006
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE WYETH	Etude clinique - Sirolimus	Investigateur principal	01/2003	12/2008
10396	THUILLEZ	Christian	16/05/2010	EC-INV	LABORATOIRE ROCHE	Etude clinique - Cellcept	Investigateur principal	01/2005	12/2008
10396	THUILLEZ	Christian	16/05/2010	EC-CO	LABORATOIRE NOVARTIS	Etude clinique - Exforge	Co-investigateur	01/2007	12/2009
10396	THUILLEZ	Christian	16/05/2010	EC-CO	LABORATOIRE SERVIER	Etude clinique - Preterax	Expérimentateur non principal	01/2004	12/2005
10396	THUILLEZ	Christian	16/05/2010	EC-CO	LABORATOIRE SOLVAY	Etude pré-clinique - Inhibiteur ECE - NEP	Co-investigateur	01/2004	12/2006
10396	THUILLEZ	Christian	16/05/2010	EC-CO	LABORATOIRE SOLVAY	Etude pré-clinique - Inhibiteur ECE - NEP	Co-investigateur	01/2007	12/2008
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE SERVIER	- International Society of Hypertension, Pekin, Chine,□□- Ivabradine	rémunération personnelle	01/2007	12/2007
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE SERVIER	- International Society for Heart Research, Bologne, Italie,□□- Ivabradine	rémunération personnelle	01/2007	12/2007
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NOVARTIS	- Collège National des Cardiologues, Marseille, France,□□- Aliskiren	rémunération personnelle	01/2007	12/2007

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE SERVIER	- Journées européennes de Cardiologie, Paris,□□- Preterax	rémunération personnelle	01/2008	12/2008
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NEGMA	- Cardiovascular Clinical Trialists, Cannes, France,□□- Nebilox	rémunération personnelle	01/2008	12/2008
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NEGMA	- Société Française d'Hypertension Artérielle,□□- Nebilox	rémunération personnelle	01/2008	12/2008
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE SERVIER	- Société Hongroise d'Hypertension Artérielle, Budapest, Hongrie,□□- Preterax	rémunération personnelle	01/2008	12/2008
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE SERVIER	- Austrian Congres of Hypertension, Autriche,□□- Fludex	rémunération personnelle	01/2008	12/2008
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NOVARTIS	- European Society of Hypertension, Milan, Italie,□□- Aliskiren	rémunération personnelle	01/2009	12/2009
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NOVARTIS	- European Society of Cardiology, Barcelone, Espagne,□□- Exforge	rémunération personnelle	01/2009	12/2009
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NEGMA	- Société Française d'Hypertension Artérielle, Paris,□□- Nebivolol	rémunération personnelle	01/2009	12/2009
10396	THUILLEZ	Christian	16/05/2010	CF-INT	LABORATOIRE NOVARTIS ET MENARINI	- Journées Européennes de Cardiologie, Paris,□□- Aliskiren□□- Ranolazine	rémunération personnelle	01/2010	12/2010
10396	THUILLEZ	Christian	16/05/2010	IP-AC	LABORATOIRE MENARINI	Groupe de Travail (2 réunions) - Ranexa	rémunération personnelle	01/2008	12/2010
10396	THUILLEZ	Christian	16/05/2010	VB	LABORATOIRE SERVIER	Achat IRM	Université de Rouen	01/2006	12/2009
10396	THUILLEZ	Christian	22/09/2005	IP-EC	SERVIER	Ivabradine		01/2002	12/2005
10396	THUILLEZ	Christian	22/09/2005	IP-EC	ROCHE	Cellcept		01/2005	12/2005
10396	THUILLEZ	Christian	22/09/2005	IP-EC	SOLVAY	Inhibiteurs des peptidases		01/2004	12/2005
10396	THUILLEZ	Christian	22/09/2005	IP-EC	NOVARTIS	Inhibiteurs des peptidases		01/2002	12/2005
10396	THUILLEZ	Christian	22/09/2005	IP-CF	KNOLL, PFIZER, SERVIER	Pharmacologie			
10396	THUILLEZ	Christian	22/09/2005	VB	NOVARTIS, SERVIER, SOLVAY	INSERM			
10396	THUILLEZ	Christian	22/09/2005	VB	ROCHE	CHU			
10396	THUILLEZ	Christian	22/09/2005	(Autre)	MERCK SHARP & DOHME, PFIZER	Jury de bourses			
10396	THUILLEZ	Christian	04/05/2000	IP-EC	SERVIER				
10396	THUILLEZ	Christian	04/05/2000	IP-EC	KNOLL				
10396	THUILLEZ	Christian	04/05/2000	VB	BRISTOL MYERS SQUIBB				
10396	THUILLEZ	Christian	04/05/2000	IP-AC	LAFON				
10396	THUILLEZ	Christian	04/05/2000	IP-CF	SERVIER, GLAXO WELLCOME, BRISTOL MYERS SQUIBB, ASTRA, LIPHA	Ponctuellement			
10396	THUILLEZ	Christian	04/05/2000	VB		Contrats de Recherche avec versements au CHU			
10396	THUILLEZ	Christian	28/02/2000	IP-EC	SERVIER				
10396	THUILLEZ	Christian	28/02/2000	IP-RE	SCHWARZ PHARMA	Il y a 2 ans			
10396	THUILLEZ	Christian	28/02/2000	IP-CF	SERVIER, GLAXO WELLCOME, BRISTOL MYERS SQUIBB, ASTRA, LIPHA	Ponctuellement			
10396	THUILLEZ	Christian	28/02/2000	VB		Contrats de recherche avec versements au CHU			
10396	THUILLEZ	Christian	28/02/2000	IP-EC	KNOLL				
10396	THUILLEZ	Christian	28/02/2000	IP-AC	LAFON				
10396	THUILLEZ	Christian	02/02/2000	IP-EC	SERVIER				
10396	THUILLEZ	Christian	02/02/2000	IP-EC	KNOLL				
10396	THUILLEZ	Christian	02/02/2000	IP-RE	SCHWARZ PHARMA	(1998)			
10396	THUILLEZ	Christian	02/02/2000	IP-CF	SERVIER				
10396	THUILLEZ	Christian	02/02/2000	IP-CF	GLAXO WELLCOME				
10396	THUILLEZ	Christian	02/02/2000	IP-AUT	BRISTOL-MYERS-SQUIBB				
10396	THUILLEZ	Christian	02/02/2000	IP-CF	ASTRA				
10396	THUILLEZ	Christian	02/02/2000	VB		Contrats de recherche avec versements au CHU			
10396	THUILLEZ	Christian	02/02/2000	IP-AC	LAFON				
10396	THUILLEZ	Christian	01/01/1998	LD	L. Lafon				
10396	THUILLEZ	Christian	01/01/1998	IP-AUT	Servier				
10396	THUILLEZ	Christian	01/01/1998	IP-AUT	Synthélabo				
10396	THUILLEZ	Christian	01/01/1998	IP-AUT	Roche				
10396	THUILLEZ	Christian	01/01/1998	IP-AUT	BMS				
10396	THUILLEZ	Christian	01/01/1998	IP-AUT	Schwarz				
10396	THUILLEZ	Christian	01/01/1998	IP-AUT	Roussel				
10396	THUILLEZ	Christian	01/01/1998	VB	Servier				
10396	THUILLEZ	Christian	01/01/1998	VB	Roche				
10396	THUILLEZ	Christian	01/01/1998	VB	Synthélabo				
10397	THUILLIER	Alain	27/01/2004	IP-AUT	ASTA MEDICA	Prise en charge d'une partie des frais de participation à l'ASHP - Congrés dec. 2003			
10397	THUILLIER	Alain	27/01/2004	PAR	SCIENCE UNION	Epouse salariée - Groupe de recherche SERVIER (jusqu'au 01/04/04)			
10397	THUILLIER	Alain	04/10/2001	IP-CF	SERVIER	Conférences Moissan - Formation pour préparation au concours de Praticiens Pharmaciens des Hôpitaux			
10397	THUILLIER	Alain	04/10/2001	IP-AUT	ASTA MEDICA	Prise en charge d'une partie des frais de participation à l'ASHP - Décembre 1999 - Décembre 2000			
10397	THUILLIER	Alain	04/10/2001	PAR	SCIENCE UNION (Groupe de Recherche Servier)	Epouse			
10397	THUILLIER	Alain	10/05/1999	IP-CF	SERVIER	Conférences Moissan (formation pour préparation au concours de Praticien des hopitaux - Phamaciens)			
10397	THUILLIER	Alain	10/05/1999	IP-AUT	ROCHE	Prise en charge d'une partie des frais de participation à l'ASHP (USA, 1998)			
10397	THUILLIER	Alain	10/05/1999	PAR	SCIENCE UNION (Groupe de recherche SERVIER)	Epouse salariée			
10397	THUILLIER	Alain	01/01/1999	IP-AUT	ASCO BRISTOL MYERS SQUIBB	Lors d'un congrès par an, participation d'un laboratoire à la prise en charge des frais. 1995			
10397	THUILLIER	Alain	01/01/1999	IP-AUT	ASCO SMITHKLINE BEECHAM	1996			
10397	THUILLIER	Alain	01/01/1999	IP-AUT	Ashp ROCHE	1997 :			
10397	THUILLIER	Alain	01/01/1999	IP-AUT	ASCO BRISTOL MYERS SQUIBB	1997 :			
10397	THUILLIER	Alain	01/01/1999	IP-AUT	ASCO SMITHKLINE BEECHAM	1998			
10397	THUILLIER	Alain	01/01/1999	VB	SERVIER	Actions de formation, préparation au concours de Pratical, Servier pour une association SETOP (Etudes Thr	SETOP, (Etudes Thérapeutiques Odonto-Pharmacologiques)		
10397	THUILLIER	Alain	01/01/1999	PAR	Science Union/Groupe recherche SERVIER	Epouse salariée			
10397	THUILLIER	Alain	01/01/1998	IP-AUT	Roche		Participation d'un laboratoire à la prise en charge des frais d'un congrès annuel		
10397	THUILLIER	Alain	01/01/1998	IP-AUT	BMS		Participation d'un laboratoire à la prise en charge des frais d'un congrès annuel		
10397	THUILLIER	Alain	01/01/1998	IP-AUT	SKB		Participation d'un laboratoire à la prise en charge des frais d'un congrès annuel		
10397	THUILLIER	Alain	01/01/1998	PAR	Epouse salariée Science Union : Groupe Recherche Servier				
60873	THULLIEZ	Philippe	04/01/2007	LD-AR	ABBOTT DIAGNOSTIC	réunions périodiques d'une journée (Relais) d'un groupe d'experts sur les sérodiagnostics de toxoplasmose,	aucune rémunération	07/2004	07/2004
60873	THULLIEZ	Philippe	04/01/2007	EC-INV	BIOMERIEUX	évaluation des performances du réactif VIDAS toxo IgG IV avidité	investigateur principal	05/2004	06/2004

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60873	THULLIEZ	Philippe	04/01/2007	EC-INV	BIOMERIEUX	évaluation des performances des réactifs VIDIA IgG et toxo IgM	Investigateur principal	09/2005	11/2005
60873	THULLIEZ	Philippe	04/01/2007	EC-CO	ORTHO CLINICAL DIAGNOSTICS	Evaluation des performances des réactifs sur le système VITROS ECI : Rubéole IgG	co-investigateur	09/2004	09/2004
60873	THULLIEZ	Philippe	04/01/2007	EC-CO	ROCHE	évaluation des performances du réactif Elecsys Toxo IgG	collaborateur à l'étude	07/2006	11/2006
60873	THULLIEZ	Philippe	04/01/2007	IP-AC	ROCHE	groupe de réflextion : analyse des performances des réactifs Toxo IgG et IgM sur Elecsys	aucune rémunération	11/2006	
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	ABBOTT DIAGNOSTIC	Paris - Abbott Diagnostic et les nouveaux enjeux de la Biologie Médicale / Toxoplasmose et femmes enceint	rémunération personnelle	12/2004	12/2004
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	BIOMERIEUX	Bourg St Maurice - formation interne / Epidémiologie et diagnostic de la toxoplasmose	aucune rémunération	01/2006	01/2006
60873	THULLIEZ	Philippe	04/01/2007	LD-AR	ABBOTT DIAGNOSTIC	Réunions périodiques d'une journée (Relais) d'un groupe d'experts sur les sérodiagnostics de toxoplasmose	aucune rémunération	12/2004	12/2004
60873	THULLIEZ	Philippe	04/01/2007	LD-AR	ABBOTT DIAGNOSTIC	Réunions périodiques d'une journée (Relais) d'un groupe d'experts sur les sérodiagnostics de toxoplasmose	aucune rémunération	05/2005	05/2005
60873	THULLIEZ	Philippe	04/01/2007	LD-AR	ABBOTT DIAGNOSTIC	Réunions périodiques d'une journée (Relais) d'un groupe d'experts sur les sérodiagnostics de toxoplasmose	aucune rémunération	01/2006	01/2006
60873	THULLIEZ	Philippe	04/01/2007	LD-AR	ABBOTT DIAGNOSTIC	Réunions périodiques d'une journée (Relais) d'un groupe d'expers sur les sérodiagnostics de toxoplasmose,	aucune rémunération	06/2006	06/2006
60873	THULLIEZ	Philippe	04/01/2007	LD-AR	ABBOTT DIAGNOSTIC	Réunions périodiques d'une journée (Relais) d'un groupe d'experts sur les sérodiagnostics de toxoplasmose	aucune rémunération	12/2006	12/2006
60873	THULLIEZ	Philippe	04/01/2007	EC-CO	ORTHO CLINICAL DIAGNOSTICS	Evaluation des performances des réactifs sur le système VITROS ECI : Toxoplasmose IgG	co-investigateur	11/2004	11/2004
60873	THULLIEZ	Philippe	04/01/2007	EC-CO	ORTHO CLINICAL DIAGNOSTICS	Evulation des performances des réactifs sur le système VITROS ECI : CMV IgG	co-investigateur	12/2004	12/2004
60873	THULLIEZ	Philippe	04/01/2007	EC-CO	ORTHO CLINICAL DIAGNOSTICS	Evaluation des performances des réactifs sur le système VITROS ECI : Rubéole IgM	co-investigateur	04/2005	04/2005
60873	THULLIEZ	Philippe	04/01/2007	EC-CO	ORTHO CLINICAL DIAGNOSTICS	Evaluation des performances des réactifs sur le système VITROS ECI : Toxoplasmose IgM	co-investigateur	12/2006	12/2006
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	BIOMERIEUX	Annecy - journées de formation / Surveillance sérologique de la femme enceinte	rémunération personnelle	09/2005	09/2005
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	BIOMERIEUX	Annecy - journées de formation / Surveillance sérologique de la femme enceinte	rémunération personnelle	05/2006	05/2006
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	BIOMERIEUX	Chamonix - journées d'hiver de biologie hospitalière / Diagnostic de la toxoplasmose chez la femme enceint	aucune rémuneration	03/2006	03/2006
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	BIOMERIEUX	Nice - 16th ECCMID / performance évaluation of the VIDIA toxoplasmosis IgG and IgM assays	aucune rémunération	04/2006	04/2006
60873	THULLIEZ	Philippe	04/01/2007	CF-INT	BIOMERIEUX	St Malo - 35e colloque national des biologistes des hôpitaux / Toxoplasmose et grossesse : le point en 2006	aucune rémunération	09/2006	09/2006
60873	THULLIEZ	Philippe	14/10/2005	IP-RE	BIOMERIEUX, ABBOTT	Evaluation de réactifs sérologiques pour la toxoplasmose			
60873	THULLIEZ	Philippe	14/10/2005	IP-CF	BIOMERIEUX	Journée de formation : sérologie, surveillance femme enceinte			
60873	THULLIEZ	Philippe	04/05/2000	IP-EC	SERVIER				
60873	THULLIEZ	Philippe	04/05/2000	IP-EC	KNOLL				
60873	THULLIEZ	Philippe	04/05/2000	IP-EC	BRISTOL MYERS SQUIBB				
60873	THULLIEZ	Philippe	04/05/2000	IP-AC	LAFON				
60873	THULLIEZ	Philippe	04/05/2000	IP-CF	SERVIER				
60873	THULLIEZ	Philippe	04/05/2000	IP-CF	GLAXO WELLCOME				
60873	THULLIEZ	Philippe	04/05/2000	IP-CF	BRISTOL MYERS SQUIBB				
60873	THULLIEZ	Philippe	04/05/2000	IP-CF	ASTRA				
60873	THULLIEZ	Philippe	04/05/2000	IP-CF	LIPHA				
60873	THULLIEZ	Philippe	04/05/2000	VB		Contrats de recherche avec versements au CHU			
10398	TIGNOL	Jean	28/12/2005	IP-AC	PFIZER	Zoloft - consultant scientifique (2003)			
10398	TIGNOL	Jean	28/12/2005	IP-AC	LILLY	Cialis - consultant scientifique (2002)			
10398	TIGNOL	Jean	28/12/2005	IP-AC	GSK	Deroxat - consultant scientifique (2001)			
10398	TIGNOL	Jean	28/12/2005	EC-INV	BOEHRINGER INGELHEIM	Flibanserine (2004)			
10398	TIGNOL	Jean	28/12/2005	EC-INV	AKZO NOBEL	Org 43517 (2001)			
10398	TIGNOL	Jean	28/12/2005	EC-INV	LILLY	Zyprexa IM (2001)			
10398	TIGNOL	Jean	28/12/2005	EC-INV	PFIZER	Viagra (2000)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	WYETH	Effexor - exposé scientifique (2004 et 2005)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	SANOFI	Depakote - exposé scientifique (2005)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	PFIZER	Zoloft - exposé scientifique (2005)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	VEDIM	Atarax - exposé scientifique (2004)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	LILLY	Zyprexa - exposé scientifique (2004)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	GSK	Deroxat - exposé scientifique (2002 et 2004)			
10398	TIGNOL	Jean	28/12/2005	CF-INT	PFIZER	Viagra - compte-rendu d'étude (2001)			
10398	TIGNOL	Jean	28/12/2005	IP-AUT	PFIZER	Zoloft - consultant scientifique (2002)			
10398	TIGNOL	Jean	28/12/2005	CF-AUD	ORGANON	Congrès annuel de l'APA - Philadelphie (2002)			
10398	TIGNOL	Jean	28/12/2005	CF-AUD	LILLY	Congrès de l'encéphale - Paris (2006)			
10398	TIGNOL	Jean	28/12/2005	VB	LILLY	Prozac, Zyprexa	Université Victor Segalen - Bordeaux - Au titre de coordonnteur du DES de psychiatrie à l'Université Victor Segalen de Bordeaux, organisation depuis 2000 de journées inter-régionales annuelles dites journées Aquitaine-Languedoc-Pyrénées (JALP) pour les in		
10398	TIGNOL	Jean	15/07/2004	IP-EC	PFIZER, ORGANON, LILLY	Coordonateur national d'essais cliniques			
10398	TIGNOL	Jean	15/07/2004	IP-AC	BOEHRINGER, INGELHEIM,PFEIZER, GSK, LILLY, JANSSEN,LUNDBECK,GSK, LILLY, PFIZER, ARDIX	Conseils sur l'organisation d'études,de docments pédagogiques, de réunions ou de colloques			
10398	TIGNOL	Jean	15/07/2004	IP-CF	SANOFI SYNTHELABO, BIOCODEX	Troubles anxieux, troubles de l'humeur, troubles sexuels, psychothérapies, psychopharmacologie			
10398	TIGNOL	Jean	15/07/2004	VB	GSK	Centre hospitalier Charles PERRENS			
10398	TIGNOL	Jean	15/07/2004	VB	LUNDBECK	Association Française des Troubles Anxieux (AFTA)			
10398	TIGNOL	Jean	15/07/2004	(Autre)	LILLY	Jury bourse de recherche internationale			
10398	TIGNOL	Jean	04/07/2000	IP-EC	LILLY	Essai olonzopine IM			
10398	TIGNOL	Jean	04/07/2000	IP-EC	SMITHKLINE BEECHAM	Subvention recherche / BDD			
10398	TIGNOL	Jean	04/07/2000	IP-EC	JANSSEN	Etude RIS FRAP			
10398	TIGNOL	Jean	04/07/2000	IP-EC	PFIZER	Etude VIAGRA / Déprimés			
10398	TIGNOL	Jean	04/07/2000	IP-EC	PHARMACIA UPJOHN	Etude reboxotine personnes âgées			
10398	TIGNOL	Jean	04/07/2000	IP-CF	SCHERING PLOUGH	Présidence colloques, congrès			
10398	TIGNOL	Jean	04/07/2000	IP-CF	LILLY	Formation internes DES et médecins			
10398	TIGNOL	Jean	04/07/2000	IP-CF	SMITHKLINE BEECHAM	Rédactions livres			
10398	TIGNOL	Jean	04/07/2000	IP-CF	PFIZER	Formation médecins			
10398	TIGNOL	Jean	04/07/2000	IP-CF	UBC PHARMA-VEDIM	Formation psychiatres et médecins			
10398	TIGNOL	Jean	04/07/2000	IP-CF	SANOFI SYNTHELABO	Conférences			
10398	TIGNOL	Jean	04/07/2000	VB	LILLY	Association RP3			
10398	TIGNOL	Jean	04/07/2000	VB	SMITHKLINE BEECHAM	Subvention recherche / BDD - Association RP3			
10398	TIGNOL	Jean	04/07/2000	IP-AUT	ORGANON	Association RP3 (/ mère)			
10398	TIGNOL	Jean	01/01/1999	IP-EC	Servier				
10398	TIGNOL	Jean	01/01/1999	IP-EC	Lilly				

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Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10398	TIGNOL	Jean	01/01/1999	IP-AC	SmithKline Beecham				
10398	TIGNOL	Jean	01/01/1999	IP-AC	Pfizer				
10398	TIGNOL	Jean	01/01/1999	IP-CF	Lilly				
10398	TIGNOL	Jean	01/01/1999	IP-CF	Janssen				
10398	TIGNOL	Jean	01/01/1999	IP-CF	Servier				
10398	TIGNOL	Jean	01/01/1999	VB	Lilly				
10398	TIGNOL	Jean	01/01/1999	VB	Schering-Plough				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Pierre Fabre				
10398	TIGNOL	Jean	01/01/1998	IP-AUT					
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Servier				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Dupont Pharma				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Roxane				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Roche				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Prodefarma				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	RPR				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Lilly				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	BMS				
10398	TIGNOL	Jean	01/01/1998	IP-AUT	Sanofi				
10398	TIGNOL	Jean	01/01/1998	VB	Schering Plough				
10398	TIGNOL	Jean	01/01/1998	VB	Lilly				
10398	TIGNOL	Jean	01/01/1998	VB	Roche				
10398	TIGNOL	Jean	01/01/1998	VB	Sanofi				
10398	TIGNOL	Jean	01/01/1998	VB	Ciba Geigy				
10398	TIGNOL	Jean	01/01/1998	VB	Dupont Pharma				
10398	TIGNOL	Jean	01/01/1998	VB	GSK	Centre hospitalier Charles PERRENS : Association Française des Troubles Anxieux (AFTA)			
64295	TILLEMENT	Jean-Paul	20/11/2010	LD-AR	GROUPE SERVIER	Consultant	rémunération personnelle	09/2010	09/2011
64295	TILLEMENT	Jean-Paul	20/11/2010	EC-CO	GROUPE SERVIER	Etude de la trimétazidine dans les liquides de conservation des greffes , rôle : conseil (en cours)		01/2008	
64295	TILLEMENT	Jean-Paul	20/11/2010	CF-INT	INSTITUT SERVIER	Colloque pharmacogénétique et pharmacodynamique 18 novembre 2010 : maison de la chimie - Paris	aucune rémunération	11/2010	11/2010
64295	TILLEMENT	Jean-Paul	20/12/2009	IP-AC	AUCUNE ACTUELLEMENT	fixation plasmatique des médicaments□□maladies mitochondriales	Aucune rémunération		
64295	TILLEMENT	Jean-Paul	20/12/2009	LD-AR	ADIR (GROUPE SERVIER)	trimétazidine, ajouté aux liquides de conservation d'organes	Rémunération personnelle	10/2007	
62492	TIMSIT	José	22/10/2002	VB	AVENTIS	Essai clinique : Participation à l'essai multicentrique français HOE 901/4024 (ALADIN) comparant l'efficacité de la LANTUS selon l'horaire d'administration chez des diabétiques			
62492	TIMSIT	José	22/10/2002	VB	LILLY France	Activité de conseil : Participation à un advisory board en novembre 2001 (Association FRED)			
62492	TIMSIT	José	22/10/2002	VB	NOVO NORDISK	Participation à organisation des 3ème et 4ème rencontres des internes en endocrinologie en 2001 et 2002 (Association FRED)			
62492	TIMSIT	José	22/10/2002	VB	SERVIER	Participation à l'enquête multicentrique Pré-di-re (hypertension artérielle et diabète de type 2) (Association FRED)			
65155	TISSIER	Renaud	30/06/2008	LD-AR	SOGEVAL (LABORATOIRE PHARMACEUTIQUE VETERINAIRE)	Consultance pour le développement d'un produit destiné à usage vétérinaire	rémunération personnelle	01/2007	12/2008
65155	TISSIER	Renaud	30/06/2008	EC-CO	SERVIER	Participation à deux études pré-cliniques	expérimentateur non principal	01/2005	12/2008
65155	TISSIER	Renaud	30/06/2008	EC-CO	PIERRE FABRE	Participation à une étude pré-clinique	expérimentateur non principal	01/2005	12/2006
65155	TISSIER	Renaud	30/06/2008	IP-AC	SOGEVAL (LABORATOIRE PHARMACEUTIQUE VETERINAIRE)	Consultance pour le développement d'un produit destiné à usage vétérinaire	rémunération personnelle	01/2007	12/2008
65155	TISSIER	Renaud	30/06/2008	CF-AUD	SERVIER	Invitation comme participant au congrès de l'international Society for Heart Research - Bologne		06/2007	06/2007
65155	TISSIER	Renaud	30/06/2008	CF-AUD	SERVIER	Invitation comme participant à l'European Society of Cardiology - Vienne		09/2007	09/2007
65155	TISSIER	Renaud	30/06/2008	CF-AUD	SERVIER	Invitation comme participant à l'European Society of Cardiology - Munich		09/2008	09/2008
65155	TISSIER	Renaud	30/06/2008	PAR	CEPHALON	Responsable BPC Europe	conjointe	01/2006	
10403	UNGER	Philippe	23/12/2000	IF	EURAXI S.A.	Actionnaire			
10403	UNGER	Philippe	23/12/2000	IF	MONARC S.A.	Actionnaire			
10403	UNGER	Philippe	23/12/2000	LD	EURAXI S.A.	Salarié			
10403	UNGER	Philippe	23/12/2000	IP-CF	Institut for International Research	Recrutement des patients et SMO			
10403	UNGER	Philippe	01/01/1999	IF	Euraxi, SA				
10403	UNGER	Philippe	01/01/1999	IF	Monarc SA				
10403	UNGER	Philippe	01/01/1999	LD	Salarié Euraxi				
10403	UNGER	Philippe	01/01/1999	LD	Salarié Monarc				
10403	UNGER	Philippe	01/01/1999	IP-EC	Pfizer				
10403	UNGER	Philippe	01/01/1999	IP-EC	Lederlé				
10403	UNGER	Philippe	01/01/1999	IP-EC	UCB Pharma				
10403	UNGER	Philippe	01/01/1999	IP-EC	Roussel				
10403	UNGER	Philippe	01/01/1999	IP-EC	Boehringer				
10403	UNGER	Philippe	01/01/1999	IP-EC	Takéda				
10403	UNGER	Philippe	01/01/1999	IP-EC	Servier				
10403	UNGER	Philippe	01/01/1999	IP-EC	Novartis				
10403	UNGER	Philippe	01/01/1999	IP-EC	Sanofi				
10403	UNGER	Philippe	01/01/1999	IP-EC	Pierre Fabre Médicaments				
10403	UNGER	Philippe	01/01/1999	IP-EC	Bayer Pharma				
10403	UNGER	Philippe	01/01/1999	IP-EC	Smithkline Beecham				
10403	UNGER	Philippe	01/01/1999	IP-EC	Synthélabo				
10403	UNGER	Philippe	01/01/1999	IP-EC	Yamanouchi Pharma				
10403	UNGER	Philippe	01/01/1999	IP-EC	Innothéra				
10403	UNGER	Philippe	01/01/1999	IP-EC	Astra France				
10403	UNGER	Philippe	01/01/1998	IF	Société Euraxi S.A.				
10403	UNGER	Philippe	01/01/1998	LD	Société Euraxi S.A.				
10404	VALLEUR	Marc	09/04/2001	VB	IRIS SERVIER	Dons Association Marmottan			
10404	VALLEUR	Marc	09/04/2001	VB	PIERRE FABRE	Dons Association Marmottan			
10404	VALLEUR	Marc	09/07/1999	Néant					
10404	VALLEUR	Marc	01/01/1999	Néant					
60132	VASSAL	Gilles	28/03/2009	EC-INV	RHONE POULENC RORER	Phase II pédiatrie - Irinotecan	Investigateur principal	01/1999	12/2002
60132	VASSAL	Gilles	28/03/2009	EC-INV	SANOFI	Phase I pédiatrie - Oxaliplatine	Investigateur principal	01/2001	12/2003
60132	VASSAL	Gilles	28/03/2009	EC-INV	PIERRE FABRE	Etude pharmacologique : busilvex	Investigateur principal	01/2001	12/2006
60132	VASSAL	Gilles	28/03/2009	EC-INV	PIERRE FABRE	Etude toxicologique : Busilvex	expérimentateur	01/2006	
60132	VASSAL	Gilles	28/03/2009	EC-INV	ROCHE	Etude phase II R1507	Investigateur principal	01/2007	12/2009
60132	VASSAL	Gilles	28/03/2009	EC-CO	SANOFI AVENTIS	Etude préclinique : anticorps anti IFG1R	Co investigateur	01/2005	12/2007
60132	VASSAL	Gilles	28/03/2009	EC-CO	ASTRA ZENECA	Etude préclinique : GEFITINIB	Co investigateur	01/2003	12/2005
60132	VASSAL	Gilles	28/03/2009	EC-CO	NOVARTIS	Etude préclinique GLIVEC	Co investigateur	01/2003	12/2005

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60132	VASSAL	Gilles	28/03/2009	IP-AC	ROCHE	Conseil - Bevacizumab, anti IGF1R, Erlotinib, Trastuzumab	Rémunération institution	01/2006	
60132	VASSAL	Gilles	28/03/2009	IP-AC	SANOFI AVENTIS	Conseil - anti igf1r	rémunération institution	01/2006	12/2006
60132	VASSAL	Gilles	28/03/2009	IP-AC	PHARMAMAR	Conseil - Aplidine - ET 743	Rémunération personnelle	01/2007	
60132	VASSAL	Gilles	28/03/2009	IP-AC	NOVARTIS	Conseil - Zometa	rémunération institution	01/2007	12/2008
60132	VASSAL	Gilles	28/03/2009	IP-AC	LILLY	Conseil - Gemcitabine - alimta	aucune rémunération	01/2005	
60132	VASSAL	Gilles	28/03/2009	IP-AC	PFIZER	Conseil - Irinotecan	Aucune rémunération	01/2006	12/2006
60132	VASSAL	Gilles	28/03/2009	IP-AC	PIERRE FABRE	Conseil - Busulfan	Aucune rémunération	01/2007	12/2007
60132	VASSAL	Gilles	28/03/2009	IP-AC	SANOFI AVENTIS	Conseil - AVE 1582	Aucune rémunération	01/2008	12/2008
60132	VASSAL	Gilles	28/03/2009	CF-INT	PIERRE FABRE	Dusseldorf - réunion Greffeurs - Pharmacologie du Busulfan	Rémunération institution	01/2007	01/2007
60132	VASSAL	Gilles	28/03/2009	CF-INT	PIERRE FABRE	Hambourg EBMT - Pharmacologie Busilvex	Rémunération personnelle	01/2006	01/2006
60132	VASSAL	Gilles	28/03/2009	CF-INT	PIERRE FABRE	Londres - réunions greffeurs - pharmacologie du Busulfan	rémunération personnelle	01/2005	01/2005
60132	VASSAL	Gilles	28/03/2009	CF-INT	PIERRE FABRE	Geneve EBMT - pharmacologie Busilvex	rémunération personnelle	01/2004	01/2004
60132	VASSAL	Gilles	28/03/2009	CF-INT	SANOFI AVENTIS	Vancouver - SIOPE : chimiothérapie des cancers pédiatriques	rémunération personnelle	01/2005	01/2005
60132	VASSAL	Gilles	28/03/2009	CF-AUD	PFIZER	Chicago - asco		01/2008	01/2008
60132	VASSAL	Gilles	28/03/2009	CF-AUD	ROCHE	SAN DIEGO - AACR		01/2008	01/2008
60132	VASSAL	Gilles	28/03/2009	CF-AUD	PFIZER	CHICAGO - ASCO		01/2007	01/2007
60132	VASSAL	Gilles	28/03/2009	CF-AUD	ROCHE	LOS ANGELES AACR		01/2007	01/2007
60132	VASSAL	Gilles	28/03/2009	CF-AUD	LILLY	ATLANTA - ASCO		01/2006	01/2006
60132	VASSAL	Gilles	28/03/2009	CF-AUD	ROCHE	WASHINGTON - AACR		01/2006	01/2006
60132	VASSAL	Gilles	28/03/2009	CF-AUD	PIERRE FABRE	ORLANDO AACR		01/2005	01/2005
60132	VASSAL	Gilles	28/03/2009	VB	ASTRA ZENECA, SANOFI AVENTIS, BMS, GLAXOSMITHKLINE, NOVARTIS, ROCHE, PHARMAMAR, AMGEN, MERCK, PFIZER, J&J, SCHERING PLOUGH, BAYER, MGI PHARMA, WYETH, LILLY, SERVIER	Etudes cliniques partenariats pour projets promus par l'IGR et partenariats pour projets précliniques et MTA	Institut de cancérologie Gustave Roussy	01/2005	
60132	VASSAL	Gilles	13/09/2007	EC-INV	RHONE POULENC RORER	Phase II pédiatrie - IRINOTECAN	investigateur principal	01/1999	12/2002
60132	VASSAL	Gilles	13/09/2007	EC-INV	SANOFI	Phase I pédiatrie : OXALIPLATINE	investigateur principal	01/2001	12/2003
60132	VASSAL	Gilles	13/09/2007	EC-INV	PIERRE FABRE	Etude pharmacologique : BUSILVEX	investigateur principal	01/2001	12/2006
60132	VASSAL	Gilles	13/09/2007	EC-INV	PIERRE FABRE	Etude toxicologique : BUSILVEX (en cours)	expérimentateur	01/2006	
60132	VASSAL	Gilles	13/09/2007	EC-CO	SANOFI AVENTIS	Etude pré-clinique : anticorps anti IFGIR	co-expérimentateur	01/2005	12/2007
60132	VASSAL	Gilles	13/09/2007	EC-CO	ASTRAZENECA	Etude pré-clinique : GEFITINIB	co-expérimentateur	01/2003	12/2005
60132	VASSAL	Gilles	13/09/2007	EC-CO	NOVARTIS	Etude pré-clinique : GLIVEC	co-expérimentateur	01/2003	12/2005
60132	VASSAL	Gilles	13/09/2007	IP-AC	ROCHE	Conseil : BEVACIZUMAB - ANTI IGF-IR - ERLOTINIB - TRASTUZUMAB (en cours)	rémunération institution	01/2006	
60132	VASSAL	Gilles	13/09/2007	IP-AC	SANOFI AVENTIS	CONSEIL ANTI IGFIR	rémunération institution	01/2006	12/2006
60132	VASSAL	Gilles	13/09/2007	IP-AC	PHARMAMAR	conseil APLIDINE	rémunération personnelle	01/2007	12/2007
60132	VASSAL	Gilles	13/09/2007	IP-AC	NOVARTIS	conseil ZOMETA (en cours)	rémunération institution)	01/2007	
60132	VASSAL	Gilles	13/09/2007	IP-AC	LILLY	conseil GEMCITABINE	aucune rémunération	01/2005	12/2006
60132	VASSAL	Gilles	13/09/2007	IP-AC	PFIZER	conseil IRINOTECAN	aucune rémunération	01/2006	12/2006
60132	VASSAL	Gilles	13/09/2007	CF-INT	PIERRE FABRE	DUSSELDORF - REUNION GREFFEURS - PHARMACOLOGIE DU BUSULFAN	rémunération institution	01/2007	12/2007
60132	VASSAL	Gilles	13/09/2007	CF-INT	PIERRE FABRE	Londres : réunion greffeurs - pharmacologie du BUSULFAN	rémunération personnelle	01/2006	12/2006
60132	VASSAL	Gilles	13/09/2007	CF-INT	PIERRE FABRE	Hambourg EBMT : pharmacologie BUSILVEX	rémunération personnelle	01/2006	12/2006
60132	VASSAL	Gilles	13/09/2007	CF-INT	PIERRE FABRE	Genève EBMT : pharmacologie BUSILVEX	rémunération personnelle	01/2004	12/2004
60132	VASSAL	Gilles	13/09/2007	CF-INT	SANOFI AVENTIS	Vancover - SIOPE : chimiothérapie des cancers pédiatriques	rémunération personnelle	01/2005	12/2005
60132	VASSAL	Gilles	13/09/2007	CF-AUD	PFIZER	Chicago : ASCO		01/2007	12/2007
60132	VASSAL	Gilles	13/09/2007	CF-AUD	ROCHE	Los Angeles : AACR		01/2007	12/2007
60132	VASSAL	Gilles	13/09/2007	CF-AUD	LILLY	Atlanta : ASCO		01/2006	12/2006
60132	VASSAL	Gilles	13/09/2007	CF-AUD		Washington : AACR		01/2006	12/2006
60132	VASSAL	Gilles	13/09/2007	CF-AUD	PIERRE FABRE	Orlando : AACR		01/2005	12/2005
60132	VASSAL	Gilles	13/09/2007	VB	ASTRAZENECA - SANOFI AVENTIS - BRISTOL MYERS SQUIBB - GLAXOSMITHKLINE - NOVARTIS - ROCHE - PHARMAMAR - AMGEN - MERCK - PFIZER - JOHNSON & JOHNSON - SHERING PLOUGH - BAYER - MGI PHARMA - WYETH - LILLY - SERVIER	Etudes cliniques, partenariats pour projets cliniques promus par l'IGR et partenariats pour projets précliniques	Institut de cancérologie Gustave Roussy	01/2005	
60132	VASSAL	Gilles	27/12/2000	VB	AVENTIS	IGR			
60132	VASSAL	Gilles	27/12/2000	VB	PIERRE FABRE ONCOLOGIE	IGR			
60132	VASSAL	Gilles	27/12/2000	VB	IRI SERVIER	IGR, CNRS			
60132	VASSAL	Gilles	27/12/2000	VB	SCHERING-PLOUGH	IGR			
60132	VASSAL	Gilles	27/12/2000	VB	NOVARTIS	IGR			
62077	VERGES	Bruno	31/01/2008	EC-INV	ASTRA ZENECA	Rosuvastatine	Investigateur principal	01/2005	12/2006
62077	VERGES	Bruno	31/01/2008	EC-CO	SANOFI AVENTIS	RIMONABANT	investigateur principal	09/2007	
62077	VERGES	Bruno	31/01/2008	CF-INT	SANOFI AVENTIS	3 ème international summit on cardiometabolic risk associated with abdominal obesity (/ Rimonabant / Prag	rémunération personnelle	10/2007	10/2007
62077	VERGES	Bruno	31/01/2008	CF-INT	TAKEDA	Diabets Master Class " Maintaining metabolic control in T2DM, treating to target - Pioglitazone / Vienne		05/2007	05/2007
62077	VERGES	Bruno	07/02/2006	EC-INV	NOVO-NORDISK	insuline Levemir (en cours)	Investigateur	01/2005	
62077	VERGES	Bruno	07/02/2006	EC-INV	LILLY	Raloxifene	investigateur	01/2000	12/2005
62077	VERGES	Bruno	07/02/2006	EC-INV	ASTRA ZENECA	Crestor (en cours)	investigateur	01/2005	
62077	VERGES	Bruno	07/02/2006	IP-AC	TAKEDA	Pioglitazone	rémunération personnelle	01/2004	12/2005
62077	VERGES	Bruno	07/02/2006	IP-AC	GSK	Rosiglitazone	rémunération personnelle	01/2005	12/2005
62077	VERGES	Bruno	07/02/2006	CF-INT	TAKEDA	European Actos Masterclass - Edimbourgh	rémunération personnelle	11/2005	
62077	VERGES	Bruno	28/01/2004	IP-EC	SERVIER - ASTRA ZENECA - TAKEDA	Essai clinique			
62077	VERGES	Bruno	28/01/2004	IP-AC	NOVO NORDISK - TAKEDA	Conseil sur produits en développement			
62077	VERGES	Bruno	28/01/2004	IP-CF	ASTRA ZENECA - GSK - TAKEDA - NOVO NORDISK	Conférences			
62077	VERGES	Bruno	17/12/2001	IP-EC	NOVO-NORDISK	Essai clinique			
62077	VERGES	Bruno	17/12/2001	IP-EC	SERVIER	Essai clinique + travaux scientifiques			
62077	VERGES	Bruno	17/12/2001	IP-EC	IPSEN-BIOTECH	Essai clinique			
62077	VERGES	Bruno	17/12/2001	IP-EC	LILLY	Essai clinique			
62077	VERGES	Bruno	17/12/2001	IP-EC	AVENTIS	Essai clinique			
62077	VERGES	Bruno	17/12/2001	IP-AC	NOVO-NORDISK	Conseil sur produits en développement			
62077	VERGES	Bruno	17/12/2001	IP-CF	GSK	Conférences			
62077	VERGES	Bruno	17/12/2001	IP-CF	NOVO-NORDISK	Conférences			
62077	VERGES	Bruno	17/12/2001	IP-CF	ASTRA-ZENECA	Formations de représentants médicaux			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
63469	VESPIGNANI	Hervé	08/10/2004	IP-EC	SANOFI - PFIZER - JANSSEN - GSK - CEPHALON - NOVARTIS	Essai clinique phase IV			
63469	VESPIGNANI	Hervé	08/10/2004	IP-CF	SANOFI - PFIZER - JANSSEN - NOVARTIS - SERVIER - GSK - CEPHALON				
63469	VESPIGNANI	Hervé	08/10/2004	PAR	LCB	Epouse , attachée de recherche			
61284	VEXIAU	Patrick	02/11/2009	LD-AR	MSD	Groupe d'experts pour la SITAGLIPTINE (JANUVIA, JANUMET)□□En cours	Rémunération personnelle	01/2007	
61284	VEXIAU	Patrick	02/11/2009	LD-AR	ALMIRALL	Groupe d'experts pour Vaniqa (en cours)	Rémunération personnelle	01/2007	
61284	VEXIAU	Patrick	02/11/2009	EC-CO	NOVO NORDISK	Etude prédictive insuline LEVEMIR.	Investigateur	11/2005	11/2006
61284	VEXIAU	Patrick	02/11/2009	EC-CO	NOVO NORDISK	Etude sur la liraglutide	Investigateur	05/2009	05/2010
61284	VEXIAU	Patrick	02/11/2009	EC-CO	AVENTIS	Etude épidémiologique MONODIA	Investigateur	09/2003	03/2005
61284	VEXIAU	Patrick	02/11/2009	EC-CO	LILLY	Etude multicentrique / insuline inhalée	Investigateur	12/2006	06/2007
61284	VEXIAU	Patrick	02/11/2009	EC-CO	MSD	Etude multicentrique/ Januvia	Investigateur	06/2007	12/2009
61284	VEXIAU	Patrick	02/11/2009	EC-CO	MERCK SERONO	Etude multicentrique glucophage poudre	Coordonnateur	01/2009	12/2010
61284	VEXIAU	Patrick	02/11/2009	RE-DE	PIERRE FABRE MEDICAMENT	Patch à la testostérone	Rémunération personnelle	01/2005	01/2005
61284	VEXIAU	Patrick	02/11/2009	RE-DE	ALMIRALL	VANIQA	Rémunération personnelle	09/2009	09/2009
61284	VEXIAU	Patrick	02/11/2009	IP-RE	ALMIRALL	Rapport sur Vaniqa. Demande de remboursement	Rémunération personnelle	09/2009	09/2009
61284	VEXIAU	Patrick	02/11/2009	IP-AC	SCHWARTZ PHARMA	Réunions d' experts : dysfonction érectile	Rémunération personnelle	03/2006	01/2008
61284	VEXIAU	Patrick	02/11/2009	IP-AC	NOVO NORDISK	Expertise sur les transferts d'insulines humaines aux analogues	Rémunération personnelle	01/2006	12/2006
61284	VEXIAU	Patrick	02/11/2009	IP-AC	SANOFI-AVENTIS	Expertise ponctuelle ACOMPLIA	Rémunération personnelle	03/2007	03/2007
61284	VEXIAU	Patrick	02/11/2009	IP-AC	LILLY	Réalisation de documents sur les PREMIX, HUMALOGMIX 25 et 50	Rémunération personnelle	01/2007	09/2007
61284	VEXIAU	Patrick	02/11/2009	CF-INT	MERCK	Conférence de presse à paris pour le produit DIABION	Rémunération personnelle	05/2006	
61284	VEXIAU	Patrick	02/11/2009	CF-INT	LILLY	Conférence de presse à Paris pour le produit HUMALOG	Rémunération personnelle	02/2007	
61284	VEXIAU	Patrick	02/11/2009	CF-INT	ABBOTT	Conférence de presse à Paris pour le produit FREE STYLE	Rémumération personnelle	05/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-INT	LILLY	Conférence de presse à Paris pour le produit BYETTA	rémunération personnelle	07/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-INT	NOVO	Conférence de presse à Paris	Rémunération personnelle	12/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-INT	MERCK LIPHA	Conférence de presse à Paris pour le produit GLUCOPHAGE poudre	Rémunération personnelle	05/2009	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	SERVIER	Congrès EASD ROME		09/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	VITALAIR	Congrès ALFEDIAM BRUXELLES		03/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	AMGEN	Réunion d'experts Cannes (intervenant)		06/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	IPSEN	Congrès d' Endocrinologie,LILLE		10/2008	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	NOVO	Congrès ALFEDIAM		03/2007	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	SANOFI AVENTIS	Congrès EASD AMSTERDAM		09/2007	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	PIERRE FABRE	Réunion d'experts AVENE		03/2007	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	SANOFI AVENTIS	Réunion d'experts Cannes		01/2006	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	ROCHE	Congrès ALFEDIAM		03/2009	
61284	VEXIAU	Patrick	02/11/2009	CF-AUD	LILLY	Congrès international diabètes fédération monTréal		10/2009	
61284	VEXIAU	Patrick	02/11/2009	VB	LABORATOIRES PHARMACEUTIQUES	Lien: secrétaire général de l'association	Association française des diabétiques.□		
61284	VEXIAU	Patrick	02/11/2009	VB	Laboratoires pharmaceutiques, DIRECTION GENERALE DE LA SANTE, CNAMTS	Lien: Secrétaire général de l'association.□□Il s'agit de financement pour les programmes (information, préve	Date de début > 5ans En cours□ Travail d'intérêt public.□ Association reconnue d'utilité		
61284	VEXIAU	Patrick	02/11/2009	(Autre)	AFD	Défense de l'interêt de l'association française des diabétiques, en particulier dans ce cadre par rapport à l'in publique		03/2003	
61284	VEXIAU	Patrick	02/11/2009	IP-AC	LILLY	Conférence de presse "10 ans d'humalog"	Rémunération personnelle	01/2007	
61284	VEXIAU	Patrick	09/07/2008	EC-INV	MSD	Groupe d'experts / Januvia	expert	01/2007	12/2008
61284	VEXIAU	Patrick	09/07/2008	EC-CO	NOVO NORDISK	Etude Predictive insuline Lévémir	investigateur	11/2005	11/2006
61284	VEXIAU	Patrick	09/07/2008	EC-CO	AVENTIS	Etude épidémiologique Monodia	investigateur	09/2003	03/2005
61284	VEXIAU	Patrick	09/07/2008	EC-CO	LILLY	Etude multicentrique - insuline inhalée	investigateur	12/2006	06/2007
61284	VEXIAU	Patrick	09/07/2008	EC-CO	MSD	Etude multicentrique / Januvia	investigateur	06/2007	12/2008
61284	VEXIAU	Patrick	09/07/2008	RE-DE	PIERRE FABRE MEDICAMENT	Patch à la testostérone	rémunération personnelle	01/2005	01/2005
61284	VEXIAU	Patrick	09/07/2008	IP-AC	MSD	Réunion d'experts : inhibiteur de la DPPIV - Januvia	rémunération personnelle	11/2005	06/2007
61284	VEXIAU	Patrick	09/07/2008	IP-AC	SCHWARTZ PHARMA	Réunion d'experts : dysfonction érectile	rémunération personnelle	03/2006	01/2007
61284	VEXIAU	Patrick	09/07/2008	IP-AC	NOVO NORDISK	Expertise sur les transferts d'insulines humaines aux analogues	rémunération personnelle	01/2006	12/2006
61284	VEXIAU	Patrick	09/07/2008	IP-AC	SANOFI AVENTIS	Expertise ponctuelle Acomplia	rémunération personnelle	03/2007	03/2007
61284	VEXIAU	Patrick	09/07/2008	IP-AC	LILLY	Réalisation de documents sur les Prémix - HumalogMix 25 et 50	rémunération personnelle	01/2007	09/2007
61284	VEXIAU	Patrick	09/07/2008	IP-AC	LILLY	Conférence de presse " 10 ans d'Humalog"	rémunération personnelle	01/2007	01/2007
61284	VEXIAU	Patrick	09/07/2008	CF-INT	MERCK	Conférence de presse à Paris pour le produit Diabion	rémunération personnelle	05/2006	05/2006
61284	VEXIAU	Patrick	09/07/2008	CF-INT	LILLY	Conférence de presse à Paris pour le produit Humalog	rémunération personnelle	02/2007	02/2007
61284	VEXIAU	Patrick	09/07/2008	CF-INT	ABBOTT	Conférence de presse à Paris pour le produit Free Style	rémunération personnelle	05/2008	05/2008
61284	VEXIAU	Patrick	09/07/2008	CF-INT	LILLY	Conférence de presse à Paris pour le produit Byetta	rémunération personnelle	07/2008	07/2008
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	SERVIER	Congrès EASD - Rome		09/2008	09/2008
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	VITALAIR	Congrès ALFEDIAM - Bruxelles		03/2008	03/2008
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	AMGEN	Réunion d'experts - Cannes (intervenant)		06/2008	06/2008
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	NOVO NORDISK	Congrès ALFEDIAM		03/2007	03/2007
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	SANOFI AVENTIS	Congrès EASD - Amsterdam		09/2007	09/2007
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	PIERRE FABRE	Réunion d'experts Avène		03/2007	03/2007
61284	VEXIAU	Patrick	09/07/2008	CF-AUD	SANOFI AVENTIS	Réunion d'experts Cannes		03/2006	03/2006
61284	VEXIAU	Patrick	09/07/2008	(Autre)	ASSOCIATION FRANCAISE DES DIABETIQUES	Défense de l'intérêt de l'Asssociation Française des Diabétiques, en particulier dans ce cadre par rapport à l	secrétaire général -Travail d'intérêt public - association reconnue d'utilité publique	03/2003	
61284	VEXIAU	Patrick	11/02/2008	EC-CO	NOVO NORDISK	Etude Predictive insuline LEVEMIR (investigateur)		11/2005	11/2006
61284	VEXIAU	Patrick	11/02/2008	EC-CO	AVENTIS	Etude épidémiologique MONODIA (investigateur)		09/2003	03/2005
61284	VEXIAU	Patrick	11/02/2008	EC-CO	LILLY	Etude multicentrique : insuline inhalée (investigateur)		12/2006	06/2007
61284	VEXIAU	Patrick	11/02/2008	EC-CO	MSD	Etude multicentrique : Januvia (investigateur) - (fin en début 2008)		06/2007	
61284	VEXIAU	Patrick	11/02/2008	IP-RE	PIERRE FABRE MEDICAMENT	Patch à la testostérone		01/2005	01/2005
61284	VEXIAU	Patrick	11/02/2008	IP-AC	MSD	Réunion d'experts : inhibiteur de la DPPIV (Januvia)		11/2005	06/2007
61284	VEXIAU	Patrick	11/02/2008	IP-AC	SCHWARTZ PHARMA	Réunions d'experts : dysfonction érectile		03/2006	01/2007
61284	VEXIAU	Patrick	11/02/2008	IP-AC	NOVO NORDISK	Expertise sur les tranferts d'insulines humaines aux analogues		01/2006	12/2006
61284	VEXIAU	Patrick	11/02/2008	IP-AC	SANOFI AVENTIS	Expertise ponctuelle Acomplia		03/2007	03/2007
61284	VEXIAU	Patrick	11/02/2008	IP-AC	LILLY	Réalisation de documents sur les prémix humalog Mix 25 et 50		01/2007	09/2007
61284	VEXIAU	Patrick	11/02/2008	IP-AC	LILLY	Conférence du presse "10 ans d'humalog"		01/2007	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61284	VEXIAU	Patrick	11/02/2008	IP-CF	MERCK	Conférence de presse à Paris pour le produit DIABION		05/2006	05/2006
61284	VEXIAU	Patrick	11/02/2008	VB	LILLY	Congrès EASD Copenhague		09/2006	09/2006
61284	VEXIAU	Patrick	11/02/2008	VB	NOVO NORDISK	Congrès ALFEDIAM		03/2007	03/2007
61284	VEXIAU	Patrick	11/02/2008	VB	SANOFI AVENTIS	Congrès EASD Amsterdam		09/2007	09/2007
61284	VEXIAU	Patrick	11/02/2008	VB	PIERRE FABRE	Réunion d'experts Avène		03/2007	03/2007
61284	VEXIAU	Patrick	11/02/2008	VB	SANOFI AVENTIS	Réunion d'experts - Cannes		01/2006	12/2006
61284	VEXIAU	Patrick	11/02/2008	(Autre)	ASSOCIATION FRANCAISE DES DIABETIQUES	Secrétaire général : défense de l'intérêt de l'association française des diabétiques, en particulier dans ce cadre par rapport à l'industrie pharr		03/2003	
61284	VEXIAU	Patrick	30/06/2007	EC-CO	NOVONORDISK	Etude prédictive insuline Lévémir	Investigateur	11/2005	11/2006
61284	VEXIAU	Patrick	30/06/2007	EC-CO	AVENTIS	Etude épidémiologique Monodia	Investigateur	09/2003	03/2005
61284	VEXIAU	Patrick	30/06/2007	EC-CO	LILLY	Etude multicentrique insuline inhalée	Investigateur	12/2006	06/2007
61284	VEXIAU	Patrick	30/06/2007	EC-CO	MSD	Etude multicentrique Januvia	investigateur	06/2007	01/2008
61284	VEXIAU	Patrick	30/06/2007	EC-CO	PFIZER	Etude multicentrique Exubera	investigateur	06/2007	01/2008
61284	VEXIAU	Patrick	30/06/2007	RE-DE	PIERRE FABRE MEDICAMENT	Patch à la testostérone		01/2005	01/2005
61284	VEXIAU	Patrick	30/06/2007	IP-AC	MSD	Réunions d'experts : Inhibiteur de la DPPIV (Januvia)	Rémunération personnelle	11/2005	06/2007
61284	VEXIAU	Patrick	30/06/2007	IP-AC	SCHWARTZ PHARMA	Réunions d'experts : dysfonction érectile	rémunération personnelle	03/2006	01/2007
61284	VEXIAU	Patrick	30/06/2007	IP-AC	NOVONORDISK	Expertise sur les transferts d'insulines humalnes aux analogues	Rémunération personnelle	01/2006	12/2006
61284	VEXIAU	Patrick	30/06/2007	IP-AC	SANOFI AVENTIS	Expertise ponctuelle Acomplia	Rémunération personnelle	03/2007	03/2007
61284	VEXIAU	Patrick	30/06/2007	IP-AC	LILLY	Réalisation de documents sur les Prémix HumalogMix 25 et 50	Rémunération personnelle	01/2007	09/2007
61284	VEXIAU	Patrick	30/06/2007	IP-AC	LILLY	Conférence de presse "10 ans d'Humalog"	Rémunération personnelle	01/2007	01/2007
61284	VEXIAU	Patrick	30/06/2007	CF-INT	MERCK	Conférence de presse à Paris pour le produit DIABION	Rémunération personnelle	05/2006	05/2006
61284	VEXIAU	Patrick	30/06/2007	CF-AUD	LILLY	Congrès EASD - Copenhague		09/2006	09/2006
61284	VEXIAU	Patrick	30/06/2007	CF-AUD	NOVO	Congrès ALFEDIAM		03/2007	03/2007
61284	VEXIAU	Patrick	30/06/2007	CF-AUD	SANOFI AVENTIS	Congrès EASD - Amsterdam		09/2007	09/2007
61284	VEXIAU	Patrick	30/06/2007	CF-AUD	PIERRE FABRE	Réunion d'experts Avène		03/2007	03/2007
61284	VEXIAU	Patrick	30/06/2007	CF-AUD	SANOFI AVENTIS	Réunion d'experts - Cannes		01/2006	12/2006
61284	VEXIAU	Patrick	30/06/2007	LD	Association Française des Diabétiques	Défense de l'intérêt de l'Association Française des Diabétiques, en particulier dans ce cadre par rapport à l'a	Secrétaire général de l'Association - Travail d'intérêt publique Association reconnue d'utilité publique	03/2003	
61284	VEXIAU	Patrick	11/06/2006	EC-CO	NOVO NORDISK	Etude Predictive insuline Lévémir	investigateur	11/2005	11/2006
61284	VEXIAU	Patrick	11/06/2006	EC-CO	AVENTIS	Etude épidémiologique MONODIA	investigateur	09/2003	03/2005
61284	VEXIAU	Patrick	11/06/2006	RE-DE	PIERRE FABRE MEDICAMENT	Patch à la testostérone		01/2005	01/2005
61284	VEXIAU	Patrick	11/06/2006	IP-AC	MSD	réunion d'experts : Inhibiteur de la DPPIV	rémunération personnelle	11/2005	06/2006
61284	VEXIAU	Patrick	11/06/2006	IP-AC	SCHWARTZ PHARMA	réunion d'experts : Dysfonction erectile	rémunération personnelle	03/2006	
61284	VEXIAU	Patrick	11/06/2006	CF-INT	MERCK	Conférence de presse à Paris pour le produit DIABION	rémunération personnelle	05/2006	05/2006
61284	VEXIAU	Patrick	11/06/2006	CF-AUD	MSD	Congrès EASD - Athènes		09/2005	09/2005
61284	VEXIAU	Patrick	11/06/2006	CF-AUD	NOVONORDISK	Congrès de l'ALFEDIAM		03/2006	03/2006
61284	VEXIAU	Patrick	11/06/2006	CF-AUD	MERCK LIPHA	Congrès de l'ALFEDIAM		03/2005	03/2005
61284	VEXIAU	Patrick	11/06/2006	(Autre)	ASSOCIATION FRANCAISE DES DIABETIQUES EN PARTICULIER PAR RAPPORT A L'INDUSTRIE PHARMACEUTIQUE	Secrétaire Général de l'Asoociation	Travail d'intérêt Publique Assocation reconnue d'utilité publique	03/2003	
61284	VEXIAU	Patrick	11/06/2006	LD	AFD	Trésorier		01/1996	12/2002
61284	VEXIAU	Patrick	11/06/2006	LD	AFD	Secrétaire général		01/2003	
61284	VEXIAU	Patrick	11/06/2006	LD-AR		Uniquement des expertises ponctuelles			
61284	VEXIAU	Patrick	11/12/2002	IP-EC	AVENTIS	Phase IV Lantiss			
61284	VEXIAU	Patrick	11/12/2002	IP-CF		Multiples interventions - Transmission de mon CV éventuel			
10414	VICAUT	Eric	04/12/2006	LD-AR	PFIZER - SERVIER	Expertise statistique - Groupe européen d'expert en microcirculation			
10414	VICAUT	Eric	04/12/2006	LD-AR	ABBOTT	Expertise statistique			
10414	VICAUT	Eric	04/12/2006	IP-EC	ASTRA	Membre du Comité scientifique français Hypo essai Centaurus Rosuvastatin	Expertise méthodologique	01/2005	12/2007
10414	VICAUT	Eric	04/12/2006	IP-AC	ABBOTT	Expertise méthodologique pour étude SYNAGIS			
10414	VICAUT	Eric	04/12/2006	IP-AC	IPSEN - BIOTECH	Conseil pour analyse Essai GFEA06 - Essai Botox - Hormonothérapie dans le cancer du sein			
10414	VICAUT	Eric	04/12/2006	IP-AC	AVENTIS	Conseil méthodologique pour registre Plavix chez le patient coronarien□□Analyse registre RIVIERA			
10414	VICAUT	Eric	04/12/2006	IP-AC	FERRING	Expertise pour observation pharmacovigilance			
10414	VICAUT	Eric	04/12/2006	CF-INT	SERVIER	Conférence microcirculation et perfusion tissulaire - PRETERAX			
10414	VICAUT	Eric	04/12/2006	CF-INT	PFIZER	Conférence microcirculation			
10414	VICAUT	Eric	04/12/2006	VB	THERVAL - MEDICAL	Subvention recherche		01/2006	01/2006
10414	VICAUT	Eric	14/03/2005	IP-EC	SERVIER				
10414	VICAUT	Eric	14/03/2005	IP-AC	PFIZER - ABBOTT - IPSEN BIOTECH				
10414	VICAUT	Eric	14/03/2005	IP-CF	BMS - PFIZER SERVIER				
10414	VICAUT	Eric	14/03/2005	VB	PFIZER				
10414	VICAUT	Eric	10/03/2003	IP-EC	IPSEN BIOTECH				
10414	VICAUT	Eric	10/03/2003	IP-EC	SERVIER				
10414	VICAUT	Eric	10/03/2003	IP-AC	PFIZER				
10414	VICAUT	Eric	10/03/2003	IP-CF	BRISTOL MYERS SQUIBB				
10414	VICAUT	Eric	10/03/2003	VB	PFIZER				
10414	VICAUT	Eric	26/11/2002	IP-AC	PFIZER	Conseils pour analyses statistiques			
10414	VICAUT	Eric	26/11/2002	IP-AC	IPSEN	Conseils pour analyses statistiques			
10414	VICAUT	Eric	26/11/2002	IP-AC	SERVIER	Conseils pour analyses statistiques			
10414	VICAUT	Eric	26/11/2002	IP-AC	ABBOTT	Conseils pour analyses statistiques			
10414	VICAUT	Eric	26/11/2002	IP-CF	AVENTIS	Conférence			
10414	VICAUT	Eric	26/11/2002	IP-CF	ABBOTT	Action de formation			
10414	VICAUT	Eric	26/11/2002	VB	SERVIER				
10414	VICAUT	Eric	01/01/1999	IP-EC	AIR LIQUIDE				
10414	VICAUT	Eric	01/01/1999	IP-AC	PARKE DAVIS				
10414	VICAUT	Eric	01/01/1999	IP-AC	IPSEN				
10414	VICAUT	Eric	01/01/1999	IP-CF	Institut de recherche SERVIER	Une conférence en septembre 1997			
10414	VICAUT	Eric	01/01/1999	IP-EC	THERVAL				
10414	VICAUT	Eric	01/01/1999	VB	THERVAL				
10414	VICAUT	Eric	01/01/1998	LD	Parke Davis				
10414	VICAUT	Eric	01/01/1998	LD	Ipsen				
10414	VICAUT	Eric	01/01/1998	IP-AUT	Hoechst				
10414	VICAUT	Eric	01/01/1998	IP-AUT	Roussel				

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10414 VICAUT		Eric	01/01/1998	IP-AUT	transfert international				
10414 VICAUT		Eric	01/01/1998	IP-AUT	Servier				
10414 VICAUT		Eric	01/01/1998	VB	membre de la société française de microcirculation pris en charge par Lafont				
55633 VIDAILHET		Marie	06/12/2005	EC-CO	SERVIER	Peribidil	co-investigateur	01/2005	12/2006
55633 VIDAILHET		Marie	06/12/2005	EC-INV	SERVIER	Etude PERIBIDIL	co-investigateur	01/2005	12/2006
55633 VIDAILHET		Marie	06/12/2005	RE-AUT	DRC, INSERM	expertises			
55633 VIDAILHET		Marie	06/12/2005	IP-AC		Pas d'activité de conseil à un haut niveau industriel			
55633 VIDAILHET		Marie	06/12/2005	CF-INT	JNLF, ENS, EFNS, NOV. DUORDUS SOCIETY, etc	Quasi exclusivement interventions institutionnelles		01/2005	
55633 VIDAILHET		Marie	06/12/2005	CF-INT	BOEHRINGER	1 symposium Pramipexole			
55633 VIDAILHET		Marie	06/12/2005	CF-INT	MEDTRONIC	1 symposium		01/2005	12/2005
55633 VIDAILHET		Marie	06/12/2005	RE-AUT		pas de rapport d'expertise pour l'industrie			
55633 VIDAILHET		Marie	17/08/2004	IP-EC	SANOFI	Essai cliniques (phase III), SR 57667B (arrêt octobre 2004)			
55633 VIDAILHET		Marie	17/08/2004	IP-EC	AP-HP - DRPC (public)	pas d'autre essai rémunéré, PHRC98, PHRC2002			
55633 VIDAILHET		Marie	17/08/2004	IP-RE		Pas de rapport d'expertise pour industrie			
55633 VIDAILHET		Marie	17/08/2004	IP-AC	BOEHRINGER	Conseil ou formations (ponctuelle) et indépendante (2004-2005), Novartis (2004-2003)			
55633 VIDAILHET		Marie	22/12/2003	IP-EC		Travaux scientifiques (Promotion INSERM - Promotion AP-HP)			
55633 VIDAILHET		Marie	22/12/2003	IP-CF	LILLY, GLAXO SMITHKLINE	Colloques dont le contenu de mes présentations est indépendant de la firme pharmaceutique (sujet, mouvements anormaux)			
55633 VIDAILHET		Marie	01/10/2003	Néant					
55633 VIDAILHET		Marie	17/12/2002	Néant			"Je ne suis salariée d'aucune firme pharmaceutique"		
55633 VIDAILHET		Marie	14/10/2002	Néant					
55633 VIDAILHET		Marie	14/04/2001	Néant					
10417 VIGE		Patrick	19/02/2001	IP-EC	PHENIX	Essai clinique Aerodiol			
10417 VIGE		Patrick	19/02/2001	IP-EC	ARKO PHARMA	2001 : Essai clinique Soja			
10417 VIGE		Patrick	19/02/2001	IP-RE	ARKO PHARMA	Rapport d'expertise sur Ca D3 génétique			
10417 VIGE		Patrick	19/02/2001	IP-RE	ADRIAN	Rapport d'expertise sur Oracetanil 1000			
10417 VIGE		Patrick	20/05/1999	IP-EC	FERRING	Essai Propess			
10417 VIGE		Patrick	20/05/1999	IP-EC	PHENIX SERVIER	Essai Aerodiol			
10417 VIGE		Patrick	20/05/1999	IP-RE	BIOGORAN	Rapport Copranide			
10417 VIGE		Patrick	01/01/1999	IP-EC	IRIS SERVIER	Essai clinique sur le 17B oestradiol par voie nasale			
10417 VIGE		Patrick	01/01/1999	IP-RE	GENEVRIER HMG				
10417 VIGE		Patrick	01/01/1998	IP-AUT	Servier				
10417 VIGE		Patrick	01/01/1998	IP-AUT	Genevrier				
64946 VIGNOT		Stéphane	26/04/2010	CF-AUD	NOVARTIS	Congrès ESMO Berlin		09/2009	09/2009
64946 VIGNOT		Stéphane	16/03/2009	CF-AUD	NOVARTIS	Congrès RPC sein 2009	vols + hébergement	01/2009	01/2009
64946 VIGNOT		Stéphane	16/03/2009	CF-AUD	ROCHE	Congrès ESMO 2008	vols + hébergement	09/2008	09/2008
64946 VIGNOT		Stéphane	25/01/2008	LD-AR	NOVARTIS	Participation à un groupe de réflexion sur l'utilisation des biophosphonates	Rémunération personnelle	03/2006	04/2007
64946 VIGNOT		Stéphane	25/01/2008	EC-CO	SERVIER	Etude de phase I CLI (Hôpital St-Louis)	Co-investigateur	11/2004	12/2006
64946 VIGNOT		Stéphane	25/01/2008	EC-CO	ROCHE	Etude ATHENA (Etude de phase IV : bévacizumab en première ligne métastatique des cancers du sein)	Co-investigateur	02/2007	03/2008
64946 VIGNOT		Stéphane	25/01/2008	EC-CO	SANOFI-AVENTIS	Etude de phase II du VEGF-Trap (prostate et poumon)	Co-investigateur	01/2008	
64946 VIGNOT		Stéphane	25/01/2008	EC-CO	AMGEN	Etude de phase II de l'AMG20050190 (cancer du poumon)	co-investigateur	01/2008	12/2008
64946 VIGNOT		Stéphane	25/01/2008	CF-INT	LILLY	Formation sur le cancer du sein : épidémiologie, diagnostic et stratégies thérapeutiques (une journée à Paris	Rémunération personnelle		12/2008
64946 VIGNOT		Stéphane	25/01/2008	CF-AUD	ASTRA -ZENECA	Congrès ASCO 2007		06/2007	06/2007
64946 VIGNOT		Stéphane	25/01/2008	CF-AUD	GSK	San Antonio Breast Cancer Sympusium		12/2007	12/2007
63925 VINCENEUX		Philippe	12/06/2007	LD-AR	ANAES/ HAS	College de l'Accréditation puis comission de la certification	Rémunération personnelle et versée au profit d'une institution	01/1999	12/2005
63925 VINCENEUX		Philippe	12/06/2007	EC-CO	ANRS	Interleukine 2□□Protocoles SILCAAT, ESPRIT, INTERSTART	Co-Investigateur	01/2000	12/2007
63925 VINCENEUX		Philippe	12/06/2007	EC-CO	BOEHRINGER	Tipranavir	Co-Investigateur	01/2004	
63925 VINCENEUX		Philippe	12/06/2007	EC-CO	LEO	Innohep, protocole IRIS	Co-Investigateur	01/2006	
63925 VINCENEUX		Philippe	12/06/2007	EC-CO	AP-HP	Humira (Adalimumab), protocole HECTOR	Co-Investigateur	01/2005	
63925 VINCENEUX		Philippe	12/06/2007	IP-AC	ANAES/ HAS	Participation (membre) au college de l'Accreditation depuis sa création, puis à la commission de la certificati	Rémunération personnelle et versée au profit d'une institution		
63925 VINCENEUX		Philippe	04/12/2005	LD-AR	ANAES /HAS	membre du Conseil de l'Accréditation puis de la Commission de la Certification (activité en cours)	Rémunération personnelle/institution	01/1998	
63925 VINCENEUX		Philippe	04/12/2005	EC-CO	ANRS	plusieurs protocoles de développement de molécules anti-rationnels	expérimentateur non principal		
63925 VINCENEUX		Philippe	04/12/2005	EC-CO	ABBOTT	Adalimumab (2003-2004)	expérimentateur non principal		
63925 VINCENEUX		Philippe	04/12/2005	CF-AUD	SERVIER	inscription au congrès national de la Société Française de Rhumatologie 2004 et 2005			
60027 VOIRIOT		Pascal	29/08/2010	LD-ODE	CARDIABASE (CENTRAL LAB ECG)	PDG	Contractuel	02/1999	
60027 VOIRIOT		Pascal	29/08/2010	IF	CARDIABASE (CENTRAL LAB ECG)	part sociales	>=5000 € ou >=5% du capital	02/1999	
60027 VOIRIOT		Pascal	29/08/2010	EC-INV	ACTELION, ASTELLAS, ASTRA-ZENECA, BIOPROJET, CEPHALON, CHIESI, DEBIOPHARM, DMDI, FOVEA, GENENTECH, MMV, NOVEXEL, PIERRE FABRE, ROCHE, SANOFI-AVENTIS, SERVIER, SIGMA TAU, STEBA, TROPHOS, UCB, WYETH	Lecture centralisée d'ECG, Holter, CABPM et gestion de dossiers cliniques en vue d'adjucation d'événement	depuis la dernière déclaration (mars 2009), contractualisation de >50 études de phase 1, 2 et 3 avec les firmes citées incluant 10 études "QT" (thorough QT studies) et 2 nouvelles études de gestion de dossiers pour adjudication d'évenement indésirables	04/2009	
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	DIVERSES BIOTECH ET MID SIZE LAB	Lecture Centralisée ECG pour Novexel, Basilea, Bioline, Trophos, Galderma, Medtronic, Palon, Negma, Chi	>50 études	01/2006	
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	TEVA	Lecture Centralisée ECG	1 étude phase 2	04/2007	04/2008
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	UCB	Lecture Centralisée ECG	2 études phase1□ 1 études phase2	01/2006	05/2009
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	MERCK SERONO	Lecture Centralisée ECG	3 études phase 1 Oncologie	02/2007	
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	ROCHE	Lecture Centralisée ECG	3 études phase1	08/2007	03/2009
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	SERVIER	Lecture Centralisée ECG	2 études phase1□ 6 études phase 2/3	02/2006	03/2009
60027 VOIRIOT		Pascal	31/03/2009	EC-INV	GSK	Lecture Centralisée ECG	2 études phase1□ 1 étude phase 3	05/2005	09/2008

Id	Nom	Prénom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
60027	VOIRIOT	Pascal	31/03/2009	EC-INV	WYETH	Lecture Centralisée ECG	4 études phase1 >10 études phase 2D	01/2005	03/2009
60027	VOIRIOT	Pascal	31/03/2009	EC-INV	SANOFI AVENTIS	Lecture centralisée ECG□□Service de gestion de dossier pour activité d'adjudication□□Lecture centralisée	3 études phase 2/3	04/2002	03/2009
60027	VOIRIOT	Pascal	31/03/2009	LD-ODE	CARDIABASE	Fondateur et actuel PDG de cette entreprise spécialisée dans la lecture centralisée de documents cardiologi	PDG	02/1999	
60027	VOIRIOT	Pascal	31/03/2009	EC-INV	DAICHII	Lecture Centralisée ABPM	1 étude de phase 3	07/2008	
60027	VOIRIOT	Pascal	31/03/2009	EC-INV	CARDIOME	Lecture Centralisée ECG	1 étude de phase 3	10/2007	12/2009
60027	VOIRIOT	Pascal	31/03/2009	EC-INV	PIERRE FABRE MEDICAMENT	Lecture Centralisée ECG	6 études phase 1-phase 2 incluant une étude QT	11/2007	03/2009
60027	VOIRIOT	Pascal	27/11/2008	EC-INV	DAICHII	Lecture Centralisée ABPM	1 étude de phase 3	07/2008	
60027	VOIRIOT	Pascal	27/11/2008	EC-INV	CARDIOME	Lecture Centralisée ECG	1 étude de phase 3	10/2007	
60027	VOIRIOT	Pascal	27/11/2008	EC-INV	PIERRE FABRE MEDICAMENT	Lecture Centralisée ECG	6 étudese phase 1-phase 2 incluant un étude QT	11/2007	
60027	VOIRIOT	Pascal	24/09/2007	RE-DE	NOVEXEL	Rapport de lecture ECG phase 1	Rémunération personnelle/institution		
60027	VOIRIOT	Pascal	24/09/2007	RE-DE	SERVIER	Rapport de lecture ECG phase 1	Rémunération institution		
60027	VOIRIOT	Pascal	24/09/2007	RE-DE	BASILEA	Rapport de lecture ECG phase 1	Rémunération institution		
60027	VOIRIOT	Pascal	24/09/2007	EC-CO	TEVA	Lecture Centralisée ECG	1 études phase 2		
60027	VOIRIOT	Pascal	24/09/2007	EC-CO	NOVEXEL	Lecture Centralisée ECG	6 études phase 1		
60027	VOIRIOT	Pascal	24/09/2007	EC-CO	BASILEA	Lecture Centralisée ECG	8 études phase 1 à phase 3 dont 1 étude QT	11/2004	
60027	VOIRIOT	Pascal	24/09/2007	EC-INV	SERVIER	Lecture Centralisée ECG	8 études phase 1 à phase 3 dont 1 étude QT	08/2005	
60027	VOIRIOT	Pascal	24/09/2007	EC-INV	SANOFI AVENTIS	Lecture Centralisée ECG	environ 100 études de phase 1 incluant >12 études ECG. De façon marginale, activité en phase 2 et phase 3	04/2002	
60027	VOIRIOT	Pascal	24/09/2007	EC-INV	GSK	Lecture Centralisée ECG	3 études dont 12 études ECG. De façon marginale, activité en phase 2 et phase 3	06/1999	
60027	VOIRIOT	Pascal	24/09/2007	EC-INV	WYETH	Lecture Centralisée ECG	5 études phase 1	11/2004	
60027	VOIRIOT	Pascal	24/09/2007	LD-ODE	CARDIABASE	CEO		03/1999	
60027	VOIRIOT	Pascal	08/04/2005	IF	CARDIABASE	Lecture centralisée d'ECG	>=5000 € ou >=5% du capital	03/1999	
60027	VOIRIOT	Pascal	08/04/2005	IP-AC	CRITICAL EVENT COMMITEE		Aucune rémunération		
60027	VOIRIOT	Pascal	08/04/2005	IP-AC	LABORATOIRE BAYER PHARMA	Moxifloxacine, étude immédiate	Aucune rémunération		
60027	VOIRIOT	Pascal	08/04/2005	IP-AC	LABORATOIRE BAYER	Moxifloxacine	Aucune rémunération		
60027	VOIRIOT	Pascal	08/04/2005	IP-EC	ASTRA ZENECA	Megalatran, co-investigateur			
60027	VOIRIOT	Pascal	08/04/2005	IP-RE	VICURON	Anidulafungin, ECG report			
60027	VOIRIOT	Pascal	08/04/2005	IP-RE	SERVIER	33138, ECG report			
60027	VOIRIOT	Pascal	08/04/2005	IP-RE	BAYER	Moxifloxacine, étude MOHICAN, ECG report			
60027	VOIRIOT	Pascal	08/04/2005	IP-CF	SERVIER	Ivabradine, étude Vasco, avril 2005, en qualité d'intervenant			
60027	VOIRIOT	Pascal	08/04/2005	IP-CF	BAYER	ICAAC annuel, en qualité d'auditeur			
60027	VOIRIOT	Pascal	08/04/2005	IP-CF	AVENTIS	ICAAC annuel, en qualité d'auditeur			
60027	VOIRIOT	Pascal	08/04/2005	IP-CF	GLAXO	ICAAC annuel, en qualité d'auditeur			
60027	VOIRIOT	Pascal	08/04/2005	VB		Je suis PDG d'un société de service (CRO) assurant un service de lecture centralisé des ECG à l'industrie p			
60027	VOIRIOT	Pascal	08/04/2005	VB		Je suis actionnaire majoritaire de cette CRO (80%)			
60027	VOIRIOT	Pascal	08/04/2005	VB		Plus de 90% du CA produit par cette société provient de laboratoires pharmaceutiques "clients"			
60027	VOIRIOT	Pascal	08/04/2005	VB		Parmi ceux-ci, les plus importants en 2005 dans la structure du CA de CardiaBase sont : Sanofi Aventis et C			
60027	VOIRIOT	Pascal	08/04/2005	VB		Les autres industriels actuellement impliqués avec CardiaBase sont les suivants : Wyeth, Servier, financem			
60027	VOIRIOT	Pascal	08/04/2005	VB		Les autres industriels actuellement impliqués avec CardiaBase sont les suivants : Vicuron, UCB, Basilea, Ui			
60027	VOIRIOT	Pascal	08/04/2005	IP-AUT	BAYER PHARMA	Cerivastatine et Rabdomyolyse, expert judiciaire			
60027	VOIRIOT	Pascal	08/04/2005	IP-AUT	SPILF - SRLF - SFC				
60027	VOIRIOT	Pascal	15/06/2004	IF	CARDIOBASE	Associé Gérant			
60027	VOIRIOT	Pascal	12/03/2001	IF	CARDIOBASE	Gérant - Fondateur			
60027	VOIRIOT	Pascal	12/03/2001	IP-EC	SB				
60027	VOIRIOT	Pascal	12/03/2001	IP-EC	ASTRA-ZENECA				
60027	VOIRIOT	Pascal	12/03/2001	IP-EC	TAKEDA				
60027	VOIRIOT	Pascal	12/03/2001	IP-AC	SB				
60027	VOIRIOT	Pascal	12/03/2001	IP-AC	PFIZER				
60027	VOIRIOT	Pascal	12/03/2001	(Autre)		Direction de CARDIOBASE - Centre de Lecture Cardiovasculaire - Activité en cours GSK-BAYER			
10424	VRAY	Muriel	02/03/2010	LD-AR	UMANIS	salariée 1/2 jours par mois, Conseil en statistiques	rémunération personnelle	11/2005	04/2007
10424	VRAY	Muriel	02/03/2010	LD-AR	PETER HOLMES	salariée 1/2 jour par mois, Conseil en statistiques et méthodologie!	rémunération personnelle	06/2008	12/2009
10424	VRAY	Muriel	02/03/2010	IP-AC	ROCHE	membre comité scientifique étude TORPEDO (TOCILIZUMAB)	rémunération personnelle	06/2008	
10424	VRAY	Muriel	02/03/2010	IP-AC	MAYOLI SPLINDER	membre comité scientifique étude épidémiologique sur les troubles fonctionnels intestinaux	rémunération personnelle	10/2005	05/2008
10424	VRAY	Muriel	02/03/2010	IP-AC	KAPPA SANTE	membre comité scientifique étude épidémiologique image/amirage sur les troubles des jambes sans repos	rémunération personnelle	03/2005	05/2008
10424	VRAY	Muriel	02/03/2010	IP-AC	GSK	membre groupe de réflexion sur différents produits (expertise en méthodologie)	rémunération personnelle	11/2005	
10424	VRAY	Muriel	02/03/2010	IP-AC	GSK BIO	membre DSMB essai vaccin HIV	rémunération personnelle	02/2009	
10424	VRAY	Muriel	02/03/2010	IP-AC	AB SCIENCES	membre DSMB essais de phase 1,2,3 (inhibiteur de la tyrosine kinase)	rémunération personnelle	02/2009	
10424	VRAY	Muriel	23/03/2009	LD-ODE	PETER HOLMES	Consultante en statistiques	salariéé 1/2 jour par mois	06/2008	
10424	VRAY	Muriel	23/03/2009	EC-CO	ROCHE	Membre comité scientifique PR/RHUMATO	méthodologiste	06/2008	
10424	VRAY	Muriel	23/03/2009	EC-CO	MAYOLI SPINDLER	Membre comité scientifique TFI	méthodologiste	10/2005	05/2008
10424	VRAY	Muriel	23/03/2009	EC-CO	KAPPA SANTE	Membre comité scientifique : syndrome des jambes lourdes	méthodologiste	05/2007	05/2009
10424	VRAY	Muriel	23/03/2009	EC-CO	CERI MEDICAL	Membre comité scientifique : Etude Sinergence diabétologie	méthodologie	11/2005	06/2007
10424	VRAY	Muriel	23/03/2009	EC-CO	AB SCIENCES	Membre comité indépendant : essai cancéro phase II, III	méthodologiste	02/2009	
10424	VRAY	Muriel	23/03/2009	IP-AC	GSK	Conseil en méthodo	rémunération personnelle	01/2005	
10424	VRAY	Muriel	23/03/2009	CF-INT	ROCHE	Formation :□□-cours sur les essais de non infériorité□□- cours sur les BIOS	rémunération personnelle	12/2007	06/2008
10424	VRAY	Muriel	03/03/2008	LD-AR	UMANIS	Salariée consultant en statistiques 1/2 journée par mois		11/2005	04/2007
10424	VRAY	Muriel	03/03/2008	IP-AC	ROCHE	Membre comité scientifique : étude PEGASYS	rémunération personnelle	03/2004	12/2006
10424	VRAY	Muriel	03/03/2008	IP-AC	ROCHE	Membre comité scientifique : étude SMART	rémunération personnelle	10/2006	12/2007
10424	VRAY	Muriel	03/03/2008	IP-AC	ROCHE	Membre comité indépendant : étude INDEED	rémunération personnelle	11/2005	12/2006
10424	VRAY	Muriel	03/03/2008	IP-AC	CERI MEDICAL	Membre comité scientifique : Etude Sinergence	rémunération personnelle	11/2005	12/2007
10424	VRAY	Muriel	03/03/2008	IP-AC	GSK	Membre groupe de réflexion en tant que méthodologiste	rémunération personnelle	12/2006	

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
10424	VRAY	Muriel	03/03/2008	IP-AC	UMANIS	Membre comité scientifique	rémunération personnelle	10/2005	
10424	VRAY	Muriel	16/05/2006	LD	UMANIS (CRO)	salariée 1/2 journée / mois	salariée	11/2005	
10424	VRAY	Muriel	16/05/2006	IP-AC	ROCHE	Membre Comité indépendant / Fuzeon	rémunération personnelle	11/2005	
10424	VRAY	Muriel	16/05/2006	IP-AC	ROCHE	Membre Comité scientifique / Pegasys	rémunération personnelle	02/2003	
10424	VRAY	Muriel	16/05/2006	IP-AC	ROCHE	Membre Comité scientifique Mabthera	rémunération personnelle	12/2005	
10424	VRAY	Muriel	16/05/2006	IP-AC	GSK	Consultant en méthodologie sur plusieurs produits	rémunération personnelle	12/2004	
10424	VRAY	Muriel	16/05/2006	IP-AC	MAYOLI-SPINDLER	Membre Comité scientifique dans les troubles fonctionnels intestinaux	rémunération personnelle	10/2005	
10424	VRAY	Muriel	16/05/2006	IP-AC	CERI MEDICAL	Membre Conseil scientifique□□étude observance dans le diabète rosiglitazone / metformine	rémunération personnelle	11/2005	
10424	VRAY	Muriel	16/05/2006	IP-AC	STALLERGENES	Membre Comité indépendant SLIT	rémunération personnelle	11/2005	11/2005
10424	VRAY	Muriel	04/12/2005	IP-AC	SOCIETE CERI MEDICAL	Membre comité scientifique Etude Sinergence: diabétologie	Rémunération personnelle	11/2005	
10424	VRAY	Muriel	04/12/2005	IP-AC	MAYOLI SPLINDER	Membre comité scientifique Etude dans les troubles fonctionnels intestinaux	Rémunération personnelle	10/2005	
10424	VRAY	Muriel	01/12/2005	IP-AC	STALLERGENES	Membre du comité indépendant de l'essai (SLIT- principe immuno-allergie sublinguale)	Rémunération personnelle	11/2005	11/2007
10424	VRAY	Muriel	01/12/2005	IP-AC	ROCHE	Membre comité scientifique Hépatys	Rémunération personnelle	02/2003	12/2006
10424	VRAY	Muriel	01/12/2005	LD-ODE	UMANIS		salariée consultant en statistiques 1/2 journée par mois	11/2005	
10424	VRAY	Muriel	01/12/2005	IP-AC	ROCHE	Membre du comité indépendant de l'étude INDEED (Fuzéon)	Rémunération personnelle	11/2005	12/2006
10424	VRAY	Muriel	25/03/2005	LD-AR	KNOLL	Contrat terminé fin avril 2003		07/1990	05/2002
10424	VRAY	Muriel	25/03/2005	LD-AR	ABBOTT	Salariée 1/2 journée par mois, conseils en méthodologie (pas de produits particuliers)		05/2002	04/2003
10424	VRAY	Muriel	25/03/2005	IP-AC	ROCHE	Membre conseil scientifique, Observatoire HEPATYS (PEGASYS) (2003-2004-2005)	Rémunération personnelle	02/2003	12/2006
10424	VRAY	Muriel	25/03/2005	IP-AC	GSK	Consultant en méthodologie sur plusieurs produits (décembre 2004 - 02 mars 2005)	Rémunération personnelle	12/2005	
10424	VRAY	Muriel	13/01/2004	IP-EC	ROCHE	Etude Pegasys - Membre du conseil scientifique (conseils méthodologiques)			
10424	VRAY	Muriel	21/04/2003	IP-EC	ROCHE	Conseil scientifique étude Hépatite C - Conseil scientifique étude pharmacoépidémiologique EPIGRAM			
10424	VRAY	Muriel	21/04/2003	IP-AC	SANOFI SYNTHELABO	Conseil en pharmacoépidémiologie			
10424	VRAY	Muriel	21/04/2003	IP-AC	MERCK SHARP DOHME CHIBRET	Conseil en pharmacoépidémiologie			
10424	VRAY	Muriel	26/10/2002	IP-EC	ROCHE	Membre du comité scientifique d'une étude			
10424	VRAY	Muriel	26/10/2002	IP-AC	SANOFI-SYNTHELABO	Conseils en méthodologie			
10424	VRAY	Muriel	26/10/2002	IP-AC	MSD	Conseils en méthodologie			
10424	VRAY	Muriel	26/10/2002	LD	ABBOTT	Salariée - consultante en Méthodologie (4 heures/mois)			
10424	VRAY	Muriel	26/10/2002	IP-EC	ROCHE	Membre du Comité scientifique d'une étude			
10424	VRAY	Muriel	26/10/2002	IP-AC	SANOFI-SYNTHELABO	Conseils en Méthodologie			
10424	VRAY	Muriel	26/10/2002	IP-AC	MSD	Conseils en Méthodologie			
10424	VRAY	Muriel	15/01/2002	LD	KNOLL	Conseils en Méthodologie - 1 journée / mois - salariée			
10424	VRAY	Muriel	15/01/2002	IP-AC	SANOFI-SYNTHELABO	Conseils en pharmaco-épidémiologie			
10424	VRAY	Muriel	15/01/2002	IP-AC	ROCHE	Membre du conseil scientifique d'une étude épidémiologique			
10424	VRAY	Muriel	02/05/2000	LD	KNOLL	Consultante en Méthodologie - salariée 4H/mois			
10424	VRAY	Muriel	02/05/2000	IP-EC	SANOFI-SYNTHELABO	Conseils en pharmaco-épidémiologie			
10424	VRAY	Muriel	01/01/1999	LD	KNOLL	Consultante en méthodologie des essais thérapeutiques. 1/2 journée par mois			
10424	VRAY	Muriel	01/01/1999	IP-AUT	ROCHE	Prise en charge d'un congrès en Nutrition (1997)			
10424	VRAY	Muriel	01/01/1999	IP-AC	SANOFI	Conseils en pharmaco-épidémiologie			
10424	VRAY	Muriel	01/01/1999	VB	RHONE POULENC RORER	Contrat Inserm			
10424	VRAY	Muriel	01/01/1999	VB	SERVIER	INSERM			
10424	VRAY	Muriel	01/01/1999	VB	SYNTHELABO	INSERM			
10424	VRAY	Muriel	01/01/1998	LD	Knoll				
10424	VRAY	Muriel	01/01/1998	IP-AUT	Sanofi Winthrop				
10424	VRAY	Muriel	01/01/1998	IP-AUT	Fournier Debat				
10424	VRAY	Muriel	01/01/1998	VB	Synthelabo		Contrats Inserm ou Association Claude Bernard		
10424	VRAY	Muriel	01/01/1998	VB	RPR		Contrats Inserm ou Association Claude Bernard		
10424	VRAY	Muriel	01/01/1998	VB	Servier		Contrats Inserm ou Association Claude Bernard		
10432	WILMAN	Jean-François	01/01/1999	LD	MG Recherches	Salarié			
10432	WILMAN	Jean-François	01/01/1999	IP-EC	SB				
10432	WILMAN	Jean-François	01/01/1999	IP-EC	ROCHE				
10432	WILMAN	Jean-François	01/01/1999	IP-EC	SERVIER				
10432	WILMAN	Jean-François	01/01/1999	IP-EC	ZENECA				
10432	WILMAN	Jean-François	01/01/1999	IP-AC	BAYER				
10432	WILMAN	Jean-François	01/01/1998	LD	MG Recherches				
10432	WILMAN	Jean-François	01/01/1998	IP-AUT	SKB				
10432	WILMAN	Jean-François	01/01/1998	IP-AUT	Neurim				
10432	WILMAN	Jean-François	01/01/1998	IP-AUT	BMS				
10432	WILMAN	Jean-François	01/01/1998	IP-AUT	Zéneca				
64111	WION	Nelly	01/12/2009	EC-INV	ROCHE DIAGNOSTICS	Lecteur ACCU6CHEK, INFORM-COBES, IT 1000, étude de pratiques.	investigateur principal	01/2007	07/2007
64111	WION	Nelly	01/12/2009	IP-AC	ROCHE DIAGNOSTICS	Consultant ponctuel pour la création du site " diabète au féminin "	rémunération personnelle	09/2009	11/2009
64111	WION	Nelly	01/12/2009	IP-AC	BAYER SCHERING PHERME	Participation à enquete IMPECT GPP	rémunération personnelle	10/2009	
64111	WION	Nelly	01/12/2009	CF-INT	ROCHE DIAGNOSTICS	CORATA : "glycémie à l hopital" Paris	rémunération personnelle	05/2009	
64111	WION	Nelly	01/12/2009	CF-INT	GSK	Actualites diabétologie : GAP	rémunération personnelle	03/2008	
64111	WION	Nelly	01/12/2009	CF-INT	LILLY	diabète et crainte de l'infection : Grenoble	rémunération personnelle	04/2009	
64111	WION	Nelly	01/12/2009	CF-INT	SANOFI	Diabétologie en mouvement : Grenoble	rémunération personnelle	06/2008	
64111	WION	Nelly	01/12/2009	CF-INT	NOVARTIS	Mise au point sur les gliptines : Lyon	rémunération personnelle	09/2009	
64111	WION	Nelly	01/12/2009	CF-INT	TAKEDA	Echange de pratiques en diabétologie : Grenoble, place des glitazones	rémunération personnelle	05/2008	05/2008
64111	WION	Nelly	01/12/2009	CF-INT	NOVARTIS	Mise au point sur les gliptines : Grenoble	rémunération personnelle	10/2009	10/2009
64111	WION	Nelly	01/12/2009	CF-INT	TAKEDA	Echange de pratiques en diabétologie : Grenoble, place des glitazones	rémunération personnelle	03/2009	03/2009
64111	WION	Nelly	01/12/2009	CF-INT	NOVARTIS	Mise au point sur les gliptines : Grenoble	rémunération personnelle	11/2009	11/2009
64111	WION	Nelly	01/12/2009	CF-INT	SANOFI	3ème rencontre inter régionales diabète Annecy	rémunération personnelle	04/2008	04/2008
64111	WION	Nelly	01/12/2009	CF-AUD	MERCK	ALFEDIAM : Strasbourg		03/2009	03/2009
64111	WION	Nelly	01/12/2009	CF-AUD	GSK	ALFEDIAM : Marseille		03/2007	03/2007
64111	WION	Nelly	01/12/2009	CF-AUD	NOVARTIS	Journées Endocrinologie klotz : Pans		05/2009	05/2009
64111	WION	Nelly	01/12/2009	CF-AUD	NOVARTIS	Journées thématiques Alfediam : Paris		12/2008	12/2008
64111	WION	Nelly	01/12/2009	CF-AUD	IPSEN	11 th workshop MEN : Delphes		09/2008	09/2008
64111	WION	Nelly	01/12/2009	CF-AUD	MSD	ALFEDIAM : Bruxelles		03/2008	03/2008

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
64111	WION	Nelly	01/12/2009	CF-AUD	NOVARTIS	Second Global NOVARTIS CVM Standalone symposium Prague		03/2008	03/2008
64111	WION	Nelly	01/12/2009	CF-AUD	NOVARTIS	Second global NORVATIS CVM XXXX symposium : Prague		03/2008	03/2008
64111	WION	Nelly	01/12/2009	CF-AUD	MSD	Congrès coeur et diabète : Paris		02/2008	02/2008
64111	WION	Nelly	01/12/2009	CF-AUD	GSK	Journées diabétologie hotel dieu : Paris		05/2007	05/2007
64111	WION	Nelly	01/12/2009	CF-AUD	NOVARTIS	EASD 45th annuel meeting : Vienne		09/2009	09/2009
64111	WION	Nelly	01/12/2009	CF-AUD	PFIZER	EASD 43th annuel meeting : Amsterdam		09/2007	09/2007
64111	WION	Nelly	01/12/2009	CF-AUD	SERVIER	Journées européennes sf cardiologie : Paris		01/2009	01/2009
64111	WION	Nelly	01/12/2009	CF-AUD	LILLY	IDC Minéapolis		06/2007	06/2007
64111	WION	Nelly	01/12/2009	CF-AUD	LILLY	Journées LILLY diabétologie : Paris		01/2007	01/2007
64111	WION	Nelly	23/07/2008	EC-INV	CHU	Etudes de pratiques : utilisation de lecteurs Accu Chek Inform en cardiologie - penumologie - Roches Diagn	investigateur coordonnateur	01/2007	06/2007
64111	WION	Nelly	23/07/2008	CF-INT	KOBE	Ateliers d'échanges de pratiques en diabétologie 2008 - Produit Takeda Actos ® - Grenoble	rémunération personnelle	06/2008	06/2008
64111	WION	Nelly	23/07/2008	CF-INT	GSK	Actualités en diabétologie - Produit Avandia - Gap	rémunération personnelle	03/2008	03/2008
64111	WION	Nelly	23/07/2008	CF-AUD	NOVARTIS ONCOLOGIE	51 eme journées internationales Henri Pierre Klotz - Paris		05/2008	05/2008
64111	WION	Nelly	23/07/2008	CF-AUD	MSD	ALFEDIAM - Produit : Januvia - Bruxelles		03/2008	03/2008
64111	WION	Nelly	23/07/2008	CF-AUD	NOVARTIS	Journey of risk reduction - Produit : Galvus - Prague		02/2008	02/2008
64111	WION	Nelly	23/07/2008	CF-AUD	SANOFI	Congrès SFE - produit Acomplia - Lille		10/2008	10/2008
64111	WION	Nelly	23/07/2008	CF-AUD	Réunions PFIZER	Utilisation de PubMed : outil informatique - produit : Tahor		04/2008	04/2008
64111	WION	Nelly	01/07/2007	CF-INT	SANOFI AVENTIS	Le patient diabétique - Chambéry	Rémunération personnelle	10/2006	10/2006
64111	WION	Nelly	01/07/2007	CF-INT	AMGEN	Diabète et insuffisance rénale - Voreppe	Rémunération personnelle	06/2007	06/2007
64111	WION	Nelly	01/07/2007	CF-INT	GSK	Ateliers de diabétologie - Grenoble	Rémunération personnelle	06/2007	06/2007
64111	WION	Nelly	01/07/2007	CF-INT	NOVO-NORDISK	Insulinothérapie Diabète type 2 - Grenoble	Rémunération personnelle	06/2007	06/2007
64111	WION	Nelly	01/07/2007	CF-AUD	LILLY	Journées Lilly de Diabétologie		01/2007	01/2007
64111	WION	Nelly	01/07/2007	CF-AUD	GSK	ALFEDIAM		03/2007	03/2007
64111	WION	Nelly	01/07/2007	CF-AUD	GSK	Journées de l'Hôtel-Dieu		05/2007	05/2007
64111	WION	Nelly	01/07/2007	CF-AUD	PFIZER	EASD		09/2007	09/2007
64111	WION	Nelly	01/07/2007	CF-AUD	SERVIER	EASD		09/2006	09/2006
64111	WION	Nelly	01/07/2007	CF-AUD	LILLY	International Diabetes Center, Minneapolis: nouvelles thérapeutiques - incrétines		05/2007	06/2007
64111	WION	Nelly	01/07/2007	EC-INV	CHU GRENOBLE	lecteur de glycémie Accu Chek Inform - Roche Diagnostic : étude de pratique clinique	investigateur principal	01/2007	07/2007
64111	WION	Nelly	24/02/2006	IP-AC	ROCHE DIAGNOSTIC	groupe de travail pour l'élaboration d'un carnet d'autosurveillance du diabétique	rémunération personnelle	09/2005	01/2006
64111	WION	Nelly	24/02/2006	CF-AUD	NOVO NORDISK	Congrès EASD / Athènes		09/2005	
64111	WION	Nelly	24/02/2006	CF-AUD	BAYER	Congrès Cœur et diabète / Budapest		10/2005	
64111	WION	Nelly	24/02/2006	CF-AUD	LILLY	Journées de diabétologie / Paris		01/2006	01/2006
65061	WISNIEWSKI	Sandra	10/12/2010	PAR	SERVIER BIOPHARMA	DELEGUE MEDICAL VILLE	FRERE	01/2000	
65061	WISNIEWSKI	Sandra	10/12/2010	IP-AC	COOK	FORMATION DELEGUES	Rémunération personnelle	12/2009	04/2010
65061	WISNIEWSKI	Sandra	10/12/2010	IP-AC	COOK	FORMATIONS DELEGUES	Rémunération personnelle	12/2009	04/2010
65061	WISNIEWSKI	Sandra	10/12/2010	LD-AR	ABBOTT VASCULAR	GROUPE EXPERT PHARMACIENS HOSPITALIERS	Aucune rémunération	11/2010	
65061	WISNIEWSKI	Sandra	10/12/2010	LD-AR	ST JUDE MEDICAL	GROUPE EXPERTS PHARMACIENS HOSPITALIERS	Aucune rémunération	01/2009	
65061	WISNIEWSKI	Sandra	13/07/2010	IP-AC	COOK	FORMATION DELEGUES	Rémunération personnelle	12/2009	04/2010
65061	WISNIEWSKI	Sandra	29/12/2009	IP-AC	IMPLANET	expliquer les attentes des pharmaciens hospitaliers	Rémunération personnelle	10/2007	10/2007
65061	WISNIEWSKI	Sandra	29/12/2009	IP-AC	IMPLANET	expliquer les attentes des pharmaciens hospitaliers	Aucune rémunération		
65061	WISNIEWSKI	Sandra	29/12/2009	RE-AUT	CABINET AVOCATS	MATERIOVIGILANCE "PROTHESE HANCHE"	Rémunération personnelle	11/2006	11/2006
65061	WISNIEWSKI	Sandra	29/12/2009	LD-AR	ST JUDE MEDICAL	GROUPE EXPERTS PHARMACIENS HOSPITALIERS	Rémunération personnelle	01/2009	
65061	WISNIEWSKI	Sandra	12/01/2009	RE-AUT	CABINET D'AVOCAT	Matériovigilance - prothèse de hanche	rémunération personnelle	11/2006	11/2006
65061	WISNIEWSKI	Sandra	12/01/2009	IP-AC	IMPLANET	Implants orthopédie - explication contexte des achats hospitaliers / logistique	rémunération personnelle	10/2007	10/2007
65061	WISNIEWSKI	Sandra	12/01/2009	CF-AUD	BAXTER	Europharmat - Bordeaux		10/2008	10/2008
65061	WISNIEWSKI	Sandra	12/01/2009	IP-AC		Durascal	aucune rémunération		
65061	WISNIEWSKI	Sandra	12/01/2009	PAR	BIOPHARMA	Délégué médical	frère	01/2000	
65061	WISNIEWSKI	Sandra	05/05/2008	IP-RE	CABINET D'AVOCAT	matériovigilance prothèse hanche	rémunération personnelle	11/2006	11/2006
65061	WISNIEWSKI	Sandra	05/05/2008	IP-AC	IMPLANET	expliquer les attentes des pharmaciens hospitaliers	rémunération personnelle	10/2007	
65061	WISNIEWSKI	Sandra	05/05/2008	PAR	SERVIER	visiteur médical	frère	01/2000	
65061	WISNIEWSKI	Sandra	07/01/2008	RE-AUT	Cabinet d'avocat	matériovigilance	rémunération personnelle	11/2006	11/2006
65061	WISNIEWSKI	Sandra	07/01/2008	IP-AC	IMPLANET	Expliquer attentes des pharmaciens hospitaliers	rémunération personnelle	10/2007	10/2007
65061	WISNIEWSKI	Sandra	07/01/2008	CF-INT	France MEDICA	SOFCOT	aucune rémunération	11/2007	11/2007
65061	WISNIEWSKI	Sandra	07/01/2008	CF-INT	CORDIS	Europharmat	aucune rémunération	10/2007	10/2007
65061	WISNIEWSKI	Sandra	07/01/2008	PAR	SERVIER	Visiteur médical	frère	01/2000	
62810	ZAOUI	Philippe	04/02/2008	EC-INV	MSD	essai clinique - Ezetimibe	investigateur principal	01/2005	12/2010
62810	ZAOUI	Philippe	04/02/2008	EC-INV	AMGEN	essai clinique - Aranesp Mimpara	investigateur principal	01/2005	12/2011
62810	ZAOUI	Philippe	04/02/2008	EC-INV	KERYS	essai clinique - Sulodexide	investigateur principal	01/2005	12/2009
62810	ZAOUI	Philippe	04/02/2008	EC-INV	AMGEN	essai clinique - CERA	investigateur principal + responsable France	01/2006	12/2009
62810	ZAOUI	Philippe	04/02/2008	EC-INV	SANKYO	essai clinique - Olmetec	investigateur principal	01/2005	12/2009
62810	ZAOUI	Philippe	04/02/2008	EC-INV	NOVARTIS	essai clinique - Aliskiren	investigateur principal	01/2004	12/2008
62810	ZAOUI	Philippe	04/02/2008	LD-AR	ROCHE	expert essais cliniques CERA	rémunération personnelle	01/2006	12/2009
62810	ZAOUI	Philippe	21/06/2006	LD-AR	SANKYO	Board d'experts	rémunération peraonnelle	01/2003	12/2006
62810	ZAOUI	Philippe	21/06/2006	LD-AR	ROCHE	expert essais cliniques CERA	rémunération personnelle	01/2006	12/2009
62810	ZAOUI	Philippe	21/06/2006	EC-INV	NOVARTIS	essai clinique - Aliskiren	investigateur principal	01/2004	12/2008
62810	ZAOUI	Philippe	21/06/2006	EC-INV	SANKYO	essai clinique - Olmetec	investigateur principal	01/2005	12/2009
62810	ZAOUI	Philippe	21/06/2006	EC-INV	ROCHE	essai clinique - Neorecormon	Investigateur principal + coordonnateur	01/2005	12/2007
62810	ZAOUI	Philippe	21/06/2006	EC-INV	AMGEN	essai clinique - CERA	investigateur principal + responsable France	01/2006	12/2009
62810	ZAOUI	Philippe	21/06/2006	EC-INV	KERYS	essai clinique - Sulodexide	Investigateur principal	01/2005	12/2009
62810	ZAOUI	Philippe	21/06/2006	EC-INV	AMGEN	essai clinique - Aranesp Mimpara	investigateur principal	01/2005	12/2011
62810	ZAOUI	Philippe	21/06/2006	EC-INV	MSD	essai clinique - Ezetimibe	Investigateur principal	01/2005	12/2010
62810	ZAOUI	Philippe	21/06/2006	IP-AC	SANKYO	board Olmetec	rémunération partagée personnelle/ institution	01/2003	12/2006
62810	ZAOUI	Philippe	21/06/2006	IP-AC	CHIESI		rémunération personnelle	01/2004	12/2006
62810	ZAOUI	Philippe	21/06/2006	IP-AC	GENZYME	Osservatoire régional phosphocalcique	rémunération partagée personnelle/ institution	01/2005	12/2006
62810	ZAOUI	Philippe	21/06/2006	CF-INT	ROCHE	Ateliers Roche néphrologie	rémunération versée à une institution	10/2005	10/2006
62810	ZAOUI	Philippe	21/06/2006	CF-INT	HOSPAL	ARN - réunion régionale de néphrologues	aucune rémunération	11/2006	11/2006

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
62810 ZAOUI		Philippe	21/06/2006	CF-INT	AMGEN	enseignement du DES Néphrologie National	aucune rémunération	06/2006	06/2006
62810 ZAOUI		Philippe	21/06/2006	CF-INT	ROCHE	enseignement du DES Néphrologie Régional	aucune rémunération	06/2006	06/2006
62810 ZAOUI		Philippe	21/06/2006	CF-AUD	AMGEN	ASN		11/2005	11/2005
62810 ZAOUI		Philippe	21/06/2006	VB	ROCHE	don recherche formation		01/2006	12/2006
62810 ZAOUI		Philippe	21/06/2006	VB	PFIZER	don recherche foramtion	AGDUC / AGENDT	01/2006	12/2006
62810 ZAOUI		Philippe	23/06/2003	IP-EC	AMGEN	Bourse de recherche DEA			
62810 ZAOUI		Philippe	23/06/2003	IP-RE	MSD	Commission cardio-vasculaire			
62810 ZAOUI		Philippe	23/06/2003	IP-CF	BMS	HTA			
62810 ZAOUI		Philippe	23/06/2003	IP-CF	SERVIER	insuffisance rénale			
62810 ZAOUI		Philippe	23/06/2003	IP-CF	ARDIX	Néphropathie diabétique			
62810 ZAOUI		Philippe	23/06/2003	VB	AMGEN	AGENDT			
62810 ZAOUI		Philippe	23/06/2003	VB	ZENECA	AGENDT			
61146 ZUBER		Mathieu	16/06/2010	CF-AUD	EUTHERAPIE	Barcelone, European Stroke Conference / PRETERAX	déplacement	05/2010	05/2010
61146 ZUBER		Mathieu	16/06/2010	CF-AUD	EUTHERAPIE	Stockholm, European Stroke Conference / PRETERAX	déplacement	05/2009	05/2009
61146 ZUBER		Mathieu	16/06/2010	CF-AUD	TEVA	American Academy of Neurology / COPAXONE	déplacement + hébergement	04/2009	05/2009
61146 ZUBER		Mathieu	16/06/2010	CF-INT	EUTHERAPIE	Bucarest, Symposium Démence et AVC / Intérêt du controle de l'HTA / PRETERAX	Rémunération personnelle	01/2009	01/2009
61146 ZUBER		Mathieu	16/06/2010	CF-INT	EUTHERAPIE	Barcelone, Symposium HTA et AVC / Role des UNV dans la prise en charge de l'HTA en cas d'AVC / PRETI	Rémunération personnelle	01/2009	01/2009
61146 ZUBER		Mathieu	16/06/2010	IP-AC	SANOFI-AVENTIS	comité adjudication évènements (étude OBSERVE) / PLAVIX	Rémunération personnelle	06/2008	06/2010
61146 ZUBER		Mathieu	16/06/2010	EC-CO	MERCK SERONO	Interféron bêta	co-investigateur	05/2010	05/2012
61146 ZUBER		Mathieu	16/06/2010	EC-CO	SERVIER	TERUTROBAN	co-investigateur	06/2008	12/2010
60337 ZUBER		Martine	23/02/2010	Néant					
60337 ZUBER		Martine	30/01/2009	IP-AUT	IFIS	Formation			03/2009
60337 ZUBER		Martine	30/01/2009	PAR	MSD	Déléguée médicale	Fille		
60337 ZUBER		Martine	21/10/2008	PAR	MSD	Déléguée médicale	Fille		
60337 ZUBER		Martine	21/10/2008	IP-AUT	IFIS	Formation			
60337 ZUBER		Martine	21/10/2008	Néant					
61146 ZUBER		Mathieu	10/04/2008	LD-AR	SANOFI - AVENTIS	Conseil scientifique états généraux de l'athérothrombose / Plavix ®	rémunération personnelle	10/2007	10/2008
61146 ZUBER		Mathieu	10/04/2008	LD-AR	SANOFI - AVENTIS	Membre comité des évènements / étude OBSERVE / Plavix ®	rémunération personnelle	06/2007	12/2009
61146 ZUBER		Mathieu	10/04/2008	EC-CO	SANOFI AVENTIS - BMS	Plavix ®	co-investigateur	01/2006	12/2007
61146 ZUBER		Mathieu	10/04/2008	EC-CO	BOEHRINGER INGELHEIM	Asasantine®	co-investigateur	01/2006	12/2007
61146 ZUBER		Mathieu	10/04/2008	EC-CO	SERVIER	Terutroban	co-investigateur	01/2007	12/2009
61146 ZUBER		Mathieu	10/04/2008	EC-CO	JOHNSON & JOHNSON	RIVAROXABAN	co-investigateur	01/2007	12/2010
61146 ZUBER		Mathieu	10/04/2008	RE-AUT	DIRECTION POUR LA RECHERCHE CLINIQUE	Dossiers PHRC	aucune rémunération		
61146 ZUBER		Mathieu	10/04/2008	CF-INT	SANOFI AVENTIS - BMS	antiplaquettaires et AVC / Plavix ®	rémunération personnelle - institution		
61146 ZUBER		Mathieu	10/04/2008	CF-INT	EUTHERAPIE	HTA et AVC / FLUDEX ®	rémunération personnelle - institution		
61146 ZUBER		Mathieu	10/04/2008	CF-INT	PFIZER	Cholestérol et AVC / TAHOR®	rémunération personnelle - institution		
61146 ZUBER		Mathieu	10/04/2008	CF-AUD	SANOFI AVENTIS	AAN - COPAXONE® / Boston		04/2007	04/2007
61146 ZUBER		Mathieu	10/04/2008	CF-AUD	SANOFI AVENTIS	Colloque unités neurovasculaires - Plavix® / Bordeaux		04/2007	04/2007
61146 ZUBER		Mathieu	10/04/2008	CF-AUD	BOEHRINGER INGELHEIM	European Stroke Conference / ASASANTINE®		05/2009	05/2009
60337 ZUBER		Martine	11/11/2007	PAR	MSD	Déléguée médicale	Fille		
60337 ZUBER		Martine	11/11/2007	IP-AUT	IFIS	Actions de formations			
60337 ZUBER		Martine	11/11/2007	CF-INT	IFIS	Actions de formation	Rémunération versée à une institution		
61146 ZUBER		Mathieu	27/12/2006	EC-CO	SANOFI AVENTIS-BMS	Plavix ®	co-investigateur	01/2006	12/2007
61146 ZUBER		Mathieu	27/12/2006	EC-CO	BOEHRINGER INGELHEIM	Asasantine ®	co-investigateur	01/2006	12/2007
61146 ZUBER		Mathieu	27/12/2006	EC-CO	SERVIER	Terutroban	co-investigateur	01/2007	12/2009
61146 ZUBER		Mathieu	27/12/2006	RE-AUT	DIRECTION POUR LA RECHERCHE CLINIQUE	expertises pour des dossiers dans le cadre du PHRC	aucune rémunération		
61146 ZUBER		Mathieu	27/12/2006	IP-AC	SANOFI-AVENTIS BMS	consultant ponctuel / Plavix ®	rémunération personnelle / institution	01/2005	12/2007
61146 ZUBER		Mathieu	27/12/2006	CF-INT	SANOFI-AVENTIS BMS	Plusieurs réunions : Antiplaquettaire et AVC / Plavix ®	rémunération personnelle / institution		
61146 ZUBER		Mathieu	27/12/2006	CF-INT	EUTHERAPIE	HTA et AVC / Fludex ®	rémunération personnelle / institution		
61146 ZUBER		Mathieu	27/12/2006	CF-AUD	SANOFI AVENTIS	American Association of Neurology , Boston / Copaxone ®		04/2007	04/2007
60337 ZUBER		Martine	29/05/2006	IP-AUT	IFIS	Actions de formations			
60337 ZUBER		Martine	29/05/2006	CF-INT	IFIS	Actions de formation	Rémunération versée à une institution		
60337 ZUBER		Martine	03/05/2006	PAR	Laboratoires MSD	Déléguée médicale	Fille		
61146 ZUBER		Mathieu	15/02/2006	EC-CO	SANOFI ABENTIS-BMS	Plavix	co-investigateur	01/2006	12/2007
61146 ZUBER		Mathieu	15/02/2006	EC-CO	BOEHRINGER INGELHEIM	Asasantine	co-investigateur	01/2006	12/2007
61146 ZUBER		Mathieu	15/02/2006	IP-AC	SANOFI AVENTIS-BMS	Consultant ponctuel / Plavix	rémunération personnelle/institution	01/2005	12/2007
61146 ZUBER		Mathieu	15/02/2006	CF-INT	SANOFI AVENTIS-BMS	plusieurs réunions - sujet : antiplaquettaires et AVC (Plavix)	rémunération personnelle / institution		
61146 ZUBER		Mathieu	15/02/2006	CF-INT	EUTHERAPIE	sujet : HTA et AVC (Fludex LP)	rémunération personnelle / institution		
60337 ZUBER		Martine	27/04/2005	CF-INT	IFIS (INSTITUT DE FORMATION DES INDUSTRIES DE SANTE)	Formations	1014 euros		
60337 ZUBER		Martine	15/02/2005	Néant					
61146 ZUBER		Mathieu	28/01/2004	IP-EC	SANOFI SYNTHELABO - BMS - BOEHRINGER - SERVIER - MSD	Essais thérapeutiques (phase III et IV)			
61146 ZUBER		Mathieu	28/01/2004	IP-CF	SANOFI SYNTHELABO - BMS - BOEHRINGER - SERVIER - MSD	Conférences divers et participation à des symposiums sur les AVC			
60337 ZUBER		Martine	27/12/2003	IP-CF	IFIS	Actions de formations			
60337 ZUBER		Martine	15/09/2003	IP-CF	IFIS	Actions de formation			
60337 ZUBER		Martine	15/09/2003	PAR	MERCK SHARP & DOHME	Enfant			
61146 ZUBER		Mathieu	14/08/2000	IP-CF	SANOFI	Film sur les AVC (pour professionnels)			
61146 ZUBER		Mathieu	14/08/2000	IP-CF	SANOFI	Symposium sur l'épidémiologie des AVC			
61146 ZUBER		Mathieu	14/08/2000	IP-CF	SANOFI	Prise en charge de l'athérosclérose par le neurologue (conférence)			

Id	Nom	Prenom	Date de déclaration	Type d'intérêt	Entreprise	Activité, Produit, Sujet	Capital, Contrat, Rémunération	Date début	Date fin
61145	ZUBER	Mathieu	14/08/2000	IP-CF	GLAXO WELLCOME	Conférence AVC/Migraine chez la femme			
61146	ZUBER	Mathieu	14/08/2000	IP-CF	BOEHRINGER	Marqueurs de risque d'AVC (conférence)			
61145	ZUBER	Mathieu	14/08/2000	VB	BMS ; BIOGEN ; JANSSEN	Essais cliniques / Centre Hospitalier Sainte-Anne - Association loi 1901 "CRHM" (domiciliée au Centre Hospitalier Sainte-Anne)			
61146	ZUBER	Mathieu	14/08/2000	VB	GLAXO WELLCOME ; SMITHKLINE BEECHAM	Association loi 1901 "CRHM", domiciliée au Centre Hospitalier Sainte-Anne			
60337	ZUBER	Martine	05/07/2000	IP-CF	IFIP	Actions de formation			
60337	ZUBER	Martine	04/11/1999	IP-CF	IFIP	Stages			